CELLTRION Inc.
CT-P10 3.2

A Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Pharmacokinetics, Efficacy and Safety between CT-P10, Rituxan and MabThera in Patients with Rheumatoid Arthritis

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Statistical Analysis Plan

Version 3.1 Final

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

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List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	ACR 20% Improvement Criteria
ACR50	ACR 50% Improvement Criteria
ACR70	ACR 70% Improvement Criteria
ADA	Anti-Drug Antibody
AE	Adverse Event
ANCOVA	Analysis of Covariance
anti-CCP	Anti-Cyclic Citrullinated Peptide
$AUC_{0\text{-day14}}$	Area Under the Concentration-time curve from time 0 to day 14
$AUC_{0\text{-}\infty}$	Area Under the Concentration-time curve from time 0 extrapolated to infinity over both doses of the first course
$AUC_{0\text{-last}}$	Area Under the Concentration-time curve from time 0 to the last measurable concentration over both doses of the first course
B-cell	B-Lymphocyte
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
CDAI	Clinical Disease Activity Index
CI	Confidence Interval
CL	Total Clearance
C_{max}	Maximum Serum Concentration
$C_{max,1}$	Maximum Serum Concentration after the first infusion
C_{min}	Minimum Serum Concentration
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CT-P10	Rituximab (CELLTRION, Inc.)
C_{trough}	Trough Serum Concentration
CV	Coefficient of Variation
DAS28	Disease Activity Score using 28 joint counts
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of Study
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
HAQ	Health Assessment Questionnaire
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBcIg	Hepatitis B Core (total) Immunoglobulin
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IgA	Immunoglobulin A

IgG	Immunoglobulin G
IgM	Immunoglobulin M
IGRA	Interferon-Gamma Release Assay
IRR	Infusion-related Reaction
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LLN	Lower Limit of Normal
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NAb	Neutralizing antibody
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred Term
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDAI	Simplified Disease Activity Index
SE	Standard Error
SF-36	Quality-of-Life Questionnaire (Medical Outcomes Study Short-Form Health Survey)
SF-36 BP	Bodily Pain (SF-36 subscale)
SF-36 GH	General Health Perceptions (SF-36 subscale)
SF-36 MCS	Mental Component Score (SF-36 summary score)
SF-36 MH	Mental Health (SF-36 subscale)
SF-36 PCS	Physical Component Score (SF-36 summary score)
SF-36 PF	Physical Functioning (SF-36 subscale)
SF-36 VT	Vitality (SF-36 subscale)
SF-36 RE	Role Limitations due to Emotional Problems (SF-36 subscale)
SF-36 RP	Role Limitations due to Physical Health (SF-36 subscale)
SF-36 SF	Social Functioning (SF-36 subscale)
SOC	System Organ Class
$t_{1/2}$	Terminal Elimination Half-life
TB	Tuberculosis
TEAE	Treatment Emergent Adverse Event
T_{max}	Time to Reach C_{max}
TNF	Tumor Necrosis Factor
TNF- α	Tumor Necrosis Factor alpha
ULN	Upper Limit of Normal
U.S.	United States of America
VAS	Visual Analogue Scale
V_d	Volume of distribution
WHO	World Health Organization

1. Administrative Structure

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

2. Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects 0.8% to 1.0% of all populations. Rheumatoid arthritis primarily affects diarthrodial joints in a symmetrical distribution with an additive disease evolution over years (Scott et al 1987). The hallmark of the disease is damage and disruption of joint integrity, starting early in the course of RA. In most cases, bone erosions progress and lead to irreversible joint deformities. It is estimated that around one-third of patients have radiographic evidence of bone erosions at the time of diagnosis, and this increases to almost 60% 2 years after diagnosis (van der Heijde 1995). Unless the inflammatory processes are halted or controlled, the disease leads to substantial disability, comorbidities, and in some cases, premature death (Lard et al 2001).

CT-P10 is a monoclonal antibody, currently being developed by CELLTRION, Inc., which is intended to be formulated as a biosimilar candidate of Rituxan and MabThera, compounds with established efficacy in the treatment of active RA (MabThera 2015; Rituxan 2014). Rituximab is approved as Rituxan in the United States and as MabThera in other countries. CT-P10 can offer a more affordable treatment for RA than the originator protein if similar efficacy and safety are demonstrated and allow increased access to this valuable drug with a proven mechanism of action in RA patients. This is a similarity study that consists of 3 parallel arms: Rituxan (US-licensed), MabThera (EU-approved), and CT-P10. All statistical assessments will be direct comparisons between the treatment groups at specified time points.

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

- Protocol Version 5.1, including Country-Specific Protocol Amendment 1 (US) – 01 April 2016
- MSL Final Version 4.00 – 21 August 2015

According to the study protocol, the sponsor plans to prepare 2 Clinical Study Reports (CSRs). However, CSRs can be generated during the Study Period in addition to the 2 clinical study reports as planned for regulatory or academic purpose:

- To report data for each patient up to Week 24
- To report data after completion of study

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by the CELLTRION biostatistics team for final analysis.

Note that the End-of-Study (EOS) visit only needs to be completed if the patient withdraws prior to study completion (Week 48 for Main Study Period, Extension Week 24 for Extension Study Period).

3. Objectives

Primary and secondary objectives are described below. Note that all patients from Part 1 of the study will be included in Part 2 of the study and undergo all assessments performed in Part 2. The decision to enter Part 2 of the study will not be influenced by the results from Part 1.

3.1. Part 1

3.1.1. Primary Objective

- To evaluate and compare pharmacokinetics in terms of area under the concentration-time curve from time 0 to the last measurable concentration over both doses of the first course ($AUC_{0\text{-last}}$), area under the concentration-time curve from time 0 extrapolated to infinity over both doses of the first course ($AUC_{0\text{-}\infty}$), and maximum serum concentration (C_{max}) (after the second infusion) of CT-P10 to Rituxan, CT-P10 to MabThera, and Rituxan to MabThera during the first course of treatment (over the first 24 Weeks).

3.1.2. Secondary Objective

- To assess the additional Pharmacokinetic (PK) variables of CT-P10, Rituxan, and MabThera, during the first course of treatment (over the first 24 Weeks)
- To evaluate the pharmacodynamics (PD) and safety of CT-P10, Rituxan, and MabThera (over the first 24 Weeks)

3.2. Part 2

3.2.1. Primary Objective

- To demonstrate that CT-P10 is similar to reference products (Rituxan and MabThera) 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]) at Week 24.

3.2.2. Secondary Objective

- To evaluate the additional PK (up to Week 48), efficacy, PD, overall safety, and biomarkers of CT-P10 compared with reference products

4. Investigational Plan

4.1. Overall Study Design and Plan

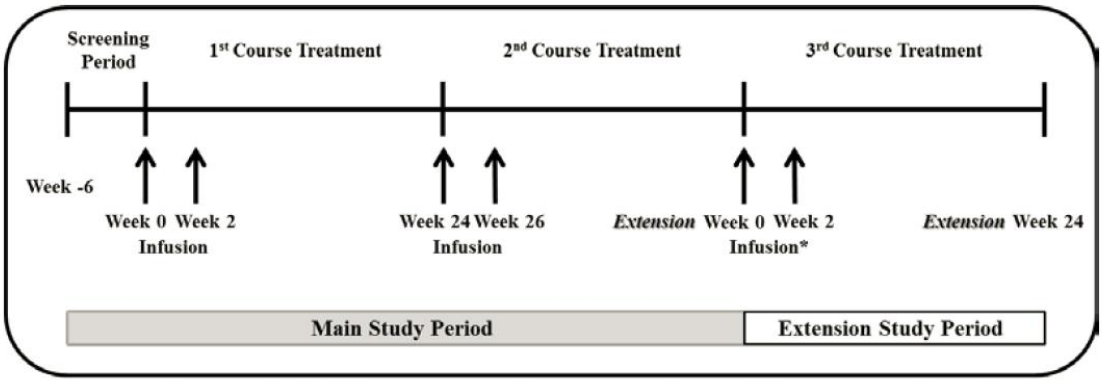
This is a randomized, controlled, multicenter, 3-arm, parallel-group, double-blind, prospective, PK, efficacy, PD, and safety Phase 3 study. There will be up to 3 periods in this study:

- Screening Period: Week -6 through Week 0 (Day -42 to Day -1)
- Main Study Period: Week 0 through Week 48 (Day 0 to Day 336)
- Extension Study Period: Extension Week 0 through Week 24 (Extension Day 0 to Day 168)

The combined main and extension study duration will be up to 76 weeks after the Week 0 infusion. Extension Study Period will be initiated between Week 48 and Week 52 of the Entire Study Period. A schematic of the study design is presented in Figure 1. There will be additional follow-up visits for patients with B-cell, IgM, and IgG values below the lower limit of normal

(LLN) or less than 50% of their baseline value until recovery is achieved for one of them. The term "Extension" will be used for all the visits in the Extension Study Period (i.e. Extension Week X or Extension Day X). Otherwise, visits will simply be stated as Week X.

Figure 1: Study Schematic



* The third course of treatment will be initiated between Week 48 and Week 52 of the Entire Study Period based on the results assessed within 8 weeks from the Extension Week 0.

Any courses of treatment after the first course will be initiated if the following safety criteria are met:

- Absolute neutrophil count should be $\geq 1.5 \times 10^3$ cells/μL (SI units: $\geq 1.5 \times 10^9$ cells/L), platelet count should be $\geq 75 \times 10^3$ cells/μL (SI units: $\geq 75 \times 10^9$ cells/L), aspartate aminotransferase or alanine aminotransferase should be ≤ 2.5 times the upper limit of normal and levels of IgG should be ≥ 500 mg/dL (5.0 g/L), at the last blood sample analysis (i.e. Week 16 for second course of treatment and within 8 Weeks from the Extension Week 0 for third course of treatment).
- The patient has not developed any conditions which, in the investigators opinion, would preclude the patient receiving further courses of treatment (e.g., any new or uncontrolled disease such as, but not limited to, cardiovascular disease, or nervous system, pulmonary, renal, hepatic, endocrine, or gastrointestinal disorder).

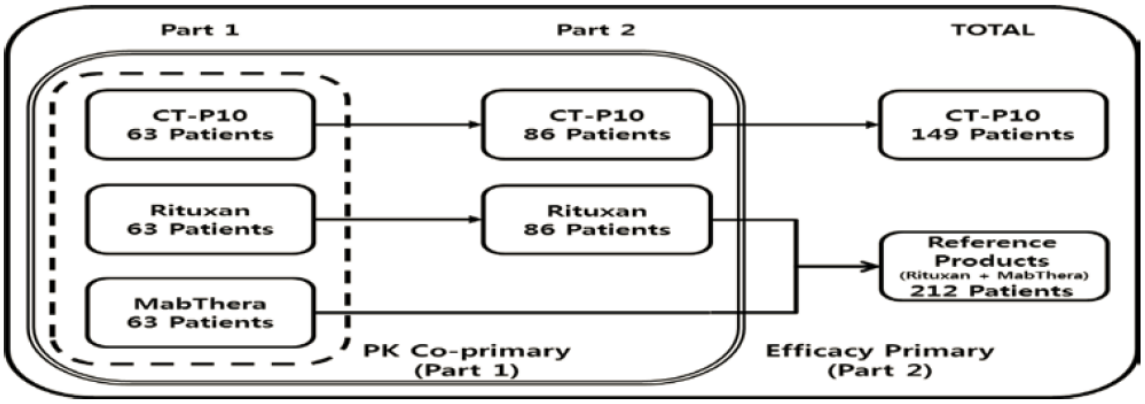
Note that Part 1 and Part 2 of the study will follow the study schematic specified in Figure 1.

In Part 1, the first approximately 189 patients with RA will be randomly assigned in a 1:1:1 ratio to 1 of 3 treatment groups, CT-P10, Rituxan, or MabThera (approximately 63 patients per treatment group).

In Part 2, approximately 172 subsequent patients with RA will be randomly assigned in a 1:1 ratio to 1 of 2 treatment groups, CT-P10 or Rituxan. In total, approximately 361 patients will be available for analysis.

Approximately 189 initial patients to be enrolled in the study will be assigned to Part 1 and all subsequent patients enrolled in the study will be assigned to Part 2. All patients from Part 1 of the study will be included in Part 2 of the study and undergo all assessments performed in Part 2. A schematic of study patient assignment for Part 1 and Part 2 is presented in Figure 2. Part 2 will run independently and in parallel with Part 1.

Figure 2: Schematic Diagram of Study Patients for the Main Study Period (up to Week 48)



The Extension Study Period is designed to evaluate additional safety and immunogenicity.

Patients can continue to the Extension Study Period with an additional course of treatment regardless of the number of treatment courses they were treated with during the Main Study Period if the following conditions are met:

- Complete all of the scheduled visits up to Week 48 and
- Meet the predefined safety criteria.

The third course of treatment should be initiated between Week 48 and Week 52. If administration of the third course of treatment is deemed necessary to be initiated after Week 52 at the discretion of the investigator, the study infusion can be administered within 72 Weeks from the first infusion of the first course of treatment after discussion with the sponsor. In this case, the study infusion must be initiated no later than 52 Weeks from Day 0 for the last enrolled patient.

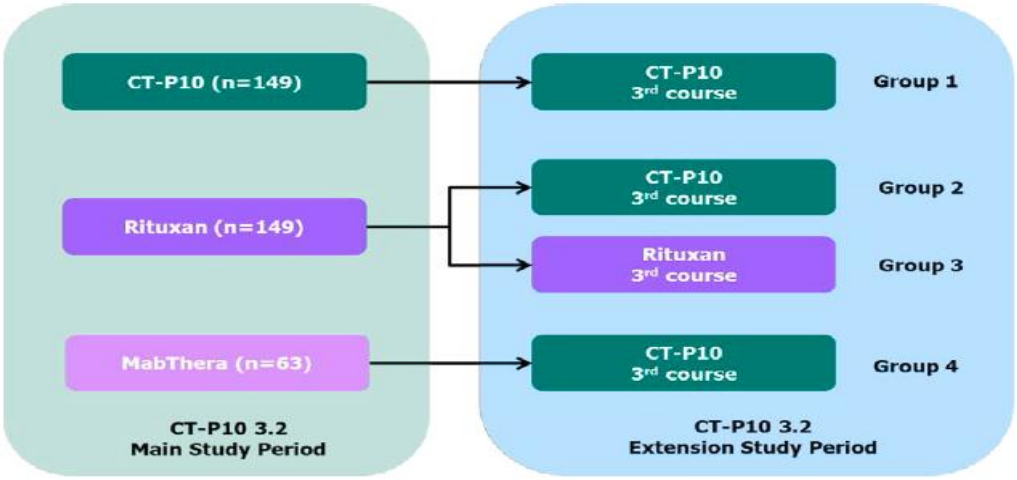
Note that patients, who have the End-of-Study (EOS) visit at Week 48, can participate in the Extension Study Period if the patients sign an informed consent form within 24 weeks from the EOS visit and do not have prohibited medications prior to entering the Extension Study Period.

All patients eligible for Extension Phase from the Rituxan group will be randomized again in a 1:1 ratio to the CT-P10 or Rituxan group at Extension Week 0. The randomization will be conducted and stratified by:

- The number of courses they are treated during the Main Study Period and
- The European League Against Rheumatism (EULAR)-CRP response status (responder vs. non-responder) assessed at Week 40.

To keep the blind during the study, stratification factors will be entered for all patients at Extension Week 0. In the case there were no EULAR-CRP response status available at Week 40, the last EULAR-CRP response status assessment done between Weeks 40 and 48 will be used. Baseline values for assessment of EULAR-CRP will be the last value from screening to Day 0 (Week 0) of the study. A schematic of the study patient assignment for this randomization is presented in Figure 3.

Figure 3: Study Schematic of Randomization



Patients, who are assigned to receive CT-P10 with their first infusion in the study, will be considered as group 1 and maintain CT-P10 for the third course.

Patients, who are assigned to receive Rituxan with their first infusion in the study, will be randomized in a 1:1 ratio to group 2 (CT-P10 will be administered for the third course) and group 3 (Rituxan will be maintained for the third course) at Extension Week 0.

Patients, who are assigned to receive MabThera with their first infusion in the study, will be considered as group 4 and receive CT-P10 for the third course at Extension Week 0.

The third course of treatment will be initiated between Week 48 and Week 52 of the Entire Study Period if patients become eligible according to the predefined safety criteria for the course based on the results assessed within 8 weeks from the Extension Week 0. A visit window is not permitted on the day of second infusion for the third course of treatment.

Unscheduled visit(s) can be conducted for assessment of safety criteria until the initiation of the third course of treatment.

For patients who receive the third course of treatment at Week 48, the scheduled assessments and samplings should be performed according to the schedule of events and sampling schemes for the Extension Week 0. Otherwise, all scheduled assessments for Week 48 should be performed separately from the Extension Week 0 according to the schedule of events for Main Study Period.

All patients will receive MTX and folic acid concomitantly. Each patient may receive up to 3 courses of treatment; the first course will be an infusion of study drug (CT-P10, Rituxan, or MabThera) at Week 0 and Week 2. If patients meet the predefined safety criteria, patients are eligible to receive the additional course(s) of study drug (2 infusions in each course with a 2-week interval between infusions) at the discretion of the investigator.

For the second course of treatment in the Main Study Period, patients, who do not meet the predefined safety criteria, will not receive an additional course of treatment, but they will be followed according to the schedule of events for Main Study Period.

For the third course of treatment in the Extension Study Period, patients, who do not meet the predefined safety criteria within the time frame for the study drug infusion, will not receive an additional course of treatment and will be terminated from the study.

5. General Statistical Considerations

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), median, minimum and maximum, unless otherwise indicated. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and SD will be presented to two more decimal places than the raw data. If the geometric mean is to be presented, it will be set to the same precision as the mean. Percent coefficient of variation (CV) will be presented to one decimal place. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001". If a p-value is greater than 0.999 it will be reported as ">0.999".

Categorical data will be summarized using counts and percentages. Percentages will be suppressed when the count is zero. A row denoted "Missing" will be included in count tabulations where necessary to account for missing values. The denominator for all percentages will be the number of patients within the treatment group for the all populations. Percentages will be presented to one decimal place.

Unless otherwise specified, summaries for visit-based data will only display scheduled visits.

Confidence intervals obtained from statistical procedures will be displayed to the same number of decimal places as the associated estimate.

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

5.1. Software

All analyses will be conducted using [redacted]. The [redacted] will be used in order to derive summary scores for the SF-36 data prior to analysis. Pharmacokinetic parameters will be calculated with [redacted]

5.2. Sample Size

For Part 1, 189 patients will be randomized in a 1:1:1 ratio to the CT-P10, Rituxan, and MabThera groups. Later, for Part 2, 172 patients will be allocated in a 1:1 ratio to the CT-P10 and Rituxan groups.

Part 1 of this study is powered to demonstrate PK similarity of CT-P10, Rituxan, and MabThera in $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max}. Similarity will be demonstrated if the 90% confidence interval (CI) for the geometric mean ratio of CT-P10 to Rituxan and MabThera in $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} is within the bounds of 80% and 125%.

In Part 1, based on overall 90% power, Two one-sided alpha equal to 0.05, an interpatient CV in $AUC_{0\text{-last}}$ of 30%, and a true of geometric mean equal to 1, fifty patients are needed in each treatment group being compared (50 patients in the CT-P10 treatment group, 50 patients in the MabThera treatment group, and 50 patients in the Rituxan treatment group: 150 patients total). The statistical power of each comparison, CT-P10 versus MabThera, CT-P10 versus Rituxan,

and MabThera versus Rituxan is 96.5% to achieve overall 90% power accounting for multiplicity with type II error correction. Allowing for a drop-out rate of 20%, 189 patients will be randomly assigned into the study in a 1:1:1 allocation.

In Part 2, the sample size of 322 evaluable patients (133 patients in the CT-P10 group and 189 patients in the reference products group [Rituxan and MabThera groups]) leads to approximately 90% power for the demonstration of similarity based on a two-sided 90% CI for the difference of mean change of DAS28 (CRP) score at Week 24 from baseline value between CT-P10 and reference products for an equivalence margin of ±0.50. In this sample size calculation, the common standard deviation of the mean change of DAS28 at Week 24 from baseline is assumed as 1.32 based on the CT-P10 1.1 study result for the therapeutic equivalence margin of ±0.50. Incorporating hypothesized drop-out rate of 10%, total sample size of 361 subjects (149 eligible patients in the CT-P10 and 212 eligible patients in the reference products group, including up to 63 patients from each of the CT-P10, Rituxan, and MabThera groups in Part 1) will be used in evaluation of efficacy endpoints.

In total, approximately 361 patients will be available for analysis (a total of approximately 149 patients for the CT-P10 group and 212 patients for the reference products group, including up to 63 patients from each treatment group in Part 1).

5.3. Randomization, Stratification, and Blinding

Patients will be randomly assigned to a treatment group on Day 0 (before administration of study drug) by using a computer-generated randomization schedule prepared before the study. The randomization will be stratified by country, prior anti-TNF-α blocker status (inadequate response versus intolerant case), and Rheumatoid Factor (RF) or Anti-Cyclic Citrullinated Peptide (anti-CCP) status (both positive versus both negative versus either RF or anti-CCP negative). Patients with positive status for either RF or anti-CCP at screening will be classified as a positive.

This study will be double-blind. 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 interactive web response system (IWRS) or interactive voice response system (IVRS).

The overall randomization code will be broken only for reporting purposes. The reporting of the co-primary endpoints for PK in Part 1 and Efficacy in Part 2 at Week 24 will be reported concurrently. The unblinded statistical analyses will be performed by CELLTRION. Only relevant [redacted] Biostatistics, Medical Writing and the sponsor will be unblinded at this stage; all other study personnel will remain blinded until the end of the study. Final determination of the analysis sets will occur prior to finalizing the database for each analysis. In addition, the blind will be broken for reporting to the Data Safety Monitoring Board (DSMB).

The randomization code will not be revealed to study patients, parents or guardians, study center staff, or investigators.

5.4. Population of Analysis

The following patient populations and subsets will be analyzed:

Table 1: Populations and Subsets of Analysis

Populations	Subsets
Main Study Period: Part 1	
all-randomized	
safety	
pharmacokinetic	pharmacokinetic (antibody negative subset) pharmacokinetic (antibody positive subset)
Main Study Period: Part 2	
all-randomized	all-randomized (antibody negative subset)
safety	safety – 2nd treatment course in Main Study Period subset
efficacy	efficacy (antibody negative subset) efficacy (antibody positive subset) efficacy – 2nd treatment course in Main Study Period subset
pharmacokinetic	pharmacokinetic (antibody negative subset) pharmacokinetic (antibody positive subset) pharmacokinetic – 2nd treatment course in Main Study Period subset
pharmacodynamic	pharmacodynamic (antibody negative subset) pharmacodynamic – 2nd treatment course in Main Study Period subset
Extension Study Period	
all-randomized	all-randomized – Extension Study Period subset
safety	safety – Extension Study Period subset
efficacy	efficacy – Extension Study Period subset
pharmacodynamic	pharmacodynamic – Extension Study Period subset

All-randomized, safety and PK populations and its subsets will be defined for the patients from Part 1 and 2, respectively. Efficacy and PD population and its subsets will be defined for the Part 2. Population for Part 2 will include patients from Part 1.

Patients who have any major protocol deviations (as defined in Section 5.6) may be excluded only from the population (PD and/or Efficacy) that would be affected by the deviation. Patients from the significant GCP non-compliance sites as defined in Section 5.6 will be excluded in all populations.

The number of patients in all populations will be tabulated by the treatment group in each relevant Part and study period. A listing will also be produced, displaying this data.

5.4.1. All-Randomized Population

The all-randomized population will consist of all patients enrolled and randomly assigned to receive a dose of study drug, regardless of whether or not any study drug dosing was completed. Patients in the all-randomized population and all-randomized population – Extension Study Period subset will be analyzed according to the treatment to which they were randomized in Main Study Period and Extension Study Period, respectively. All general section of Main Study Period (i.e. disposition, demographics, baseline characteristics, etc.) will be based on the all-randomized population. Efficacy data of Main Study Period and Extension Study Period except joint surgery information will be listed for the all-randomized population.

5.4.1.1. All-Randomized (Antibody Negative Subset)

In the all-randomized population, patients who have "Negative" ADA result at Week 24 will be considered "All-Randomized (Antibody Negative Subset)".

5.4.1.2. All-Randomized – Extension Study Period Subset

The all-randomized population – Extension Study Period subset will consist of all patients in the all-randomized population who have received at least one (full or partial) dose of study drug in the Extension Study Period. All general section of Extension Study Period (i.e. disposition, demographics, baseline characteristics, etc.) will be based on the all-randomized population – Extension Study Period subset.

5.4.2. Pharmacokinetic (PK) Population

The pharmacokinetic population for the Main Study Period will consist of all patients who received two full doses (Week 0 and Week 2) of the study drug and provided at least one post – treatment PK concentration result during the first course of treatment in Main Study Period.

The PK population will be the primary population for the summary of PK data. The analysis of first course period will be based on Part 1 and 2, respectively.

5.4.2.1. Pharmacokinetic (Antibody Negative/Positive Subset)

In the PK population, patients who show "Positive" result in ADA tests obtained at Week 24 will be considered "Pharmacokinetic (Antibody Positive Subset)". Other patients who have "Negative" ADA result at Week 24 will be considered "Pharmacokinetic (Antibody Negative Subset)".

5.4.2.2. Pharmacokinetic – 2nd treatment course in Main Study Period Subset

The PK population – 2nd treatment course in Main Study Period subset will consist of all patients in the PK population who have received two full doses (Week 24 and Week 26) of study drug and provided at least one post – treatment PK concentration result during the second course of treatment in Main Study Period.

5.4.3. Efficacy Population

The efficacy population for the Main Study Period will consist of all patients who received at least one full dose (1000 mg) of study drug and provided at least one post-treatment efficacy result during the first course of treatment in Main Study Period.

The efficacy population will be the primary population for the summary of Main Study Period efficacy data.

5.4.3.1. Efficacy (Antibody Negative/Positive Subset)

In the efficacy population, patients who show "Positive" result in ADA tests obtained at Week 24 will be considered "Efficacy (Antibody Positive Subset)". Other patients who have "Negative" ADA result at Week 24 will be considered "Efficacy (Antibody Negative Subset)".

5.4.3.2. Efficacy – 2nd treatment course in Main Study Period Subset

The efficacy population – 2nd treatment course in Main Study Period subset will consist of all patients in the efficacy population who have received at least one full dose (1000 mg) of study drug and provided at least one post-treatment efficacy result during the second course of treatment in Main Study Period.

5.4.3.3. Efficacy – Extension Study Period Subset

The efficacy population – Extension Study Period subset will consist of all patients in the efficacy population who have received at least one full dose (1000 mg) of study drug and provided at least one post-treatment efficacy result during the Extension Study Period.

The efficacy population – Extension Study Period subset will be the primary population subset for the summary of Extension Study Period efficacy data.

5.4.4. Pharmacodynamic (PD) Population

The pharmacodynamic population for the Main Study Period will consist of all patients who received at least one full dose (1000mg) of study drug and provided at least one post-treatment PD result during the first course of treatment in Main Study Period. The PD population will be the primary population for the summary of PD data.

5.4.4.1. Pharmacodynamic (Antibody Negative Subset)

In the pharmacodynamic population, patients who have "Negative" ADA result at Week 24 will be considered "Pharmacodynamic (Antibody Negative Subset)".

5.4.4.2. Pharmacodynamic – 2nd treatment course in Main Study Period Subset

The pharmacodynamic population – 2nd treatment course in Main Study Period subset will consist of all patients in the pharmacodynamic population who have received at least one full dose (1000 mg) of study drug and provided at least one post-treatment PD result during the second course of treatment in Main Study Period.

5.4.4.3. Pharmacodynamic – Extension Study Period Subset

The pharmacodynamic population – Extension Study Period subset will consist of all patients in the pharmacodynamic population who have received at least one full dose (1000 mg) of study drug and provided at least one post-treatment PD result during the Extension Study Period.

The PD population – Extension Study Period subset will be the primary population subset for the summary of Extension Study Period PD data.

5.4.5. Safety Population

The safety population will consist of all patients who received at least one (full or partial) dose of study drug during any dosing period. All patients in the safety population will be analyzed according to the treatment group. Patients receiving at least one dose of CT-P10 during the Main Study Period will be analyzed under the CT-P10 treatment group even the patient ever received Rituxan or MabThera. Otherwise, the treatment group will be determined based on the treatment for the first course.

Treatment received will be based on the kit number recorded on the "Study Treatment Infusion" electronic case report form (eCRF) page. Safety analyses will be conducted based on the safety population.

5.4.5.1. Safety – 2nd treatment course in Main Study Period Subset

The safety population – 2nd treatment course in Main Study Period subset will consist of all patients in the safety population who have received at least one (full or partial) dose of study drug during the second course of treatment in Main Study Period.

5.4.5.2. Safety – Extension Study Period Subset

The safety population – Extension Study Period subset will consist of all patients in the safety population who have received at least one (full or partial) dose of study drug during the Extension Study Period.

The safety population – Extension Study Period subset will be the primary population subset for the summary of Extension Study Period safety data.

5.5. Definition of Baseline

The baseline value will be considered to be the last non-missing value before the first infusion. Post-baseline visits will be considered to be all visits after the first date of infusion.

5.6. Protocol Deviations

Protocol deviation will be categorized as "major" or "other (or minor)". Category of protocol deviation will be identified during the Data Review Meeting (DRM). A major protocol deviation is one that may affect the interpretation of study results or the patient's rights, safety or welfare. Patients with major protocol deviation could be excluded only from the population (PD and/or Efficacy) that would be affected by the deviation.

Major protocol deviations are defined as follows:

- Mis-randomizations (defined as patients who received the another treatment to which they were assigned at any point during the study)
- Non-compliance of inclusion or exclusion criteria (to be identified by the [redacted] medical department via review of data sourced from the site monitoring database)
- Significant GCP non-compliance sites (to be identified by [redacted] as sites which have been closed due to suspected scientific misconduct and/or serious GCP non-compliance)
- Receipt of prohibited medication (based on agreement of each as from both [redacted] and CLT prior to database lock)

The major protocol deviations and other categories used for exclusion will be summarized for the all-randomized population by study part, treatment group. A listing of major protocol deviations for each patient will also be provided by treatment group.

The significant GCP non-compliance site will be excluded in all populations. The information of this site will be only listed in the Demographics and Treatment-emergent Serious Adverse Events listings, separately.

5.7. Display of Data by Treatment

All analysis result of Main Study Period excluding ANCOVA will be displayed by the following groups: CT-P10, Rituxan, MabThera, and combined Rituxan and MabThera group.

Analysis of the general and PK section in Main Study Period will be conducted in Part 1 and 2 separately.

All analysis result of Extension Study Period will be displayed by the following groups: CT-P10 maintenance (Group 1), Switched from Rituxan (Group 2), Rituxan maintenance (Group 3), Switched from MabThera (Group 4), and combined Switched from Rituxan and Switched from MabThera group.

5.8. Missing Values and Outliers

In order to evaluate the impact of missing data on the efficacy primary endpoint results, additional analyses with missing data imputation will be conducted for the primary efficacy endpoint of DAS28 (CRP) at Week 24 in all-randomized population.
Two imputation methods will be used for sensitivity analysis: Last observation carried forwards (LOCF) and Multiple imputation (MI) with the Missing at random (MAR) assumption. In addition, Tipping point analysis will be conducted based on MI results.
LOCF will impute missing values by the last value observed. MI with the MAR assumption will use regression method to impute missing data. Gender, country (or region), race, baseline value of DAS28 (CRP), prior anti-TNF alpha blocker status (intolerance case versus inadequate response), RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative), study part, treatment group and interaction of treatment group with study part will be used as regression covariates. 10 imputed datasets will be created by multiple imputations, and results from these 10 datasets will be pooled.
LOCF and MI with the MAR results will be provided displaying descriptive statistics for actual value and change from baseline in DAS28 (CRP) at Week 24. Additional, ANCOVA for the DAS 28 (CRP) will be conducted along with its 90% CI between CT-P10 and Reference products treatment group.
Tipping point analyses will be conducted under MNAR (Missing Not at Random) scenarios. Imputed values will be shifted gradually from the imputed values by MI, by treatment groups (CT-P10 versus combined Rituxan and MabThera group) to make MNAR scenarios. A point estimate and 90% confidence interval (CI) for the treatment difference will also be calculated using an analysis of covariance (ANCOVA) considering the treatment as a fixed effect and gender, country (or region), race, study part, interaction of treatment group with study part, prior anti-TNF-α blocker status (intolerance case versus inadequate response), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates under these scenarios, and the scenario under which confidence interval no longer

rules out differences in the change from baseline of DAS28 (CRP) at Week 24 for the therapeutic equivalence margin of ±0.5 will be displayed.
All the MNAR scenarios and corresponding confidence interval will be displayed using three dimensional graph, 2-dimensional contour plot, and table. In the graph, the maximum of absolute value of the lower bound and the upper bound will be used to display CI and corresponding tipping points.
Outliers for the PK primary endpoint parameters will be identified by robust regression method (90% CI) [15]. Details of outliers detected will be presented in the footnotes of the relevant outputs.

6. Patient Disposition

The number of patients who were screened will be displayed. The number and percentage of patients who randomized, initiated, completed, or discontinuing treatment will be displayed using the following categories for all-randomized population and all-randomized population – Extension Study Period subset by treatment group and part.

- Screened
  - Screening Failure
- Randomized
- Initiated first course of treatment in Main Study Period
  - Complete first Course in Main Study Period
  - Discontinued during first Course in Main Study Period
- Initiated second course of treatment in Main Study Period
  - Complete second Course in Main Study Period
  - Discontinued during second Course in Main Study Period
- Initiated treatment in Extension Study Period
  - Complete Extension Study Period
  - Discontinued Extension Study Period

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

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

The screening failure summary will include the number of patients out of all screened patients and the primary reason for screening failure. A listing of patients reported as screening failures will also be provided.
The reasons for discontinuation will be displayed using the following categories and ordering:

- Patient develops sign of disease progression
- Patient experiences no efficacy from study drug
- Patient withdraws consent or patient refuses
- Patient develops any malignancy
- Adverse Event
- Significant or major protocol violation
- Lost to follow-up

- Patient died
- Investigator decision
- Sponsor terminates the study
- Pregnancy
- Other

In addition, the treatment duration in days (calculated as date of last visit - date of first infusion in study period + 1) will be calculated and be summarized for patients who discontinue study treatment prematurely. The date of first infusion will be taken as the earliest date recorded on the "Study Treatment Infusion" eCRF page and the date of last visit will be taken as recorded on the "Study Termination" eCRF page.

The disposition listing will list all data collected on the "Study Termination" eCRF along with the date of first infusion for the all-randomized population.

7. Demographics, Baseline Characteristics, and Background Characteristics

7.1. Demographics

The following demographic measures will be tabulated for the all-randomized population and all-randomized population – Extension Study Period subset by treatment group and part: age (years); gender (male, female); female fertility status (Pre-menarche, sterile, post-menopausal, potentially able to bear children); race (white, black, Asian, other, not allowed by investigator country regulations); height (cm) and weight (kg) as recorded at the screening visit: Body-Mass Index (BMI) (kg/m^2); country; region (EU, non-EU).

Age will be automatically calculated in the eCRF system based on the date of the informed consent visit and the date of birth provided. Patients from some countries may have the information of the year of birth only. When date and month are missing for date of birth, age will be derived using the year of birth and the year of informed consent only.

7.2. Baseline Characteristics

The baseline characteristics will be also tabulated for the all-randomized population and all-randomized population – Extension Study Period subset by treatment group and part: prior anti-TNF-α blocker status (inadequate response vs. intolerant case); RF or anti-CCP status (both positive vs. both negative vs. either RF or anti-CCP negative); number of patients whose swollen joints (of 66 assessed) and tender joints (of 68 assessed) equal to or higher than 8 at baseline visit; duration of prior TNF-antagonist use, number of prior TNF-antagonist use, baseline CRP/ESR.

Demographic and baseline characteristic data will be listed for the all-randomized population.

7.3. Other Baseline Characteristics

At screening, the following assessments will be performed:

- Hepatitis B Surface Antibody (HBsAb)
- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Core (total) Immunoglobulin (HBcIg)
- Hepatitis B virus DNA (if HBsAg is negative, HBsAb is negative or positive, and HBcIg is positive)

- Hepatitis C Antibody
- Human Immunodeficiency Virus (HIV) 1&2

To obtain confirmation result, the following assessments can be performed:

- Hepatitis B Surface Antigen (HBsAg) (Confirmation)
- Hepatitis C Antibody (Confirmation)
- Human Immunodeficiency Virus (HIV) 1&2 (Confirmation)

A listing will be produced by the treatment group for the all-randomized population.

7.4. Medical History

Medical history is captured at the screening visit and will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher. Medical history will be summarized by treatment group, study part, system organ class (SOC), and preferred term (PT). Percentages will be calculated using the number of patients in the all-randomized population and all-randomized population – Extension Study Period subset as the denominator by treatment group and part. Medical history will also be listed for the all-randomized population.

7.5. Rheumatoid Arthritis History

Rheumatoid arthritis history is captured at the screening visit and is based on the Rheumatoid Arthritis Classification Criteria 1987 [2]. The number and percentage of patients with each type of criterion will be summarized for the all-randomized population and all-randomized population – Extension Study Period subset by treatment group and part. And the descriptive statistics of time since Rheumatoid Arthritis diagnosis will be tabulated for the all-randomized population and all-randomized population – Extension Study Period subset by treatment group and part. Time (years) since RA diagnosis will be calculated as ((date of randomization (Day 0 of Main Study Period) – 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. XXMAR2016) the date will be the last day of the month (i.e. 31MAR2016). If the day and month are missing (i.e. XXXXX2016) the date will be set to the 31th December (i.e. 31DEC2016). If the imputed date is later than randomization date, then it will be imputed using the randomized date. 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 all-randomized population.

7.6. Inclusion and Exclusion Criteria

Details of the inclusion and exclusion criteria can be found in Sections 4.1.1 and 4.1.2 of the protocol. Inclusion and exclusion criteria for each patient will be presented in two separate listings for all-randomized population.

A number of the 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 apply. In addition, if some criteria get added during the revisions, the criteria will be renumbered for patients recruited prior to these protocol amendments in such a manner that the criteria are mapped to the numbering as per final study protocol.

8. Biomarkers

For patients who sign a separate informed consent form for the biomarker assessments, blood sample (central laboratory) for FcγR genotype (FcγRIIa, IIIa and/or any necessary genotypes), test results will be collected after randomization and before study treatment administration on Day 0 of Week 0.

Data for each genotype will be summarized by treatment group and part for the all-randomized population, efficacy population, all-randomized population – Extension Study Period subset and efficacy population – Extension Study Period subset. A listing will be also generated for the all-randomized population.

9. Treatments and Medications

All medications except co-administration of methotrexate and folic acid will be coded according to the World Health Organization drug dictionary (WHODD September 1, 2015 or later).

9.1. Prior and Concomitant Medications

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

- Missing day: Assume the day is 1st of the month.
  However, if the partial date and the date of first infusion (defined as the earliest date recorded on the "Study Treatment Infusion" eCRF page) lie within the same month and year and the date of first infusion is not after the stop date of the medication, set to the date of first infusion. Otherwise, if date of first infusion is after the stop date for the medication, set to stop date of the medication.
- Missing day and month: Assume January 1st.
  However, if the partial date and the date of first infusion lie within the same year and the date of first infusion is not after the stop date of the medication, set to the date of first infusion. Otherwise, if date of first infusion is after the stop date for the medication, set to stop date of the medication.
- Missing day, month and year: Assume date of first infusion, if not after the stop date for the medication. Otherwise set to the stop date for the medication.

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

- Example 1:
  Medication start: JUN2016
  Medication end: 20OCT2016
  Date of first infusion: 16OCT2016
  Medication start imputed: 01JUN2016
- Example 2:
  Medication start: OCT2016
  Medication end: 20OCT2016
  Date of first infusion: 16OCT2016
  Medication start imputed: 16OCT2016

- Example 3:
  Medication start: OCT2016
  Medication end: 20OCT2016
  Date of first infusion: 24OCT2016
  Medication start imputed: 20OCT2016

Partial end dates will be imputed as follows:

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Assume that the medication is continuing.

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.

A prior medication is defined as any medication where the start and stop dates or imputed start and stop dates are before the date of first infusion. A concomitant medication is defined as any medication that has an actual or imputed stop date on or after the date of first infusion or missing. The actual or imputed start date of a concomitant medication can be before or after the date of first infusion.

Prior and concomitant medications will be tabulated separately by treatment group and part, drug class (using ATC level 2), and preferred term (PT) for the safety population and safety population – Extension Study Period subset. The total number of prior and concomitant medications and the number and percentage of patients with at least one prior or concomitant medication will be summarized. The numbers and percentages of all prior and concomitant medications will also be summarized.

Additionally, prior and concomitant medications will be listed separately by treatment group for the safety population.

9.1.1. Co-administration of Methotrexate and Folic Acid

Data on co-administration of methotrexate and folic acid will be collected separately from all other medications. The same rules for date imputation and definitions of prior and concomitant will apply. The number of patients who started methotrexate or folic acid prior to first infusion of study drug and continued on or after the first infusion date will be summarized separately for methotrexate and folic acid. Additionally, the methotrexate dose at first infusion during each treatment course (mg/week) will be summarized. Summaries will be based on the safety population and safety population – Extension Study Period subset and presented by treatment group and part.

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

9.1.2. Prior Tumor Necrosis Factor (TNF) Antagonist History

Data on prior use of anti-TNF agents administered to patients will be collected separately in the "Prior TNF Antagonist History" eCRF. The same rules for date imputation and definitions of prior and concomitant will apply. A table will be produced showing total number of prior TNF antagonists used and the number and percentage of patients with at least one prior TNF antagonist use who had prior use of TNF antagonists. Summaries will be based on the safety

population and safety population – Extension Study Period subset and presented by treatment group and part.

A listing of prior TNF antagonist history will be presented by treatment group for the safety population. The antagonist name, drug class, and PT, single dose, unit, frequency, route, start date, stop date and reason for discontinuation will be included for each patient.

9.2. Exposure to Study Drug

The number and percentage of patients with full and partial dose administered at each visit will be tabulated. For patients who are not administered study drug, the number and percentage of patients with each reason why the dose was not administered (discontinued prior to visit, adverse event, other, monitoring) will be displayed. For patients who administered study drug and total dose administered (mg) will be summarized by part, visit and treatment group. The safety population and safety population – Extension Study Period subset will be used as the denominator for percentages and patients will be summarized.

In a separate analysis, the total number of doses received by each patient during study period will be calculated. A table will be provided displaying descriptive statistics of the total number of doses received and total amount of study drug administered. Summaries will be based on the safety population and safety population – Extension Study Period subset and presented by treatment group and part.

In addition, a listing will be provided by treatment group for the safety population showing the details of study drug exposure for each patient. This listing will include all data collected on the study treatment infusion page of the eCRF.

10. Pharmacokinetics

Co-Primary PK endpoints are $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} over the first 24 weeks in the Part 1. The secondary PK endpoints are as below.

- Part 1 (over the first 24 weeks): $AUC_{0\text{-day14}}$, V_d, CL, $t_{1/2}$, T_{max}, $C_{max,1}$, C_{min} (at Week 24) and C_{trough}
- Part 2 (up to Week 48 or over the first 24 weeks if second course of treatment is not administered): T_{max}, C_{max}, $C_{max,1}$, C_{min} and C_{trough}

All pharmacokinetic analysis will be performed on the PK population and PK – 2nd treatment course in Main Study Period subset unless otherwise specified. Descriptive Statistics regarding the PK parameters will be performed by including outliers.

10.1. Serum concentrations

Pharmacokinetic samples will be listed for the safety population by each patient and sampling time point:

For Part 1, pharmacokinetic samples will be collected within 15 minutes prior to the beginning of the study drug infusion, within 15 minutes after the end of study drug infusion, and 1 hour (±15 minutes) after the end of study drug infusion on the day of each study drug infusion. For patients from Part 1 who receive only first course of treatment, additional samples will be collected after 24 hours (±2 hours) from the start of each study drug infusion in the first treatment course and on Week 1, 3, 4, 8, 12, 16 and 24, 15 samples in total. For patients from Part 1 who receive both

first and second courses of treatment, additional samples will be collected after 24 hours (±2 hours) from the start of each study drug infusion only in the first treatment course and on Week 1, 3, 4, 8, 12, 16, 48 and end of study (EOS; if patient withdraws prior to study completion), 21 samples in total.

For Part 2, pharmacokinetic samples will be collected within 15 minutes prior to the beginning of the study drug infusion, within 15 minutes after the end of study drug infusion, and 1 hour (±15 minutes) after the end of study drug infusion on the day of each study drug infusion. Additional samples will be collected on Week 24 (for patients who receive only first course of treatment) or Week 48 (for patients who receive both first and second courses of treatment) or EOS (for patients who receive both first and second courses of treatment and if patient withdraws prior to study completion).

Serum concentrations of rituximab will be summarized using descriptive statistics (consisting of n, mean, SD, CV, geometric mean, minimum, median and maximum) by part and treatment group at each scheduled collection visit and time point. Additionally, serum concentrations of rituximab for all antibody negative and positive subjects will be summarized by study part and treatment group at each scheduled collection visit and time point. In case of patients from Part 2, Combined Rituxan and MabThera group will be additionally displayed. Individual concentrations, scheduled and actual sample times will be presented in data listings by treatment group for the safety population.

Concentrations below the limit of quantification (BLQ) prior to the first infusion will be treated as zero (0). Concentrations BLQ after the first infusion will be set to the lower limit of quantification (LLoQ, 0.04 μg/mL). Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Geometric mean will not be reported if the dataset includes zero values.

For patients from Part 1, mean serum concentration versus actual time plots for rituximab will be presented up to Week 24. Plots will be presented on both linear and semi-logarithmic scales by treatment based on scheduled sample times. All BLQ and missing values will be indicated in the data listings. In addition, plots will be presented by ADA status at Week 24.

10.2. Pharmacokinetic Parameters

Individual serum concentration versus actual time data will be used to calculate PK parameters of rituximab by standard non-compartmental methods using [redacted]. All serum concentrations that are BLQ prior to the first infusion will be set to 0; all concentrations below LLoQ after first infusion will be set equal to LLoQ. Actual blood sampling times (from the start of infusion) and actual duration of the infusion will be used for all PK analyses. However, for ease of presentation, scheduled sampling times will be used to present results in summary tables and figures.

Table 2: Pharmacokinetic Parameters for Rituximab

Part 1 Primary Parameters (calculated over the first 24 weeks)	
$AUC_{0\text{-last}}$	Area under the concentration-time curve from time 0 to the last measurable concentration over both doses of the first course
$AUC_{0\text{-}\infty}$	Area under the concentration-time curve from time 0 extrapolated to infinity over both doses of the first course

C_{max}	Observed maximum concentration after the second infusion
Part 1 Secondary Parameters (calculated over the first 24 weeks)	
$AUC_{0\text{-day}14}$	Area under the concentration-time curve from time 0 to Day 14 (calculated for both infusions)
$C_{max,\ 1}$	Observed maximum concentration following the first infusion of the first course
C_{min}	Predose concentration at Day 168 (Week 24)
C_{trough}	Predose concentration at Day 14 (Week 2) prior to the second infusion
V_d	Volume of distribution, calculated from the second dose of the first course as $V_d = Dose/AUC_{0-\infty} \times \lambda_z$, where Dose is the combined total dose administered in Course 1 (i.e. Dose 1 + Dose 2)
CL	Total clearance, calculated from the second dose of the first course as $CL = Dose/AUC_{0-\infty}$, where Dose is the combined total dose administered in Course 1 (i.e. Dose 1 + Dose 2)
$t_{½}$	Terminal phase elimination half-life, calculated from the second dose of the first course as $t_{½} = \ln(2)/\lambda_z$
T_{max}	Time to maximum serum concentration after both doses in the first course
Part 2 Secondary Parameters (up to Week 48 or over the first 24 weeks if second course of treatment is not administered)	
T_{max}	Time to maximum serum concentration in the first and second course
C_{max}	Observed maximum concentration after the second infusion in the first and second course
$C_{max,\ 1}$	Observed maximum concentration after the first infusion of the first and second course
C_{min}	Predose concentration at Day 168 (Week 24) and at Day 336 (Week 48)
C_{trough}	Predose concentration at Day 14 (Week 2 prior to second infusion) and at Day 182 (Week 26 prior to second infusion)

All AUC parameters will be calculated using the linear trapezoidal rule.

The pharmacokinetic parameters will be presented for the PK population in listings and summarized in tables. The tables will display the following descriptive statistics by part: n, mean, SD, CV, geometric mean, minimum, median and maximum. In addition, descriptive statistics of PK parameter by ADA status at Week 24 will be presented.

10.3. Pharmacokinetic Statistical Analysis

In Part 1, the primary PK analysis will assess the similarity of CT-P10, Rituxan and MabThera in terms of $AUC_{0\text{-last}}$, $AUC_{0-\infty}$ and C_{max} over the first 24 weeks as co-primary PK endpoints.

ANCOVA will be performed for $AUC_{0\text{-last}}$, $AUC_{0-\infty}$ and C_{max} with treatment group as a fixed effect and country, gender, race, prior anti-TNF-α blocker status (intolerance case versus inadequate response) and RF or anti-CCP status (both positive versus both negative versus either

RF or anti-CCP negative) fitted as covariates. Clinically relevant variables at baseline are used as the covariates for adjusted means. 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 (defined as either EU or Non-EU), for use in the statistical model. The $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} will be natural log transformed prior to the analysis. Point estimates (geometric least squares means and ratios of geometric means) will be calculated by back-transforming the least squares means, and 90% CIs of the ratios (CT-P10 versus Rituxan, CT-P10 versus MabThera, and Rituxan versus MabThera) will be produced.

Similarity will be demonstrated if the 90% CI for the geometric mean ratio of CT-P10 to Rituxan and MabThera in $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} is within the bounds of 80% and 125%.

When outliers occur at some time points, primary statistical analysis of PK parameters is carried out with data excluding observed outliers. However, a sensitivity analysis will also be performed with data including observed outliers. Additional ANCOVA for the PK primary endpoint will be conducted in patients whose ADA status result at Week 24 is “Negative” both including and excluding outliers. When there are Significant GCP non–compliance sites, an additional sensitivity analysis will be performed for PK primary endpoints.

11. Efficacy Analyses

DAS28 (CRP) at Week 24 is the primary efficacy endpoint in the Part 2. The ANCOVA for primary endpoint in Part 2 will be conducted on the efficacy population and all-randomized population and its subsets.

The secondary efficacy endpoints are as below.

- ACR20, ACR50 and ACR70 (at Week 24, Week48, and Extension Week 24)
- Individual components of the ACR criteria (at Week 24, Week48, and Extension Week 24)
- Time to onset of ACR20 response (over the 24 weeks)
- DAS28 (CRP) (at Week12 and 48 and Extension Week 24)
- DAS28 (ESR) (at Week12, 24 and 48 and Extension Week 24)
- EULAR response criteria (at Week 24, Week48, and Extension Week 24)
- Hybrid ACR (at Week 24, Week48, and Extension Week 24)
- SDAI and CDAI (at Week 24, Week48, and Extension Week 24)
- Joint damage progression (at Week 48, Extension Week 24 and the EOS visit)
- HAQ (at Week 24, Week48, and Extension Week 24)
- Health-related quality of life (at Week 24, Week48, and Extension Week 24)

All secondary efficacy analysis will be based on the efficacy population and its subset. All efficacy listings except joint surgery information will be based on the all-randomized population. Joint surgery information will be listed based on the safety population.

Efficacy will be assessed by ACR criteria (individual components, ACR20, ACR50 and ACR70, hybrid ACR response), DAS28 (including number of tender joints and number of swollen joints), EULAR response criteria, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Joint Damage Progression, and Functional Disability.

Quality of life will also be included in the efficacy analysis. This will be assessed using the Medical Outcomes Study Safety Short-Form Health Survey (SF-36) questionnaire.
Patients with joint surgery records will be excluded from all efficacy analysis after the surgery but will be only presented unless otherwise specified.
For all efficacy analysis, patients with protocol prohibited initiation of new or increase in dose of RA medications that are deemed to affect efficacy will be excluded at the visit that would be only affected by prohibited medication but will be only presented unless otherwise specified.

11.1. ACR20, ACR50 and ACR70 criteria

11.1.1. Proportion of ACR20, ACR50, and ACR70 Responders

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

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

- A percentage decrease of at least 20% from baseline in the number of tender joints
- A percentage decrease of at least 20% from baseline in the number of swollen joints, and
- A percentage decrease of at least 20% from baseline in 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 = (Post-baseline value - baseline value)/baseline value * 100

The following categories of patients are considered non-responders at each week respectively:

- Patients with an improvement according to the ACR criteria of less than 20%
- Patients who discontinue the study prior to the week of interest
- Patients with missing data for the evaluation of ACR20 criteria at the week of interest
- Patients with protocol prohibited initiation of new or increase in dose of RA medications that are deemed to affect efficacy. The ACR response status of these patients will be determined prior to database lock on an individual basis after agreement from the medical monitoring department of [redacted] and the sponsor.
- Patients requiring a surgical joint procedure prior to and including the week of interest. Surgical joint procedures will be defined as those patients with a reported joint surgery on the 'Joint Surgery Yes/No' eCRF page.

Any patient not satisfying any of the responder or non-responder criteria will be assigned a non-responder status. The ACR50 and ACR70 are calculated similarly to ACR20. However, a decrease of 50% and 70%, respectively, must be achieved.

The proportion of patients demonstrating ACR20, ACR50, and ACR70 (based on 1995 ACR criteria) will be summarized for the efficacy population, efficacy – 2nd treatment course in Main

Study Period subset and efficacy – Extension Study Period subset by treatment group at each visit, accordingly.

The proportion of patients achieving clinical response according to the criteria for ACR20 at each visit will be summarized in patients whose swollen joints (of 66 assessed) and tender joints (of 68 assessed) equal to or higher than 8 at baseline by efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset.

Additionally, the proportion of patients achieving clinical response according to the criteria for ACR20 at each visit will also be summarized by Efficacy (Antibody Negative/Positive Subset).

A listing will be provided for the all-randomized population by treatment group and visit, showing ACR20, ACR50 and ACR 70 responder status at each visit.

11.1.1.1. Number of tender joints/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 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 for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset by treatment group at each visit. A listing will be provided for the all-randomized population by treatment group and visit, showing number of tender and swollen joints at each visit, along with the percentage change from baseline.

11.1.1.2. 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 Assessment of Pain, the Patient Global Assessment of Disease Activity, and the Physician Global Assessment of Disease Activity at every visit where an efficacy assessment is performed.

For these scales, descriptive statistics for actual value and change from baseline will be presented for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy –nExtension Study Period subset by treatment group at each visit. Additionally, the Patient and Physician Global Assessment of Disease Activity will be summarized at each visit. A listing will also be provided showing VAS measurements at each visit, along with the percentage change from baseline by treatment group and visit in all-randomized population.

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

The arthritis-related functional disability will be measured using the disability index of the HAQ, a validated, self-administered form that assesses functional ability in a number of relevant areas, including the ability to dress, rise from bed, eat, walk, maintain personal hygiene, reach, grip, and other activities on a scale ranging from 0 (no difficulty) to 3 (unable to perform the activity). Scores range from 0 to 3, with higher scores indicating worse disability.

There are 8 categories within the Health Assessment Questionnaire:

- Dressing and Grooming (Questions 1, 2)

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

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

In order to compute the disability index:

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

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

Table 3: Aids/Devices Items for HAQ Categories

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

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

Table 4: Help from another Person Items for HAQ Categories

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

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

Descriptive statistics for actual value and change from baseline of the HAQ estimate of physical ability will be presented for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy- Extension Study Period subset by treatment group at each 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 question, the responses to the "Aids/Devices" categories, and the "Help from Another Person" categories. These listings will all be displayed in all-randomized population by treatment group. This assessment comprise of a VAS on a scale of 0 to 100, in cases where the length of the VAS is not 100mm the score is converted into a 0 to 100 range in clinics. This scale will be listed by treatment group and visit.

11.1.1.4. C-Reactive Protein and Erythrocyte Sedimentation Rate

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 visit for the efficacy population, efficacy – ef[nd] treatment course in Main Study Period subset and efficacy – Extension Study Period subset. Note that CRP and ESR will also be summarized for the pharmacodynamic population by treatment group, and this is described in the pharmacodynamics section.

Separate listings will be provided for each of these parameters which will show the measurements at each visit, along with the percentage change from baseline, by treatment group in all-randomized population.

11.1.1.5. Joint Surgery

A listing will be produced displaying for 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 18.1 or higher) and the procedure date.

11.1.2. Time to Onset of ACR20

Time to onset of ACR20 response (in days) will be summarized by treatment group for the efficacy population up to Week 24. Patients not achieving the ACR20 response will be censored using the last time point where the ACR was assessed. Duration will be calculated as [date of event (onset of ACR20 response) or date censored (last assessment for which ACR20 responder status can be determined) – date of randomization + 1]. Kaplan-Meier estimates of the 25th percentile, median, and 75th percentile of time to onset will be presented. Also, p-value calculation from log-rank test between CT-P10 and Rituxan + MabThera group will be provided. In the event that there are not enough patients with an ACR20 response for these statistics to be produced, the result will be recorded as not estimated (N.E.). The number and percentage of patients with ACR20 response during the 24 weeks will be summarized. A listing will be provided showing time to onset of ACR20 response (in days) for each patient in the all-randomized population, by treatment group.

11.1.3. Hybrid ACR Response

The hybrid ACR is an outcome measure that combines the ACR20, the ACR50, and the ACR70 and a continuous score of the mean improvement in core set measures (Number of tender joints, Number of swollen joints, Pain (VAS), Disease activity (VAS), HAQ, CRP or ESR). Note that CRP will be used for the hybrid ACR score derivation, unless it is missing, in which case ESR will be used.

The steps to calculate the hybrid ACR score are as follows:

(1) For each core set measure, the post-baseline score is subtracted from the baseline score, and the percentage change in each measure determined.

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

(3) The percentage change for all core set measures is averaged to give the mean % change in core set measures.

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

Table 5: Scoring Method for Hybrid ACR

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

Source: 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 visit for the efficacy population, efficacy – efnd treatment course in Main Study Period subset and efficacy – Extension Study Period subset. A listing will also be provided for the all-randomized population, by treatment group, showing the hybrid ACR score, ACR responder status, and the mean % change in core set measures. Hybrid ACR score will be presented to two decimal places.

11.2. DAS28

The ANCOVA comparing the change from baseline of DAS28(CRP) and DAS28(ESR) at 24 weeks of treatment between two treatment groups, CT-P10 and combined Rituxan and MabThera group will be analyzed, considering the treatment as a fixed effect and gender, country, race, study part, interaction of treatment group with study part, prior anti-TNF-α blocker status (intolerance case versus inadequate response), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. Clinically relevant variables at baseline are used as the covariates for adjusted means. If country is found to be unsuitable as a covariate due to the number of levels, then region (EU, non-EU), which may pool countries based on continents, may be used instead. Additional ANCOVA will be conducted in patients whose ADA status result at Week 24 is "Negative".

The least squares mean and corresponding standard error of the change from baseline in DAS28 at Week 24 will be presented for each treatment group. Point estimates (least squares mean and difference of least squares means), 90% confidence interval (CI) for the treatment difference and p-value with an interaction effect between study part and treatment group will also be provided. When there are Significant GCP non–compliance sites, an additional sensitivity analysis will be performed.

All-randomized population and efficacy population will be used for analysis of change from baseline of DAS28 (ANCOVA), respectively.

Descriptive statistics for actual value and change from baseline in disease activity measured by DAS28 (CRP) and DAS28 (ESR) will be summarized at each visit for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset by treatment group. Descriptive statistics for actual value and change from baseline in DAS28 (CRP) and DAS28 (ESR) in patients whose swollen joints (of 66 assessed) and tender joints (of 68 assessed) equal to or higher than 8 at baseline at each visit will be also summarized for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset. In addition, descriptive statistics of DAS28 at each visit will be summarized for the Efficacy (Antibody Negative/Positive Subset).

Data from the eCRF, DAS28 components, DAS28 value and change from baseline for both CRP and ESR will be listed by treatment group for the all-randomized population.

Disease activity score in 28 joints (DAS28) will be calculated in two ways using the following two equations [13]:

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

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

Where:

TJC28 = number of tender joints (0-28): tender joint count (TJC)
SJC28 = number of swollen joints (0-28): swollen joint count (SJC)
ESR = ESR measurement (mm/h)
CRP = CRP measurement (mg/L)
GH = Patient Global Assessment of Disease Activity measured on VAS (0 – 100 mm)

11.3. EULAR Response Criteria

The European League Against Rheumatism Response (EULAR) response criteria [3] categorizes the DAS28 response (i.e., good, moderate, or none) based on changes in DAS28 from baseline.

Table 6: European League Against Rheumatism Response Criteria

	DAS28 Improvement from Baseline		
Present DAS28	>1.2	>0.6 and ≤1.2	≤0.6
≤3.2	Good response	Moderate response	No response
>3.2 and ≤5.1	Moderate response	Moderate response	No response
>5.1	Moderate response	No response	No response

Frequencies and percentages of EULAR response categories (based on both DAS28 (ESR) and DAS28 (CRP)) will be summarized by treatment group for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset at each visit.

EULAR response categories, corresponding DAS28 actual values and DAS28 change from baseline for both ESR and CRP, along with DAS28 components, will be listed by treatment group for the all-randomized population.

11.4. Clinical Disease Activity Index and Simplified Disease Active Index

Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) are calculated at each visit as follows:

Table 7: Clinical Disease Activity Index and Simplified Disease Activity Index Formulas

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

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 = C-reactive protein (mg/dL)

Note: Prior to calculation of the CDAI and SDAI, the Patient Global Assessment of Disease Activity and Physician Global Assessment of Disease Activity VAS results should be converted from mm to cm [1].

Descriptive statistics for actual value and change from baseline of CDAI and SDAI will be presented by treatment group for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset at each visit. In addition, a listing will be provided by treatment group for the all-randomized population showing the CDAI and SDAI values.

11.5. Joint Damage Progression

Joint damage progression based on radiographic evaluations (1 image of both the right and left hands and both the right and left feet, for a total of 4 images, van der Heijde modification of the Sharp scoring system using a dual-reader with adjudication paradigm.) will be evaluated at Screening, Week 48 and Extension Week 24 or at the End-of Study Visit (if not obtained at Week 48 or Extension Week 24), or upon use of protocol prohibited medication or study termination, as applicable.

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

- Erosion: Defects, cystic changes, and surface erosions are counted in the 10 MCP joints, the eight PIP joints, the two IP joints of the thumbs, the right and left first metacarpal bone, the right and left radius and ulnar bones, the right and left trapezium and trapezoid (as one unit; multangular), right and left navicular bones, right and left lunate bones, the 10 metatarsophalangeal (MTP) joints, and the two IP joints of the big toes. The van der Heijde modification for erosion ranges from 0 (Normal) to 5 (Complete collapse).
- Joint space narrowing: JSN(Joint space narrowing)/ankylosis is assessed in the 10 MCP joints, the eight PIP joints, right and left third, fourth and fifth carpometacarpal (CM) joints, right and left multangular-navicular joints, right and left capitate-navicular-lunate joints, right and left radiocarpal joints, the 10 MTP joints and the two IP joints of the big toes. Joint space narrowing score ranges from 0 (Normal) to 4 (Ankylosis)

Hence the maximum erosion score is 160 for hands and wrists and 120 for feet, and the maximum joint space narrowing score is 120 for hands and wrists and 48 for feet. Scores will be produced by at least two independent readers. If the change in score from baseline to the follow-up timepoints differs between the two readers by more than five, an adjudicator (Reader 3) will read the images for the subject. For cases that are not adjudicated, the average of the two reviewers' scores will be considered the final score. In cases that are adjudicated, the average of the adjudicator's score and the score of the reviewer that is closest to the adjudicator will be provided as the final score. In circumstances where the adjudicator's score is equidistant to both reader 1 and reader 2's score, the final score will be the average of reader 1 and the adjudicator's scores. The average score for each joint will be produced if scores of all readers are non-missing, otherwise the average score for each joint will not be produced. In addition, non-missing score will be used in total score summaries.

The total van der Heijde radiographic joint damage score is the sum of the erosion score (hands, wrists and feet) and the joint space narrowing score (hands, wrists and feet), and hence it ranges from 0 to 448. This will be calculated at each visit for each patient. Descriptive statistics for actual value and change from baseline of the total van der Heijde radiographic joint damage score will be presented by treatment group for the efficacy population and efficacy – Extension Study Period subset at baseline and Week 48, Extension Week 24 visit. If it is not possible to calculate the joint score for a single joint then the particular patient's total score will be excluded from the descriptive statistics.

A listing showing the total van der Heijde radiographic joint damage score will be provided by treatment group for the all-randomized population. In addition, a listing will be provided by treatment group for the all-randomized population showing the raw results for each joint.

11.6. Quality of Life (SF-36) Questionnaire

The SF-36 questionnaire consists of 36 questions regarding the quality of life of the patient. Results for each of the 36 questions will be recorded. The results will be grouped into the following 8 subscales: Physical Functioning (PF), Role Limitations due to Physical Health (RP), Bodily Pain (BP), General Health Perceptions (GH), Vitality (VT), Social Functioning (SF), Role Limitations due to Emotional Problems (RE), and Mental Health (MH). The Vitality subscale is also known as "Fatigue". The 8 subscales will also be used to derive 2 component summary measures: Physical Component Score (PCS) and Mental Component Score (MCS) [7]. The scores and scales of the SF-36 survey ranges from 0 (worst) to 100 (best), with a higher score indicating a better health-related quality of life.

[redacted] will be used in order to derive summary scores for the SF-36 data prior to analysis. The [redacted] will be used to present results. Scoring is standardized using the means and standard [redacted]. On this scale, the general population has a mean of 50 and a standard deviation of 10. SF-36 subscale results and component summary measures will be displayed to two decimal places.

Descriptive statistics for actual value and change from baseline will be presented for each of the 8 subscales and 2 summary component scores, by treatment group for the efficacy population, efficacy – 2nd treatment course in Main Study Period subset and efficacy – Extension Study Period subset at baseline, Week 24, Week 48 and Extension Week 24.

A listing will present 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. Both listings will be based on the all-randomized population.

12. Pharmacodynamics

Analysis of the PD parameters will be conducted using the PD population. The CRP, ESR, anti-CCP, rheumatoid factor (RF), and B-cell counts will be recorded as numeric pharmacodynamic parameters. Any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all subsequent analyses, summaries and plots. In the case where a duplicate measurement of CRP, ESR, anti-CCP or RF is recorded within the same visit, the highest value will be used for analysis as a conservative approach. In case B-cell repeating criteria is applied, that if the variance between repeat results and first run is higher than 10% then repeat result will be used for analysis. Otherwise, first result will be used. All PD information will be listed by treatment group using the PD population.

12.1. Descriptive Statistics of Pharmacodynamic parameters

Descriptive statistics will be provided for the CRP, ESR, anti-CCP and RF parameters (actual value and change from baseline) for the pharmacodynamic population, pharmacodynamic – opnd treatment course in Main Study Period subset and pharmacodynamic – Extension Study Period subset by treatment group and visit. Descriptive statistics will consist of n, mean, SD, geometric mean, CV, minimum, median and maximum. The number and percentage of patients within each category will be displayed for baseline and for each post-baseline visit by treatment group.

The number and percentage of patients within each category of the anti-CCP (Negative, Positive, or Missing) and RF (Negative, Positive or Missing) parameter will be displayed in shift tables for the pharmacodynamic population at Week 24, for pharmacodynamic – 2nd treatment course in Main Study Period subset at Week 24 and Week 48, and for the pharmacodynamic – Extension Study Period subset at Extension Week 0 and Extension Week 24 by treatment group. Anti-CCP results equal to or greater than 17 U/ml will be considered as “positive” while those less than 17 U/ml will be considered as “negative”. RF results greater than 10 IU/ml will be considered as “positive” while those equal to or less than 10 IU/ml will be considered as “negative”.

The descriptive statistics (actual value and change from baseline) will also be summarized for B-cell counts for the pharmacodynamic population, pharmacodynamic – 2nd treatment course in Main Study Period subset and pharmacodynamic – Extension Study Period subset by treatment group and time-point up to Extension Week 24, including the records at pre-dose, end of study drug infusion, and 1 hour after the end of study drug infusion. For patients from Part 1, additional sample will be collected after 24 hours from the end of study drug infusion. The descriptive statistics will consist of n, mean, SD, geometric mean, CV, minimum, median and maximum.

12.2. ANCOVA of Pharmacodynamic parameters

ANCOVA will be performed for the PD population at Week 24 where PD blood samples are scheduled for the PD parameters CRP, ESR, anti-CCP and RF. This will be conducted with result as the response, treatment group as fixed effect and baseline values, country, race, study part, interaction of treatment group with study part, gender, prior anti-TNF- α blocker status

(intolerance case versus inadequate response), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. Clinically relevant variables at baseline are used as the covariates for adjusted means. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into the region (EU vs. non-EU). The geometric least squares mean will be calculated by back transforming the least square means, the ratio of geometric least squares means, 95% CI of the ratio and p-value with an interaction effect between study part and treatment group will be produced.

B-cell AUC will be calculated using the linear trapezoidal rule and it will be time normalized by number of minutes since baseline. If the time of sample is missing then the time will be assumed to be 09:00am on the day of sample. If both date and time are missing then the AUC will not be calculated for that patient.
Actual B-cell sampling times will be used for AUC calculation. Patients with missing both post-baseline B-cell counts on the day of the first infusion (15 minutes after end of infusion and 60 ± 15 minutes after end of infusion) will be excluded from the AUC analysis. Patients with a baseline result which is missing or below LLoQ (20cells/mcL) will also be excluded from B-cell AUC analysis.
The additional ANCOVA will be performed for the B-cell AUC and B-cell counts data up to Week 24 on patients who received first course of study drug. These will include treatment group as a fixed effect, and baseline B-cell count, country (or region), gender, race, study part, interaction of treatment group with study part, prior anti-TNF-y blocker (intolerance case versus inadequate response), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. The geometric least squares mean will be calculated by back transforming the least square means. The ratio of geometric least squares means, 95% CI (geometric least squares mean and ratio) and p-value with an interaction effect between study part and treatment group will be produced. Additional ANCOVA for the B-cell AUC and the B-cell counts will be conducted in patients whose ADA status result at Week 24 is "Negative".
All pharmacodynamic analyses will be conducted using two treatment groups, CT-P10 and reference products group on Part 2.

12.3. Figures and listings of Pharmacodynamic parameters

In addition, a plot will be presented showing the mean concentration and Standard Error (SE) of the CRP and ESR up to Week 24 for the pharmacodynamic population and up to Week 48 for the pharmacodynamic – 2nd treatment course in Main Study Period Subset by treatment group (CT-P10 group vs. Reference products group). A plot will also be presented for the median of the B-cell counts at each visit and time point up to Week 24 for the PD population and up to Week 48 for the pharmacodynamic – 2nd treatment course in Main Study Period Subset by treatment group (CT-P10 group vs. Reference products group).

All pharmacodynamic data for CRP, ESR, anti-CCP and RF will be listed for the pharmacodynamic population by treatment group and visit. Anti-CCP and RF categories for the PD population will also be listed by treatment group, visit and time point. A listing will be produced for the PD population displaying B-cell counts, log-transformed B-cell counts, and AUC by treatment group, visit, and time point.

13. Safety Analyses

The safety analyses will be performed on the safety population and safety – Extension Study Period subset by treatment group presenting data on hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates, and temperature) and electrocardiograms (ECG), immunogenicity tests, vital sign measurements, ECGs, signs and symptoms of tuberculosis (TB), physical examination findings, adverse events (AEs), infections, Infusion-Related Reactions (IRRs), malignancy, clinical laboratory results (hematology, clinical chemistry, urinalysis, and immunoglobulins), and pregnancy tests. Combined PTs using the APPENDIX 3: Rule of combining Preferred Terms will be summarized in AE tables. Listings will include the PTs as coded without applying the PT combining rule.

13.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled (i.e., when the informed consent form (ICF) is signed) into this study regardless of its causal relationship to study drug.

The Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher will be used to code all AEs. AEs will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Listings for AEs will include the following information: SOC, PT and verbatim term; start and stop date; frequency (intermittent, continuous); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); any treatment required (no, yes with specified treatment); intensity (Grade 1 to 5); action taken by investigator (dose increased, dose decreased, no action taken, permanently discontinued, stopped temporarily, dose delay); relationship to study drug (unrelated, possible, probable, definite); whether the event was serious (no, yes); and whether subject was terminated from the study due to the AE. All adverse events will be listed.

In summaries, adverse events will be considered to be related if the relationship is possible, probable, or definite. AEs with no relationship recorded will be summarized separately under a missing category.

If the data of an AE is partial or missing, the following rules will be applied.

- If the day of an Adverse Event is missing (e.g. XXFEB2016), 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 recorded 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. 01FEB2016).

- If the day and month is missing (e.g. XXXXX2016), 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 recorded 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. 01JAN2016).

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 recorded end date of the AE.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

TEAEs will be summarized by relationship, intensity, SOC and PT for the safety population and safety – Extension Study Period subset, displaying the number and percentage of patients with at least one TEAE 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 will also be displayed. Although PML is an AE of special interest, it is captured only by a PT 'Progressive multifocal leukoencephalopathy'. Therefore, do not generate an additional table for PML and it will be summarized with TEAEs.

The following tables will be presented by treatment group:

- TEAE by intensity
- Treatment-Emergent SAE (TESAE) by intensity
- TESAE by serious criteria
- TEAE leading to permanent discontinuation of study drug by intensity
- TEAE classed as malignancy by intensity
- TEAE classed as infections by intensity
- TEAE due to infusion-related reaction by intensity
- Proportion of patients with at least one TEAE due to infusion-related reaction by ADA status

13.1.1. Death

A listing will be provided showing any deaths during the study period in the safety population including detailed in Section 13.1.

13.1.2. Serious Adverse Events

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered 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.

TESAEs will be summarized by relationship, intensity, SOC, and PT for the safety population and safety – Extension Study Period subset, 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 will also be displayed.

All SAEs will be listed including the variables detailed in Section 13.1.

13.1.3. Treatment emergent Adverse Events leading to Permanent Study Drug Discontinuation

TEAEs which lead to permanent discontinuation of the study drug will be summarized by relationship, intensity, SOC, and PT for the safety population and safety – Extension Study Period subset, displaying the number and percentage of patients with at least one TEAE leading to permanent discontinuation of the study drug, 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 permanent discontinuation of the study drug will be also displayed.

All AEs leading to permanent discontinuation of study drug will be listed.

13.1.4. Treatment emergent Adverse Events of Special Interest

Infection, malignancy and infusion-related reaction are considered TEAEs of special interest.

13.1.4.1. Infections

Infections are considered AEs of special interest and include but are not limited to serious, including fatal, bacterial including tuberculosis, fungal, and new or reactivated viral infections. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Infections are coded with a SOC of “Infections and infestations”.

Treatment-emergent infections will be summarized by relationship, intensity, SOC, and PT for the safety population and safety – Extension Study Period subset, displaying the number and percentage of patients with at least one TEAE 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 treatment-emergent infection will also be displayed.

13.1.4.2. Malignancy

TEAEs will be determined to be malignancy if they are coded with a PT of “cancer”, “carcinoma” or “lymphoma” in a SOC of “neoplasm, malignant and unspecified (including cyst and polyps)”.

Malignancy will be summarized for the safety population and safety – Extension Study Period subset, by relationship, intensity, SOC, and PT, displaying the number and percentage of patients with at least one TEAE 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 treatment-emergent malignancy will also be displayed.

13.1.4.3. Infusion-Related Reaction

Infusion-related reactions are checked in the eCRF and will be presented in listings.

Treatment emergent classed as infusion-related reaction will be summarized for the safety population, safety – 2nd treatment course in Main Study Period subset and safety – Extension Study Period subset for each treatment course, by relationship, intensity, SOC and PT displaying the number and percentage of patients with at least one TEAE 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 treatment-emergent classed as infusion-related reaction will also be displayed.

Number of patients with at least one TEAE classed as infusion-related reaction by ADA status tagged with CT-P10 will be summarized. For summary of IRR at first, second course of treatment in Main Study Period, Patients who have 'Positive' ADA result at Week 24 and Patients who have at least one 'Positive' ADA result in Week 24 and Week 48 will be defined as positive, respectively. For summary of IRR at treatment course of Extension Study Period, Patients who have at least one 'Positive' ADA result in Week 24, Week 48 and Extension Week 24 will be defined as positive.

13.2. Clinical Laboratory Evaluations

Clinical laboratory safety tests will be performed and results will be converted to standard units which are provided by the central laboratory. Clinical laboratory tests (hematology, clinical chemistry, urinalysis, and immunoglobulins) will be summarized, by laboratory test type and treatment group, at each scheduled collection time for safety population and safety – Extension Study Period subset. For continuous parameters, change from baseline and actual value will also be summarized for all scheduled collection times after the first infusion.

The results for all non-numeric urinalysis parameters will be categorized into normal and abnormal using the central laboratory normal ranges provided prior to analysis and will be summarized in a shift table for the safety population and safety – Extension Study Period subset. The number and percentage of patients within each category will be displayed for baseline and for each post-baseline visit by parameters and treatment group.

All numeric parameters will be labeled with a CTCAE term and grading will be applied to post-baseline values for all numeric parameters where possible according to CTCAE v 4.0 [6]. Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. The CTCAE terms and ranges for applicable parameters are listed in APPENDIX 2: Table of CTCAE Terms and Grades of this document. 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 CTCAE term, visit, and treatment group for safety population and safety – Extension Study Period subset. In addition, a listing will be provided showing the CTCAE results for each patient by treatment group in the safety population.

The number and percentage of patients with CTCAE grade greater than or equal to 3 will be summarized by laboratory category, parameter, level, CTCAE grade and treatment group. The summary will be performed based on the data obtained during the Main Study Period or Extension Study Period, including all post-baseline scheduled, unscheduled and repeat visits. Only the most severe result will be counted a patient received the same tests in repeated visits.

The proportion of patients with Ig levels under LLN of the IgA, IgG and IgM will be summarized separately by visit and treatment group. Percentages are calculated by using the number of patients who have Ig levels at each visit as the denominator.

All hematology, clinical chemistry, urinalysis, and immunoglobulin data will be listed, and will include high and low flags to show if a value was outside the normal range.

13.3. Vital Signs

Vital signs (including systolic and diastolic blood pressure (BP), heart rate, respiratory rate, temperature, and weight) will be summarized by treatment group for the safety population and safety – Extension Study Period subset at each scheduled collection time. Change from baseline will also be summarized for all post-first infusion scheduled collection times. Baseline will be the last available measurement prior to the first infusion. All vital sign data will be listed for safety population.

13.4. Electrocardiogram (ECG)

Findings of 12-lead ECG will be classified as either “Normal”, “Abnormal, not clinically significant”, and “Abnormal, clinically significant”. The number and percentage of patients will be provided, by treatment group and visit, in the form of a shift table to detect changes from baseline for safety population and safety – Extension Study Period subset. All ECG data will be listed by treatment group and visit for safety population.

13.5. Hypersensitivity Monitoring

13.5.1. Vital Signs

Hypersensitivity will be assessed by vital sign monitoring except for weight on each dosing day and recorded on each dosing day at the following time points:

- Before administration (within 15 minutes prior to the beginning of the study drug infusion)
- Within 15 minutes after the end of the study drug infusion
- 1 hour (±15 minutes) after the end of the study drug infusion

The number and percentage of patients who have clinically notable vital sign hypersensitivity result at the start of the infusion or any subsequent time point during hypersensitivity monitoring will be presented by treatment group, parameter, and time point. The criteria for clinically notable results are defined as follows:

Table 8: Hypersensitivity Classification for Vital Signs

Parameter	Low	High
Systolic blood pressure (mmHg)	<= 90	>= 160
Diastolic blood pressure (mmHg)	<= 50	>= 90
Respiratory rate (breaths per minute)	<= 12	>= 20
Heart rate (beats per minute)	<= 50	>= 100
Body temperature (^{o}C)	<= 35.0	>= 38.0

All hypersensitivity vital sign data will be listed by treatment group and time point.

13.5.2. Electrocardiograms

In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including 12-lead ECG monitoring 1 hour (±15 minutes) after the end of the study treatment infusion. Findings will be classified as either "Normal", "Abnormal, not clinically significant", or "Abnormal, clinically significant". The number and percentage of patients will be provided, by treatment group and visit for the safety population and safety – Extension Study Period subset, in the form of a shift table to detect changes from baseline.

All hypersensitivity data will be listed by treatment group and time point.

13.6. Physical Examination

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 (except RA symptoms)
- Lymph Nodes
- Other

Findings will be classified as either normal or abnormal. The number and percentage of patients will be provided by body system, treatment group and visit, in the form of a shift table to detect changes from baseline for safety population and safety – Extension Study Period subset. All physical examination data will be listed for safety population.

13.7. Immunogenicity (Anti-drug antibodies and Neutralizing antibody)

Blood samples for immunogenicity (ADA and NAb) assessment will be obtained at Week 0 Day 0, Week 24, Week 48, Extension Week 0, Extension Week 8, Extension Week 16, Extension Week 24 and EOS (if patient withdraws prior to study completion). Immunogenicity assessment consists of both ADA and NAb assay.

ADA assay will follow a three-tiered approach consisting of (i) a 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 confirmatory (immunodepletion) assay to determine if patients are a true positive. The test outcome for the screening or specificity/confirmatory assay will be: {'Reactive', 'Negative' and '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 assay 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 assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening assay will be: {'Reactive', 'Rejected for Hemolysis (HEM)', 'Insufficient Sample Volume (ISV)', and 'Negative'}. Samples that are 'Reactive' in the screening assay will be undergone further testing in the confirmatory (immunodepletion) assay to determine if patients were a true positive. The test outcome for the confirmatory assay will be: {'Positive', 'Negative' and 'N/A'}. 'Positive' indicates a true positive test outcome, '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 the screening or confirmatory assay will be considered negative for the overall NAb assessment.
ADA assay will be performed using the labelled antibody with CT-P10, Rituxan and MabThera tag for Part 1 patients up to Week 24, whereas a single labelled antibody with CT-P10 tag will be used for the assessment of patients in Part 2 up to Week 48 and patients in Extension Study Period.

13.7.1. Summary of ADA and NAb

The results of the ADA assay will be summarized by each assay tag. The number and percentage of patients will be presented at each scheduled visit the assessments took place, by treatment group. A listing of the ADA assay will be presented by the part, visit, tag type and treatment group. Tables will be produced for the safety population, safety - 2nd treatment course in Main Study Period subset and safety – Extension Study Period subset. Listings will be produced for the safety population.

Regarding the NAb assay, all patients in Part 1 and Part 2 will be tested in the determination of NAb using a single antibody. The results of the NAb assay will be summarized. The number and percentage of patients will be presented at each scheduled visit the assessments took place, by part and treatment group. The outcome of NAb will be listed by treatment group. Tables will be produced for the safety population, safety - 2nd treatment course in Main Study Period subset and safety – Extension Study Period subset. Listings will be produced for the safety population.

13.7.2. Evaluation of Tag Concordance of ADA Assessments

For the Part 1, the evaluation of Tag concordance of both ADA assessments (tagged with CT-P10 versus Rituxan, CT-P10 versus MabThera, Rituxan versus MabThera) will be evaluated for Week 0 Day 0 and Week 24.
The agreement in outcome between both assays will be evaluated using three methods that are commonly used to compare diagnostic tests when no standard reference test is available [14]:

- Positive percent agreement (PPA)
  - (Number of patients with positive outcome for both CT-P10 and Rituxan tags)/ (Number of patients with positive outcome for Rituxan tag) * 100
  - (Number of patients with positive outcome for both CT-P10 and MabThera tags)/ (Number of patients with positive outcome for MabThera tag) * 100
  - (Number of patients with positive outcome for both MabThera and Rituxan tags)/ (Number of patients with positive outcome for Rituxan tag) * 100
- Negative percent agreement (NPA)
  - (Number of patients with negative outcome for both CT-P10 and Rituxan tags)/ (Number of patients with negative outcome for Rituxan tag) * 100
  - (Number of patients with negative outcome for both CT-P10 and MabThera tags)/ (Number of patients with negative outcome for MabThera tag) * 100
  - (Number of patients with negative outcome for both MabThera and Rituxan tags)/ (Number of patients with negative outcome for Rituxan tag) * 100
- Cohen's Kappa statistic: the Kappa statistic is a measure of the overall agreement.

Higher percentages of PPA and NPA indicate a stronger agreement between outcomes. A higher value of the Kappa statistic indicates a stronger agreement between outcomes, with a value of 1 implying complete agreement.

The table analyzing ADA test agreement by treatment group and visit will be provided containing a cross-tabulation of test outcomes (for the CT-P10 and MabThera, CT-P10 and Rituxan, Rituxan and MabThera tagged assays), and the Kappa statistics with a 95% CI and corresponding p-value. If missing values (i.e. patients with no assessment or only one reported result from assessments) are present, the number of missing values will also be tabulated but will be excluded when deriving the PPA, NPA and Kappa statistics.

13.7.3. ADA titer Results

ADA titer values of the CT-P10, Rituxan and MabThera tagged assay for the Part 1 patients up to Week 24 and ADA titer values of the CT-P10 tagged assay for the Part 2 patients up to Week 48 and Extension Study Period patients will be transformed using a $[\log_2 x] + 1$ transformation. If the values in the data are in inequality forms, the sign of inequality will be removed and then the values will be transformed. Descriptive statistics of transformed ADA titer will be displayed for Week 0 Day 0, Week 24, Week 48, Extension Week 0, Extension Week 8, Extension Week 16, Extension Week 24 visit by treatment group on the safety population, safety – 2nd treatment course in Main Study Period subset and safety – Extension Study Period subset. The transformed results of ADA titer for each visit will also be listed by treatment group.

13.8. Interferon-gamma Release Assay

Interferon gamma release assay (IGRA) will be conducted at Baseline and results will be classified as "Positive", "Indeterminate" or "Negative". If a patient has an unscheduled screening visit, the results from the visit with the latest date will be reported as "Baseline". All results from visits will be reported in a "During the study period" category using the following methodology:

- If a patient has at least one result of "Positive" in the Study Period they will be considered as "Positive"

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

The number and percentage of patients with each result will be provided by treatment group for Baseline visit and study period for the safety population and safety – Extension Study Period subset. A listing displaying each patient's IGRA results will be provided by treatment group and visit.

13.9. Pregnancy

The following the assessments will be conducted and summarized for women of childbearing potential.

• Urine pregnancy dipstick test: Results will be classified as "Positive" or "Negative" and the number and percentage of patients will be provided by treatment group and visit.

• Serum pregnancy test: Results will be classified as "Positive" or "Negative" and the number and percentage of patients will be provided by treatment group and visit.

Separate summaries of urine pregnancy dipstick test and serum pregnancy test will be provided by treatment group and visit for the safety population and safety – Extension Study Period subset. A listing of urine pregnancy dipstick test and serum pregnancy test will be provided by treatment group and visit.

14. References

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15. Appendices

APPENDIX 1: Schedule of Events

Schedule of Events for Screening and the Main Study Period (for patients who receive both first and second courses of treatment)

Week and Day[1] of Study Period	Screen	Wk 0		Wk 1	Wk 2		Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk20	Wk 24	Wk 26	Wk 32	Wk 40	Wk 48	EOS[2]
Procedure	**Day -42 to -1**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 15**	**Day 21**	**Day 28**	**Day 56**	**Day 84**	**Day 112**	**Day 140**	**Day 168**	**Day 182**	**Day 224**	**Day 280**	**Day 336**	
Informed consent	X																	
Demography	X																	
Medical history	X																	
Hepatitis B[3] & C, and HIV	X												(X)[3]				(X)[3]	(X)[3]
Serum pregnancy test	X																X	X
Cardiac disorder[4]	X																	
Urine pregnancy test (local)		X[5]			X[5]								X[5]	X[5]				
Inclusion/exclusion criteria	X	X[5]																
Randomization		X[5,6]																
Vital signs[7]	X	X[5]		X	X[5]		*X*	X	X	X	X		X[5]	X[5]	X	X	X	X
Physical examination	X	X[5]			X[5]				X		X		X[5]	X[5]	X	X	X	X
Hematology and clinical chemistry[8]	X[1]	X[5]			X[5]				X		X		X[5]	X[5]	X	X	X	X
Urinalysis[9]	X[1]	X[5]			X[5]				X		X		X[5]	X[5]	X	X	X	X
12-lead ECG (local)[10]	X	X			X								X	X			X	X
TB screening and monitoring[11]	X	*X*																
Hand and foot x-ray[12]	X																X	X
ACR [13]including:																		
Tender joint count	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
Swollen joint count	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
VAS pain score	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X

Week and Day[1] of Study Period	Screen	Wk 0		Wk 1	Wk 2		Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk20	Wk 24	Wk 26	Wk 32	Wk 40	Wk 48	EOS[2]
Procedure	**Day -42 to -1**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 15**	**Day 21**	**Day 28**	**Day 56**	**Day 84**	**Day 112**	**Day 140**	**Day 168**	**Day 182**	**Day 224**	**Day 280**	**Day 336**	
VAS global assessment of disease activity (patient and physician) score	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
Health Assessment Questionnaire	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
ESR (local)	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
CRP	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
DAS28 examination[14]	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
QOL (SF-36) assessment	X	X[5]											X[5]				X	X
Rheumatoid factor	X												X[5]				X	X
Anticyclic citrullinated peptide	X												X[5]				X	X
Immunoglobulin testing[15,16]		X[5]							X		X		X[5]		X	X	X	X
Immunogenicity		X[5]											X[5]				X	X
Study drug infusion		X			X								X	X				
Hypersensitivity monitoring[17]		X			X								X	X				
PK blood sampling for Part 1		X[18]	X[18]	X	X[18]	X[18]	*X*	X	X	X	X		X[18]	X[18]			X	X[19]
PK blood sampling for Part 2		X[18]			X[18]								X[18]	X[18]			X	X[19]
B-cell kinetics blood sampling for both Part 1 and Part 2[16]		X[20]	X[20]	X	X		*X*	X	X	X	X		X[20]	X	X	X	X	X
Biomarker (FcγR genotypes)[21]		X																
Previous and concomitant medications monitoring[22]	X	*X*																

Week and Day[1] of Study Period	Screen	Wk 0		Wk 1	Wk 2		Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk20	Wk 24	Wk 26	Wk 32	Wk 40	Wk 48	EOS[2]
Procedure	Day -42 to -1	Day 0	Day 1	Day 7	Day 14	Day 15	Day 21	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 182	Day 224	Day 280	Day 336	
Adverse event monitoring[23]	X	*X*																

Abbreviations: ACR, American College of Rheumatology; CRP, C-reactive protein; DAS28, Disease Activity Score using 28 joint counts; ECG, electrocardiogram; eCRF, electronic case report form; EOS, end of study; ESR, erythrocyte sedimentation rate; HBcIg, hepatitis B core (total) Ig; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HIV, human immunodeficiency virus; ICF, informed consent form; Ig, immunoglobulin; QOL, quality of life; SF-36, Medical Outcomes Study Short-Form Health Survey; TB, tuberculosis; Wk, Week; VAS, visual analogue scale.

*** IMPORTANT! For patients who receive the first course of treatment in Extension Study Period at Week 48, the scheduled assessments and samplings should be performed according to the schedule of events and sampling schemes for the Extension Week 0 Schedule. Otherwise, all scheduled assessments for Week 48 should be performed separately from the Extension Week 0 according to this schedule of events.**

1. If the assessments or tests are done within 14 days from the randomization date, the omitting of that assessment or tests will be allowed. A visit window is not permitted from Day 0 to Day 21 (study drug may continue after discussion with the sponsor if a deviation occurs). A visit window of ±3 days is allowed from Week 4 to Week 24, a visit window of ±5 days is allowed thereafter, including the EOS Visit. If patients receive the second course of infusion, the first infusion will be administered at Week 24 with a visit window of ±3 days, and the second infusion should be administered after 2 weeks (14 days) from the first infusion. A visit window is not permitted on the day of second infusion in the second course of treatment (study drug may continue after discussion with the sponsor if a deviation occurs). Visit days during the second course of treatment will be calculated based on the date of the first infusion in the second course of treatment (Week 24 visit).
2. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Week 48 of study period if a patient withdraws prior to the completion of Week 48 visit. If the patient has completed the Study Period, a separate EOS Visit is not required. In this case, the last visit will be considered the EOS Visit.
3. Hepatitis B surface antigen, HBsAb, and HBcIg should be assessed at Screening in all patients (mandatory). If the result is HBsAg (positive), the patient should be excluded from the study. For patients whose HBsAg is negative, HBsAb is negative or positive, and HBcIg is positive, a DNA test should be performed at Screening. If the DNA test result is positive, the patient should be excluded from the study and if the DNA test result is negative, the patient can be included. For those patients who have enrolled based on the DNA test, the DNA test will be done every 24 weeks for monitoring purposes. During the study, if hepatic symptoms are suspected, HBsAg, HBsAb, HBcIg, and DNA tests should be performed. Hepatitis C antibody and HIV-1 and -2 should be assessed at Screening in all patients (mandatory). Hepatitis and HIV testing will be performed at the central laboratory.

4. At Screening, patients will be assessed for the presence of New York Heart Association class III or IV (Appendix 12.4) heart failure, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinically significant ECG abnormalities), or myocardial infarction within the previous 6 months prior to the date of consent. Patients with these cardiac disorders will be excluded from the study.
5. Assessed prior to study drug infusion.
6. Tender joint count and swollen joint count need to be reconfirmed for inclusion criteria prior to randomization.
7. Vital signs (including blood pressure, heart and respiratory rates, and temperature) and weight will be measured by the investigator or his or her designee after 5 minutes of rest (sitting). In addition, measurement of height will be documented at Screening.
8. Hematology (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, platelets), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, cholesterol, triglycerides, creatine phosphokinase, creatinine, creatinine clearance [estimated by weight and by Cockcroft-Gault formula], gamma-glutamyl transferase, glucose, high-density lipoprotein cholesterol, lactate dehydrogenase, low-density lipoprotein cholesterol, phosphorous, potassium, sodium, total bilirubin, total protein). Testing will be performed at the central laboratory.
9. Urinalysis (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination of sediment, only if urinalysis dipstick results are abnormal). Testing will be performed at the central laboratory.
10. All scheduled 12-lead ECGs (performed locally) must be performed after the patient has rested quietly for at least 5 minutes in the supine position. On the day of infusion, 12-lead ECGs will be performed after 1 hour (15 minutes) after the end of the study drug infusion for the hypersensitivity monitoring.
11. Interferon-γ release assay will be performed at Screening and Week 48 (or End-of-Study Visit). The results of the test should be entered in the electronic case report form. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.
12. One image of each hand and each foot (both the right and left hands and feet, a total of 4 images) for analysis of efficacy will be obtained at the scheduled times. Joint damage, as determined by radiography, will be assessed by change in the van der Heijde modification of the Sharp scoring system. The baseline radiographs must be assessed within 42 days prior to the randomization date. Hand and foot x-rays will be evaluated centrally by an independent reviewer for reporting purposes and on a local level for treatment practice.
13. ACR20, ACR50, ACR70, and hybrid ACR will be calculated from these assessments. It is recommended that the joint count assessments are performed by the same physician when possible.
14. The European League Against Rheumatism response criteria will be derived from the DAS28.
15. Immunoglobulin (IgM, IgG and IgA) testing will be performed at the central laboratory.
16. Patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value should be monitored every 8 weeks after the study completion until recovery is achieved for one of them (equal to or higher than the lower limit of normal OR at least 50% of the baseline value). Upon the study completion, additional follow-up of B-cell, IgM and IgG monitoring will be determined by the Data Safety Monitoring Board (DSMB).

17. Additional vital signs including blood pressure, heart and respiratory rates, and temperature (before administration [within 15 minutes prior to the beginning of the study drug infusion], within 15 minutes after the end of the study drug infusion, and at 1 hour (±15 minutes) after the end of the study drug infusion) will be assessed to monitor for possible hypersensitivity reactions. In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including 12-lead ECG monitoring 1 hour (±15 minutes) after the end of the study drug infusion. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator must be available.
18. Pharmacokinetic samples will be collected within 15 minutes prior to the beginning of the study drug infusion, within 15 minutes after the end of study drug infusion, and 1 hour (±15 minutes) after the end of study drug infusion on the day of each study drug infusion. For patients from Part 1, additional samples will be collected after 24 hours (±2 hours) from the start of each study drug infusion in the first treatment course and on Days 7, 21, 28, 56, 84 and 112. Testing will be performed at the central laboratory.
19. Pharmacokinetic sampling should be done at EOS Visit if the last visit occurs before Week 48.
20. B-cell kinetic samples will be collected in the each treatment course within 15 minutes prior to the beginning of the first study drug infusion, within 15 minutes after the end of first study drug infusion and 1 hour (±15 minutes) after the end of first study drug infusion. For patients from Part 1, additional sample will be collected after 24 hours from the start of the first study drug infusion in the first course of treatment.
21. Before dosing on Day 0 of Week 0 (after randomization only). Only for patients who sign a separate informed consent form for the biomarker study (genotypes). Blood samples will be evaluated for FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes). Testing will be performed at the central laboratory.
22. Use of all concomitant medications, from within 30 days of randomization until the last assessment date or End of Study Visit, will be recorded in the patient's eCRF.
23. Adverse events will be assessed from the date the ICF is signed until the last assessment date or End of Study Visit.

Schedule of Events for the Main Study Period between Weeks 24 and 48 (for patients who receive only first course of treatment)

Week and Day[1] of Study Period / Procedure	Week 24 / Day 168	Week 32 / Day 224	Week 40 / Day 280	Week 48 / Day 336	EOS[2]
Hepatitis B[3] & C, and HIV	(X)[3]			(X)[3]	(X)[3]
Serum pregnancy test				X	X
Vital signs[4]	X				
Physical examination	X				
Hematology and clinical chemistry[5]	X				
Urinalysis[6]	X				
12-lead ECG (local)[7]	X			X	X
TB monitoring[8]	X				
Hand and foot x-ray				X	X
ACR[9] including:					
Tender joint count	X				
Swollen joint count	X				
VAS pain score	X				
VAS global assessment of disease activity (patient and physician) score	X				
Health Assessment Questionnaire	X				
Erythrocyte sedimentation rate (local)	X				
C-reactive protein	X				
DAS28 examination[10]	X				
QOL (SF-36) assessment	X			X	X
Rheumatoid factor	X			X	X
Anti-cyclic citrullinated peptide	X			X	X
Immunoglobulin testing[11,12]	X				
Immunogenicity	X			X	X
Pharmacokinetic blood sampling for both Part 1 and 2	X				
B-cell kinetics blood sampling for both Part 1 and 2[12]	X				

Procedure \ Week and Day[1] of Study Period	Week 24	Week 32	Week 40	Week 48	EOS[2]
	Day 168	Day 224	Day 280	Day 336	
Previous and concomitant medications monitoring[13]	X				
Adverse event monitoring[14]	X				

Abbreviations: ACR, American College of Rheumatology; DAS28, Disease Activity Score using 28 joint counts; ECG, electrocardiogram; EOS, end of study; HBcIg, hepatitis B core (total) Ig; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; QOL, quality of life; SF-36, Medical Outcomes Study Short-Form Health Survey; TB, tuberculosis; VAS, visual analogue scale.

*** IMPORTANT! For patients who receive the first course of treatment in Extension Study Period at Week 48, the scheduled assessments and samplings should be performed according to the schedule of events and sampling schemes for the Extension Week 0 Schedule. Otherwise, all scheduled assessments for Week 48 should be performed separately from the Extension Week 0 according to this schedule of events.**

1. A visit window of ±3 days is allowed at Week 24, and a visit window of ±5 days is allowed thereafter, including the EOS Visit.
2. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Week 48 of study period if a patient withdraws prior to the completion of Week 48 visit. If the patient has completed by Week 48 of the Study Period, a separate EOS Visit is not required.
3. For those patients who have enrolled based on the DNA test, the DNA test will be done every 24 weeks for monitoring purposes. During the study, if hepatic symptoms are suspected, HBsAg, HBsAb, HBcIg, and DNA tests should be performed. Hepatitis C antibody and HIV-1 and -2 should be assessed at Screening in all patients (mandatory). Hepatitis and HIV testing will be performed at the central laboratory.
4. Vital signs (including blood pressure, heart and respiratory rates, and temperature) and weight will be measured after 5 minutes of rest (sitting).
5. Hematology (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, platelets), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, cholesterol, triglycerides, creatine phosphokinase, creatinine, creatinine clearance [estimated by weight and by Cockcroft-Gault formula], gamma-glutamyl transferase, glucose, high-density lipoprotein cholesterol, lactate dehydrogenase, low-density lipoprotein cholesterol, phosphorous, potassium, sodium, total bilirubin, total protein). Testing will be performed at the central laboratory.
6. Urinalysis (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination of sediment [only if urinalysis dipstick results are abnormal]). Testing will be performed at the central laboratory.
7. All scheduled 12-lead ECGs (performed locally) must be performed after the patient has rested quietly for at least 5 minutes in the supine position.
8. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.
9. ACR20, ACR50, ACR70, and hybrid ACR will be calculated from these assessments. It is recommended that the joint count assessments are performed by the same physician when possible.
10. The European League Against Rheumatism response criteria will be derived from the DAS28.
11. Immunoglobulin (IgM, IgG and IgA) testing will be performed at the central laboratory.
12. Patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value should be monitored every 8 weeks after the study completion until recovery is achieved for one of them (equal to or higher than the lower limit of normal OR at least 50% of the baseline value). Upon the study completion, additional follow-up of B-cell, IgM and IgG monitoring will be determined by the Data Safety Monitoring Board (DSMB).
13. Use of all concomitant medications, from within 30 days of randomization until the last assessment date or End of Study Visit, will be recorded in the patient's eCRF.
14. Adverse events will be assessed from the date the ICF is signed until the last assessment date or End of Study Visit.

Schedule of Events for the Extension Study Period

Week and Day[1] of Extension Study Period / Procedure	Ext Week 0 / Ext Day 0	Ext Week 2 / Day 14	Ext Week 8 / Day 56 (±5days)	Ext Week 16 / Day 112 (±5days)	Ext Week 24 / Day 168 (±5days)	EOS[2]
Randomization[3]	X					
*Hepatitis B[4]	*(X)				(X)	(X)
*Serum pregnancy test	*(X)				X	X
Urine pregnancy test (local)	X[5]	X[5]				
Vital signs[6]	X[5]	X[5]	X	X	X	X
Physical examination	X[5]	X[5]	X	X	X	X
Hematology and clinical chemistry[7]	X[5]	X[5]	X	X	X	X
Urinalysis[8]	X[5]	X[5]	X	X	X	X
12-lead electrocardiogram (local)[9]	X[5, 10]	X[10]			X	X
Hand and foot x-ray	*(X)				X	X
ACR[11] including:						
Tender joint count	X[5]		X	X	X	X
Swollen joint count	X[5]		X	X	X	X
VAS pain score	X[5]		X	X	X	X
VAS global assessment of disease activity (patient and physician) score	X[5]		X	X	X	X
Health Assessment Questionnaire	X[5]		X	X	X	X
ESR (local)	X[5]		X	X	X	X
CRP	X[5]		X	X	X	X
DAS28 examination[12]	X[5]		X	X	X	X
QOL (SF-36) assessment	X[5]				X	X
Rheumatoid factor	X[5]				X	X
Anticyclic citrullinated peptide	X[5]				X	X
Immunoglobulin testing	X[5]		X	X	X[13]	X[13]
Immunogenicity	X[5]		X	X	X	X
Study drug infusion	X	X				
Hypersensitivity monitoring[10]	X	X				
PK blood sampling for both Parts 1 and 2	*(X)					
B-cell kinetics blood sampling	X[14]	X[5]	X	X	X[13]	X[13]
TB monitoring[15]	X					
Previous and concomitant medications monitoring	X					
Adverse event monitoring[16]	X					

Abbreviations: ACR, American College of Rheumatology; DAS28, Disease Activity Score using 28 joint counts; ECG, electrocardiogram; EOS, end of study; ESR, erythrocyte sedimentation rate; HBcIg, hepatitis B core (total) Ig; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; Ig, immunoglobulin; QOL, quality of life; SF-36, Medical Outcomes Study Short-Form Health Survey; TB, tuberculosis; Wk, Week; VAS, visual analogue scale.

*** IMPORTANT! Assessments for hepatitis B, serum pregnancy test, hand and foot x-ray, PK blood sampling will be performed at Extension Week 0 according to this schedule of events ONLY IF patients receive the first course of treatment in Extension Study Period on the same day with Week 48.**
Samples for PK at Week 48 should be obtained ONLY for patients who receive the second course of treatment during the Main Study Period and who receive the first course of treatment in Extension Study Period on the same day with Week 48.

1. The first course of treatment in Extension Study Period will be initiated between Week 48 and Week 52 of the Entire Study Period if patients become eligible according to the predefined safety criteria for the course based on the results assessed within 8 weeks from the Extension Week 0. A visit window of ±5 days is allowed throughout the study period except the day of second infusion of each course (study drug may continue after discussion with the sponsor if a deviation occurs). Visit days during the treatment course will be calculated based on the date of the first infusion in the Extension Study Period. Unscheduled visit(s) can be conducted for assessment of safety criteria until the initiation of the first course of treatment in Extension Study Period.

2. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Extension Week 24 if a patient withdraws prior to the completion of Extension Week 24. If the patient has completed the Study Period, a separate EOS Visit is not required. In this case, the last visit will be considered the EOS Visit.
3. To keep the blind during the study, stratification factors, the number of courses they are treated during the Main Study Period and the EULAR-CRP response status (responder vs non-responder) assessed at Week 40, will be entered for all patients at Extension Week 0. In the case there were no EULAR-CRP response status available at week 40, the last EULAR-CRP response status assessment done between Weeks 40 and 48 will be used. Baseline values for assessment of EULAR-CRP will be the last value from screening to Day 0 (Week 0) of the study.
4. If hepatic symptoms are suspected during the study, HBsAg, HBsAb, HBcIg, and DNA tests should be performed. For those patients who have been enrolled based on the DNA test in the main study, the DNA test will be done at Extension Week 24 for monitoring purposes. Hepatitis testing will be performed at the central laboratory.
5. Assessed prior to study drug infusion
6. Vital signs (including blood pressure, heart and respiratory rates, and body temperature) will be measured after 5 minutes of rest (sitting).
7. Hematology (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, platelets), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, cholesterol, triglycerides, creatine phosphokinase, creatinine, creatinine clearance [estimated by weight and by Cockcroft-Gault formula], gamma-glutamyl transferase, glucose, high-density lipoprotein cholesterol, lactate dehydrogenase, low-density lipoprotein cholesterol, phosphorous, potassium, sodium, total bilirubin, total protein). Testing will be performed at the central laboratory.
8. Urinalysis (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination of sediment, only if urinalysis dipstick results are abnormal). Testing will be performed at the central laboratory.
9. All scheduled 12-lead electrocardiograms (ECG) must be performed after the patient has rested quietly for at least 5 minutes in the supine position. On the day of infusion, 12-lead ECGs will be also performed after 1 hour (±15 minutes) after the end of the study drug infusion for the hypersensitivity monitoring. At Extension Week 0, 12-lead ECG will be performed prior to study drug infusion. If Extension Week 0 is conducted on the same day with Week 48, assessment result of 12-lead ECG performed prior to study drug infusion will be used for the ECG assessment to be performed at Week 48.
10. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (before administration [within 15 minutes prior to the beginning of the study drug infusion], within 15 minutes after the end of the study drug infusion, and at 1 hour [±15 minutes] after the end of the study drug infusion) will be assessed to monitor for possible hypersensitivity reactions. In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including ECG (12-lead) monitoring 1 hour (±15 minutes) after the end of the study drug infusion. Emergency equipment and medication, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator must be available.
11. ACR20, ACR50, ACR70, and hybrid ACR will be calculated from these assessments. It is recommended that the joint count assessments are performed by the same physician when possible.
12. Twenty eight tender and swollen joints, ESR or CRP, and patient's general health or global disease activity measured on VAS will be assessed for DAS28 calculation. The European League Against Rheumatism response criteria will be derived from the DAS28.
13. Patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value of Main Study Period should be monitored every 8 weeks (±14 days) after the study completion until recovery is achieved for one of them (equal to or higher than the lower limit of normal OR at least 50% of the baseline value of Main Study Period). Upon the study completion, additional follow-up of B-cell, IgM and IgG monitoring will be determined by the Data Safety Monitoring Board (DSMB).
14. Blood sampling for B-cell assessment at the first infusion date of the first course in Extension Study Period will be performed at predose (before administration [within 15 minutes prior to the beginning of the study drug infusion]), end of infusion (within 15 minutes after the end of the study drug infusion), and at 1 hour [±15 minutes] after the end of the study drug infusion.
    If Extension Week 0 is conducted on the same day with Week 48, the predose result from the B-cell samples obtained according to the scheduled schemes for Extension Week 0 will be the result of B-cell counts at Week 48.
15. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.
16. Adverse events will be assessed from the date the ICF is signed until the last assessment date or End of Study Visit.

Sampling Times for Pharmacokinetic, Pharmacodynamic, and Safety Assessments for the Main Study Period (for patients who receive both first and second courses of treatment)

Study Period				PD			Safety		
Week	Day	PK for Part 1	PK for Part 2	B-cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urinalysis
0	0	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Pretreatment[4]	NA	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]
	1	24 hours after start of infusion[5]	NA	24 hours after start of infusion[5] (only for patients from Part 1)	NA	NA	NA	NA	NA
1	7	Time not specified[6]	NA	Time not specified[6]	NA	NA	NA	NA	NA
2	14	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Time not specified[6]	NA	NA	NA	NA	Pretreatment[4]
	15	24 hours after start of infusion[5]	NA	NA	NA	NA	NA	NA	NA
3	21	Time not specified[6]	NA	Time not specified[6]	NA	NA	NA	NA	NA

Study Period				PD			Safety		
Week	Day	PK for Part 1	PK for Part 2	B-cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urinalysis
4	28	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	NA	NA	NA
8	56	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
12	84	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	NA	NA	NA
16	112	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
20	140	NA	NA	NA	Time not specified[6]	NA	NA	NA	NA
24	168	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]
26	182	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Time not specified[6]	NA	NA	NA	NA	Pretreatment[4]
32	224	NA	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
40	280	NA	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]

Study Period				PD			Safety		
Week	Day	PK for Part 1	PK for Part 2	B-cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urinalysis
48	336	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]
EOS[7]		Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]

Abbreviations: anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; EOS, end of study; ESR, erythrocyte sedimentation rate; NA, not applicable; PD, pharmacodynamic; PK, pharmacokinetic; RF, rheumatoid factor.

*** IMPORTANT! For patients who receive the first course of treatment in Extension Study Period at Week 48, the samples should be obtained according to the sampling schemes for the Extension Week 0 Schedule. Otherwise, all scheduled samplings for Week 48 should be performed separately from the Extension Week 0 according to this sampling scheme.**

1. Predose: Blood samples will be obtained within 15 minutes prior to the beginning of the study drug infusion.
2. End of infusion: Blood samples will be obtained within 15 minutes after the end of study drug infusion.
3. 1 hour after end of infusion: Blood samples will be obtained 1 hour (±15 minutes) after the end of study drug infusion on dosing days.
4. Pretreatment: Blood samples will be obtained prior to the study drug infusion.
5. 24 hours after start of infusion: Blood samples will be obtained 24 hours (±2 hours) after the start of study drug infusion.
6. Time not specified: Blood samples will be obtained any time during the day.
7. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Week 48 of Study Period if a patient withdraws prior to the completion of Week 48 visit. If the patient has completed by Week 48 of Study Period, an EOS Visit is not required.

Sampling Times for Pharmacokinetic, Pharmacodynamic, and Safety Assessment for the Main Study Period between Weeks 24 and 48 (for patients who receive only first course of treatment)

Study Period			PD			Safety		
Week	Day	PK	B-cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urine
24	168	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]
32	224	NA	Time not specified[1]	Time not specified[1]	NA	Time not specified[1]	NA	Time not specified[1]
40	280	NA	Time not specified[1]	Time not specified[1]	NA	Time not specified[1]	NA	Time not specified[1]
48	336	NA	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]
EOS[2]		NA	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]	Time not specified[1]

Abbreviations: anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; EOS, end of study; ESR, erythrocyte sedimentation rate; NA, not applicable; PD, pharmacodynamic; PK, pharmacokinetic; RF, rheumatoid factor.

*** IMPORTANT! For patients who receive the first course of treatment in Extension Study Period at Week 48, the samples should be obtained according to the sampling schemes for the Extension Week 0 Schedule. Otherwise, all scheduled samplings for Week 48 should be performed separately from the Extension Week 0 according to this sampling scheme.**

1. Time not specified: Blood samples will be obtained any time during the day.
2. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Week 48 of study period if a patient withdraws prior to the completion of Week 48 visit. If the patient has completed by Week 48 of the Study Period, an EOS Visit is not required.

Sampling Times for Pharmacodynamic, and Safety Assessments for the Extension Study Period

Study Period		PD			Safety		
Ext Week	Ext Day	B-cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urinalysis
0	0	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]
2	14	Pretreatment[4]	NA	NA	NA	NA	Pretreatment[4]
8	56	Time not specified[5]	Time not specified[5]	NA	Time not specified[5]	Time not specified[5]	Time not specified[5]
16	112	Time not specified[5]	Time not specified[5]	NA	Time not specified[5]	Time not specified[5]	Time not specified[5]
24	168	Time not specified[5]	Time not specified[5]	Time not specified[5]	Time not specified[5]	Time not specified[5]	Time not specified[5]
EOS[6]		Time not specified[5]	Time not specified[5]	Time not specified[5]	Time not specified[5]	Time not specified[5]	Time not specified[5]

Abbreviations: anti-CCP, anti-cyclic citrullinated peptide; CRP, C-reactive protein; EOS, end of study; ESR, erythrocyte sedimentation rate; NA, not applicable; PD, pharmacodynamic; RF, rheumatoid factor.

1. Predose: Blood samples will be obtained within 15 minutes prior to the beginning of the study drug infusion.
2. End of infusion: Blood samples will be obtained within 15 minutes after the end of study drug infusion.
3. 1 hour after end of infusion: Blood samples will be obtained 1 hour (±15 minutes) after the end of study drug infusion on dosing days.
4. Pretreatment: Blood samples will be obtained prior to the study drug infusion.
5. Time not specified: Blood samples will be obtained any time during the day.
6. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Extension Week 24 if a patient withdraws prior to the completion of Extension Week 24 visit. If the patient has completed the Study Period, a separate EOS Visit is not required. In this case, the last visit will be considered the EOS Visit.

APPENDIX 2: Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <100 - 80g/L	<8.0 g/dL; <80 g/L;	-
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Chronic kidney disease	Creatinine Clearance (Est by Weight)	Low	<LLN - 60 ml/min	<60 - 30 ml/min	<30 - 15 ml/min	<15 ml/min

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	-
Hypercalcemia	Calcium	High	>ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L	>13.5 mg/dL; >3.4 mmol/L
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L

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	-
Hypocalcemia	Calcium	Low	<LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L	<8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L	<7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L	<6.0 mg/dL; <1.5 mmol/L
Hypoglycemia	Glucose	Low	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L
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	<800 - 500/mm^3; <0.8 - 0.5 x 10e^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10e^9	<200/mm^3; <0.2 x 10e^9 /L

			$10e^9$/L		/L	
Lymphocyte count increased	Lymphocytes	High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Neutrophil count decreased	Total Neutrophils	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /L
Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3; <LLN - 75.0 x $10e^9$ /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x $10e^9$ /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x $10e^9$ /L	<25,000/mm^3; <25.0 x $10e^9$ /L
White blood cell decreased	White Blood Cells	Low	<LLN - 3000/mm^3; <LLN - 3.0 x $10e^9$ /L	<3000 - 2000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2000 - 1000/mm3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$ /L

Note: The LLN and ULN values will be the normal ranges as provided by the central laboratory at each relevant transfer.

APPENDIX 3: Rule of combining Preferred Terms

AESOC	AEPT	Combined PT
Gastrointestinal disorders	Abdominal pain	Abdominal pain
	Abdominal pain lower	
	Abdominal pain upper	
Infections and infestations	Abscess oral	Abscess
	Subcutaneous abscess	
Blood and lymphatic system disorders	Anaemia	Anaemia
	Iron deficiency anaemia	
Psychiatric disorders	Anxiety	Anxiety
	Anxiety disorder	
Musculoskeletal and connective tissue disorders	Arthritis reactive	Arthritis
	Arthritis	
Infections and infestations	Bacterial vaginosis	Bacterial vaginosis
	Vaginitis bacterial	
Infections and infestations	Asymptomatic bacteriuria	Bacteriuria
	Bacteriuria	
Cardiac disorders	Bradycardia	Bradycardia
	Sinus bradycardia	
Cardiac disorders	Cardiac failure	Cardiac failure
	Cardiac failure chronic	
General disorders and administration site conditions	Chest pain	Chest pain
	Non-cardiac chest pain	
Hepatobiliary disorders	Bile duct stone	Cholelithiasis
	Cholelithiasis	
Infections and infestations	Conjunctivitis	Conjunctivitis

	Conjunctivitis bacterial	
Respiratory, thoracic and mediastinal disorders	Cough	Cough
	Productive cough	
Skin and subcutaneous tissue disorders	Dermatitis	Dermatitis
	Dermatitis allergic	
	Dermatitis atopic	
	Dermatitis contact	
	Seborrhoeic dermatitis	
	Solar dermatitis	
Metabolism and nutrition disorders	Diabetes mellitus	Diabetes mellitus
	Type 2 diabetes mellitus	
Skin and subcutaneous tissue disorders	Drug eruption	Drug eruption
	Toxic skin eruption	
Skin and subcutaneous tissue disorders	Dyshidrotic eczema	Eczema
	Eczema	
	Eczema nummular	
Injury, poisoning and procedural complications	Ankle fracture	Fracture
	Facial bones fracture	
	Femur fracture	
	Foot fracture	
	Hand fracture	
	Humerus fracture	
	Lower limb fracture	
	Lumbar vertebral fracture	
	Rib fracture	
	Tibia fracture	
	Ulna fracture	

	Wrist fracture	
Infections and infestations	Fungal infection	Fungal infection
	Fungal skin infection	
	Genital infection fungal	
	Oral candidiasis	
	Oral fungal infection	
	Vulvovaginal candidiasis	
Nervous system disorders	Headache	Headache
	Tension headache	
Infections and infestations	Helicobacter gastritis	Helicobactor infection
	Helicobacter infection	
Infections and infestations	Herpes simplex	Herpes virus infection
	Herpes zoster	
	Oral herpes	
Metabolism and nutrition disorders	Glucose tolerance impaired	Hyperglycaemia
	Hyperglycaemia	
	Impaired fasting glucose	
Immune system disorders	Drug hypersensitivity	Hypersensitivity
	Hypersensitivity	
General disorders and administration site conditions	Catheter site pain	Injection site reaction
	Injection site haematoma	
	Injection site pain	
	Puncture site pain	
Injury, poisoning and procedural complications	Chest injury	Injury
	Craniocerebral injury	
	Concussion	
	Contusion	

	Eye contusion	
	Fall	
	Injury	
	Limb injury	
	Meniscus injury	
	Skin injury	
	Tendon rupture	
	Wound	
Musculoskeletal and connective tissue disorders	Intervertebral disc disorder	Intervertebral disc disorder
	Intervertebral disc protrusion	
Infections and infestations	Bacterial infection	Localised infection
	Localised infection	
	Pulpitis dental	
	Skin infection	
	Tooth infection	
	Eczema infected	
Infections and infestations	Bronchiolitis	Lower respiratory tract infection
	Bronchitis	
	Lower respiratory tract infection	
	Lung infection	
	Respiratory tract infection	
	Respiratory tract infection viral	
Nervous system disorders	Neuropathy peripheral	Neuropathy peripheral
	Peripheral sensory neuropathy	
	Toxic neuropathy	
General disorders and administration site conditions	Face oedema	Oedema
	Generalised oedema	

	Localised oedema	
	Oedema peripheral	
	Peripheral swelling	
Infections and infestations	Otitis externa	Otitis
	Otitis media	
	Otitis media acute	
	Otosalpingitis	
Infections and infestations	Pneumocystis jirovecii pneumonia	Pneumonia
	Pneumonia	
Skin and subcutaneous tissue disorders	Pruritus	Pruritus
	Pruritus generalised	
Skin and subcutaneous tissue disorders	Rash	Rash
	Rash erythematous	
	Rash generalised	
	Rash macular	
	Rash maculo-papular	
	Rash pruritic	
Infections and infestations	Rhinitis	Rhinitis
	Viral rhinitis	
Infections and infestations	Acute sinusitis	Sinusitis
	Sinusitis	
Gastrointestinal disorders	Mouth ulceration	Stomatitis
	Stomatitis	
Cardiac disorders	Sinus tachycardia	Tachycardia
	Supraventricular tachycardia	
	Tachycardia	
	Ventricular tachycardia	

Infections and infestations	Body tinea	Tinea infection
	Tinea capitis	
	Tinea infection	
	Tinea pedis	
Infections and infestations	Laryngitis	Upper respiratory tract infection
	Nasopharyngitis	
	Pharyngitis	
	Pharyngitis bacterial	
	Pharyngotonsillitis	
	Tonsillitis	
	Tracheitis	
	Tracheobronchitis	
	Upper respiratory tract infection	
	Viral upper respiratory tract infection	
Infections and infestations	Cystitis	Urinary Tract Infection
	Urinary tract infection	
Skin and subcutaneous tissue disorders	Mechanical urticaria	Urticaria
	Urticaria	
Vascular disorders	Venous thrombosis	Venous thrombosis
	Venous thrombosis limb	
Ear and labyrinth disorders	Vertigo	Vertigo
	Vertigo positional	