CELLTRION Inc.

CT-P47 3.1

A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis

7th February 2024

Statistical Analysis Plan

Final Version 1.1(A)

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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	American College of Rheumatology 20% improvement
ACR50	American College of Rheumatology 50% improvement
ACR70	American College of Rheumatology 70% improvement
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
Anti-CCP	Anti-cyclic citrullinated peptide
AST	Aspartate aminotransferase
CDAI	Clinical disease activity index
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Percent Coefficient of variation
DAS28	Disease Activity Score 28
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EOS	End-of-study
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ	Health assessment questionnaire
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IGRA	Interferon-gamma release assays
IM	Intramuscular
ITT	Intent-to-treat
IWRS	Interactive web response system
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MNAR	Missing not at random
MTX	Methotrexate
PK	Pharmacokinetic

Abbreviation	Definition
PP	Per-protocol
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SC	Subcutaneous
SD	Standard deviation
SDAI	Simplified disease activity index
SF-36	36-item short form health survey
sIL-6R	Soluble interleukin-6 receptor
SJC	Swollen joint count
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
ULN	Upper limit of normal
USA	United States of America
VAS	Visual analogue scale
WHO	World Health Organizations

1. ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of CELLTRION, Inc. (hereinafter referred to as "CELLTRION"). The clinical monitoring is being performed under contract with EastHORN, in collaboration with CELLTRION. Central lab analysis is being performed under contract with MEDICOVER, in collaboration with CELLTRION. Bioanalytical lab analysis is being performed under contract with Syneos in collaboration with CELLTRION. X-ray image analysis is being performed under contract with CLARIO, in collaboration with CELLTRION. Randomization is being performed under contract with LSK Global PS, in collaboration with CELLTRION. The data management and statistical analysis are being performed by CELLTRION.

2. INTRODUCTION

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data from CELLTRION study number CT-P47 3.1, entitled as "A Randomized, Active-Controlled, Double-Blind, Phase 3 Study to Compare Efficacy and Safety of Two Intravenous Infusion Formulations of Tocilizumab (CT-P47 and RoActemra) when Co-administered with Methotrexate in Patients with Moderate to Severe Active Rheumatoid Arthritis".

Two clinical study reports (CSRs) will be generated.

- The first CSR with available data for each patient up to Week 32. The following data will be included.

	Study Ongoing at Week 32 *	**Study Terminated prior to Week 32 administration***
Scheduled Visit	- Up to Week 32	All available data
Unscheduled Visit	On or before the date of Week 32 administration* for each patient	All available data up to the latest date of all patients' Week 32 visit date
Non-visit based data (e.g. adverse events and medications)	All available data having a start date or imputed start date on or before the date of Week 32 administration* for each patient	

* If the date of Week 32 administration is missing, or patients discontinued study drug before Week 32, the date of Week 32 visit will be used as cut-off date. For patients who skipped Week 32, planned Week 32 visit date calculate as [actual date of last scheduled visit before Week 32 (Week A) + (32-A)x7] will be used for cut-off.

- Final clinical study report with all data after completion of the study (up to Week 52)

If additional CSRs are required for regulatory or academic purposes, CSRs will be generated after the first database lock and unblinding process.

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

- Study Protocol Version 1.1 A.0 – 7th July 2022

- Unique CRF Version 2.0 – 8th July 2022

3. STUDY OBJECTIVES

Primary and secondary objectives are described as below.

3.1. Primary Objective

- To demonstrate that CT-P47 is equivalent to RoActemra, in terms of efficacy as determined by clinical response according to the change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (Erythrocyte-Sedimentation Rate [ESR]) at Week 24.

3.2. Secondary Objective

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

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

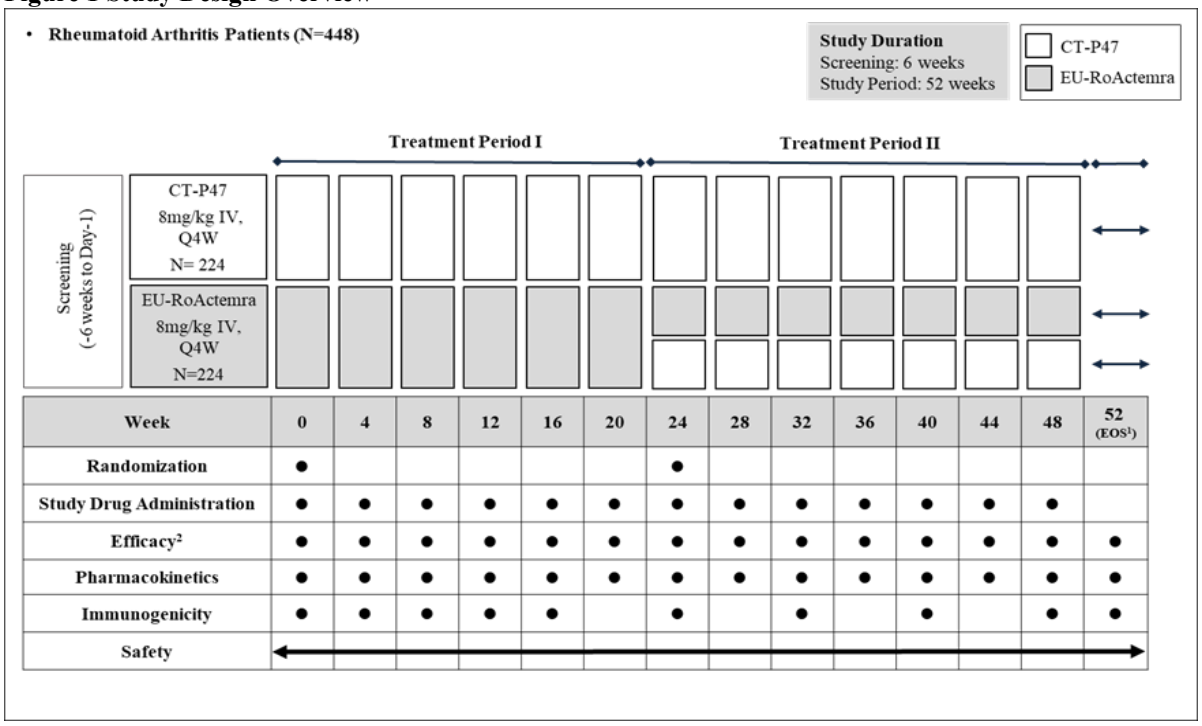
This study is a randomized, active-controlled, double-blind, multicenter, Phase 3 study designed to evaluate efficacy, PK and overall safety including immunogenicity of multiple dose (8 mg/kg, not exceeding 800 mg/dose) of either CT-P47 or RoActemra administered by intravenous (IV) infusion every 4 weeks (Q4W) in combination with MTX (between 10 to 25 mg/week, oral or parenteral; intramuscular [IM] or subcutaneous [SC] dose) and folic acid (≥ 5 mg/week, oral dose). The MTX dose and route must be maintained from the beginning to the end of the study.

Approximately 448 male and female patients with moderate to severe active RA will be enrolled in a 1:1 ratio (approximately 224 patients per treatment group) into the CT-P47 or RoActemra treatment groups.

The duration of the study will be up to 58 weeks, which includes Screening (up to 6 weeks) and the last dose at 48 weeks plus the following 4 weeks off-dose period, prior to the End-of-Study (EOS) visit.

The study design and patient assessment overview is presented in Figure 1.

Figure 1 Study Design Overview



Abbreviations: EOS, end-of-study; IV, intravenous; Q4W, every 4 weeks.
* Prior to dosing at Week 24, all patients will undergo a second randomization process. Patients who are initially randomized to RoActemra will be randomized again in a ratio of 1:1 to either continue with RoActemra or undergo transition to CT-P47. Patients who are randomized to CT-P47 or RoActemra will receive assigned study drug Q4W from Week 24 and thereafter up to Week 48.

1. The EOS assessments will be performed at Week 52 for all patients who completed or discontinued study drug. The patients who early discontinued from the study drug will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they change their RA medication (including those prohibited by the protocol).
2. An independent joint count assessor assigned to each study center will assess joint counts. If possible, it is recommended that the joint count assessments are performed independently by the same person, at each study center throughout the entire study period.

Screening Period:

Screening will take place between Day –42 and Day –1 (6 weeks), prior to the first study drug administration (Day 1). The Day 0 will not be used in the study day counting. The date immediately before the study drug administration will be counted as Day -1.

Treatment Periods:

- Treatment Period I (from Week 0 [Day 1] to Week 24 Predose)
- Treatment Period II (from Week 24 to Prior to Week 52 [EOS visit])

The study will comprise 2 treatment periods (I and II). During Treatment Periods I and II, patients will receive either CT-P47 or RoActemra 8 mg/kg (not exceeding 800 mg/dose), as per first and second randomization, by IV infusion Q4W, co-administered with MTX between 10 to 25 mg/week, oral or parenteral dose (IM or SC; dose and route must be maintained from the beginning to the EOS) and folic acid (≥5 mg/week, oral dose).

On Day 1, Week 0, patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study and randomly assigned to receive either CT-P47 or RoActemra prior to treatment.

Patients will comply with all appropriate visits and assessments that will be performed at the time points specified in the schedule of events (Appendix 1). At each visit, the patient will be questioned about AEs and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB).

Rescue therapy will be allowed to patients who meet the following criteria:

- From Week 16 and thereafter, patients who have less than a 20% improvement in both swollen and tender joint counts (of 66/68 assessed) compared to baseline may receive rescue treatment at the discretion of the investigator by initiating or increasing background RA medications (including those prohibited by the protocol). The choice of medication is at the discretion of the investigator. The patient will be discontinued from the study drug and treated according to standard of care and at the discretion of the investigator. Patients receiving rescue treatment will attend all visits until Week 52.

End-of-Study (Week 52) Visit:

An EOS visit will occur at Week 52 for all patients who completed or discontinued study drug. The patients who early discontinued from the study drug will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments, even if they change their medication (including those prohibited by the protocol).

The schedule of events is presented in Appendix 1.

5. GENERAL STATISTICAL CONSIDERATIONS

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

- Minimum and maximum will be displayed without rounding from values in the source listing.
- Mean, median, geometric mean and percent coefficient of variation (CV%) will be rounded to one more decimal place than the maximum decimal place of values in the source listing. If the minimum value from the data is zero, then the geometric mean will not be calculated. CV% will not be reported if the mean is zero.
- SD and Standard Error (SE) will be rounded to one more decimal place than mean.
- Point estimate and confidence intervals (CI) obtained from statistical procedures will be displayed with two decimal places.

Categorical data will be summarized in a frequency table showing the numbers and percentages of patients. Percentages and corresponding CIs will be rounded to one decimal place and will be suppressed when the count is zero. The denominator for all percentages will be the number of patients within each treatment group for the analysis set of interest, unless otherwise specified.

For visit-based summaries, Treatment Period I will be summarized from Week 0 (or baseline) to Week 24 and Treatment Period II will be summarized from Week 24 to EOS including baseline (as defined in Section 5.5). Unscheduled visit will not be summarized in visit-based tables, unless otherwise specified. But all data will be displayed in listings. Listings will be sorted by the treatment group, patient number, and visit, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.

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

A dry-run analysis and a Data Review Meeting (DRM) will be held prior to database lock. The main purpose of the dry-run analysis is to ensure that all outputs are prepared as expected as per the finalized SAP using whatever data presented in the current database in which the subjects be assigned to the dummy dry-run treatment group irrespective of their actual treatment. This SAP could be updated after the blinded DRM but prior to database lock.

5.1. Software

All analyses will be conducted using Statistical Analysis System (SAS®) software (SAS Institute Inc., Cary, North Carolina, United States of America [USA]) Version 9.4 or higher.

5.2. Sample Size

A sample size of 336 patients (168 patients in each treatment group of CT-P47 and RoActemra) leads to at least 85% statistical power to demonstrate equivalence of CT-P47 and RoActemra based on the two-sided 90% confidence interval for the difference of mean change from baseline of DAS28 (ESR) score at Week 24. In the sample size calculation, equivalence margin of -0.6 to +0.5, two one-sided 5% significance level, standard deviation of 1.53 and actual difference of 0 in mean change from baseline at Week 24 are assumed. The drop-out rate has been hypothesized at 25%; therefore, approximately 448 patients (224 patients in each treatment group of CT-P47 and RoActemra) will be randomized. The sample size with sufficient number of patients remaining at the time of single transition was also considered.

5.3. Randomization, Stratification, and Blinding

An interactive web response system (IWRS) will be used for the randomization. Unblinded biostatisticians will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes. The randomization numbers will be blocked, and within each block the pre-specified ratio of patients will be allocated to each treatment group. The block size will not be revealed.

Approximately 448 male and female patients with moderate to severe active RA will be enrolled in a 1:1 ratio (approximately 224 patients per treatment group) into the CT-P47 or RoActemra treatment groups.

The first randomization to treatment assignment will be stratified by the following;

- Body weight (<100 kg or ≥100kg) measured on Day 1
- Disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤ 5.1)
- Prior biologic use approved for RA treatment (yes or no)

Patients will receive CT-P47 or RoActemra Q4W up to Week 20. Prior to dosing at Week 24, patients in the RoActemra treatment group will be randomly assigned in a ratio of 1:1 to either continue with RoActemra (Cohort 2) or undergo transition to CT-P47 (Cohort 3). All patients who are initially assigned to CT-P47 treatment group at Day 1 (Week 0) will continue their treatment with CT-P47 (Cohort 1) until Week 48. Second randomization process will also be conducted in Cohort 1 prior to dosing at Week 24 to maintain the study blind.

The second randomization to Cohorts 2 or 3 will be stratified by the following:

- Disease activity by DAS28 (ESR) score at Week 20; <2.6 vs. ≥2.6

This study will be double-blind, and will remain blinded to the investigator, all designated study staff (with the exception of the unblinded study pharmacists or unblinded staffs designated to prepare the study drug for infusion and predefined unblinded teams in the sponsor and CRO), and patients until the final CSR is generated.

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated as knowing the study drug assignment is required for medical management. In such cases, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS (see study manual, which is provided as a separate document).

The date, time and reason for the unblinding must be documented in the appropriate field of the eCRF and the medical monitor will be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medical monitor and the sponsor. Any patients for whom the blind is broken may continue in the study and receive the study drug at the investigator's discretion.

For regulatory reporting purposes, the randomization code will be broken for a suspected unexpected serious adverse reaction (SUSAR) before submission, if required.

The overall randomization code will be broken only for reporting purposes. Unblinding will occur after database lock for data up to 32 weeks for all patients. The unblinded team will be pre-defined and documented prior to performing the analyses. The study will remain blinded to the investigators, patients, and pre-defined CELLTRION and CRO blinded teams until all patients have completed the study and the database has been finalized for study termination.

5.4. Analysis Sets

Analysis sets to be used in statistical analysis will be specified in related sections. The following patient analysis sets are defined: Intent-to-Treat (ITT) Set, Per-Protocol Set (PPS), Pharmacokinetic (PK) Set and Safety Set. The following analysis subsets are also defined: ITT-Treatment Period II subset, PK-Treatment Period II subset and Safety-Treatment Period II subset.

Patients who have any major protocol deviations (as defined in Section 5.6) may be excluded from related analysis sets. The relevant decision will be taken at the blinded Data Review Meeting (DRM) prior to database lock.

The ITT Set, PPS and ITT-Treatment Period II subset will be analyzed according to randomly assigned treatment. The randomized treatment group will be assigned as follows:

- CT-P47 vs. RoActemra according to randomization at Week 0
- CT-P47 Maintenance vs. RoActemra Maintenance vs. Switched to CT-P47 according to randomization at Week 24

The other sets will be analyzed by actual treatment group. The actual treatment group will be assigned according to their actual treatment, not according to the randomized group, even if there is a discrepancy between the actual treatment administered dose and the randomized group. The actual treatment groups will be defined as follows:

- CT-P47: Patients receiving at least one CT-P47 in Treatment Period I
- RoActemra: Patients receiving only EU-RoActemra in Treatment Period I
- CT-P47 Maintenance: Patients receiving at least one CT-P47 in Treatment Period I and any study drugs in Treatment Period II
- RoActemra Maintenance: Patients receiving only EU-RoActemra in both Treatment Period I and Treatment Period II
- Switched to CT-P47: Patients receiving only EU-RoActemra in Treatment Period I and at least one CT-P47 in Treatment Period II

The number of patients in each analysis set will be tabulated by the treatment group. A listing will also be produced displaying data on ITT Set, unless otherwise specified.

5.4.1. Intent-to-Treat (ITT) Set

The ITT Set is defined as all patients randomly assigned to receive study drugs (CT-P47 or RoActemra) at Day 1 (Week 0).

5.4.2. ITT-Treatment Period II subset

The ITT-Treatment Period II subset is defined as all patients in ITT Set who are randomly assigned to receive study drug (CT-P47 or RoActemra) prior to dosing at Week 24.

5.4.3. Per-Protocol Set (PPS)

The PPS is defined as all randomly assigned patients who are compliant with therapy (defined to be ≥80% of planned cumulative doses up to Week 20) and have a DAS28 (ESR) assessment at baseline and Week 24 and do not have any major protocol deviation affecting primary efficacy endpoint. The planned cumulative doses will be calculated using a planned dose of 8mg/kg. If the body weight is not evaluated at the visit, the last measured body weight will be used for planned dose calculation. Patients who received rescue therapy before Week 24 will be excluded. Final determinations of the PPS will be made at the blinded data review meeting (DRM) for the primary efficacy endpoint before unblinding.

5.4.4. Pharmacokinetic (PK) Set

The PK Set is defined as all randomly assigned patients who receive at least 1 full 8 mg/kg dose of study drug (CT-P47 or RoActemra) and who have at least 1 post-treatment PK result. If any patient is found to be non-compliant with respect to dosing, a determination of the PK Set will be made on a case-by-case basis at the blinded DRM.

5.4.5. PK-Treatment Period II subset

The PK-Treatment Period II subset will consist of all patients in PK set who receive at least 1 full 8 mg/kg dose of either of study drug (CT-P47 or RoActemra) and have at least 1 post-treatment PK result at or after Week 24.

5.4.6. Safety Set

The Safety Set is defined as all randomly assigned patients who receive at least 1 dose (full or partial) of study drug (CT-P47 or RoActemra).

5.4.7. Safety-Treatment Period II subset

The Safety-Treatment Period II subset will consist of all patients in Safety Set who receive at least 1 dose (full or partial) of study drug (CT-P47 or RoActemra) at or after Week 24.

5.5. Definition of Baseline

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

5.6. Protocol Deviations

Protocol deviation will be categorized as “major” or “minor”. Category of protocol deviation will be identified during the DRM. A major protocol deviation is one that may affect the interpretation of study results or the patient’s rights, safety, or welfare. CELLTRION will identify major protocol deviation prior to database lock, and it will be discussed during the blinded DRM.

Major protocol deviations and analysis sets to be excluded are defined as follow (but not limited to):

- Mis-randomization (defined as patients who received the opposite treatment to which they were assigned at any point during the study):
  - up to Week 20: PPS, PK Set
  - on or after Week 24: PK-Treatment Period II subset
- Non-adherence to Inclusion or Exclusion criteria, which may affect the interpretation of study results of primary efficacy endpoint: PPS
- Significant ICH GCP non-compliance: All Sets
- Receipt of prohibited therapy (as defined in CT-P47 3.1 Protocol Section 5.9) before Week 24 without study drug discontinuation which may affect the interpretation of study results of primary efficacy endpoint (based on agreement of each as from both medical monitor and CELLTRION prior to database lock): PPS

The major protocol deviations and other categories used for exclusion will be summarized for ITT Set by treatment group and mis-randomization on or after Week 24 will also be presented for ITT– Treatment Period II subset. A listing of major protocol deviations for each patient will also be provided by treatment group.

5.7. Outliers

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

6. PATIENT DISPOSITION

The number of patients who were screened and failed at screening will be displayed along with the primary reason for screening failure on the ‘Eligibility Criteria’ page of eCRF. A patient will be considered to be enrolled if the patient is successfully screened.

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

- Inclusion/Exclusion Criteria not met
- Subject withdrew consent
- Other

A listing of patients for eligibility criteria will be provided.

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

Patient disposition will be listed for the ITT Set by treatment group and defined as follows:

- Randomized: The randomized ID is recorded on ‘Randomization’ eCRF page at Day 1 (Week 0) and at Week 24 for each Treatment Period.

- Treated in Treatment Period I: A patient will be considered to have been treated in the Treatment Period I if it is recorded as at least one 'Yes' to 'Was study drug administered?' on the 'Study Drug Administration' page of the eCRF from Week 0 to Week 20.
- Treated in Treatment Period II: A patient will be considered to have been treated in the Treatment Period II if it is recorded as at least one 'Yes' to 'Was study drug administered?' on the 'Study Drug Administration' page of the eCRF on or after Week 24.
- Discontinued the Study Drug: A patient will be considered to have discontinued the study drug if it is recorded that the patient did not complete the study drug administration ('No' box checked) on the 'Study Drug Discontinuation' page of the eCRF. If the patient has been assigned with study drug at 2nd randomization and discontinued the study drug after the 2nd randomization, the patient will be considered to have discontinued the study drug in the Treatment Period II, whereas if discontinuation of study drug occurred before 2nd randomization, the patient will be considered to have discontinued the study drug in Treatment Period I.
- Completed the Study Drug: Conversely, a patient will be considered to have completed the study drug if it is recorded that the patient did complete the study drug administration ('Yes' box checked) on the 'Study Drug Discontinuation' page of the eCRF.
- Terminated from the Study: A patient will be considered to have terminated from the study if it is recorded that the patient did not complete the EOS visit ('No' box checked) on the 'Study Termination' page of the eCRF. If the patient has been assigned with study drug at 2nd randomization and terminated the study on or after 2nd randomization, the patient will be considered to have terminated the study in the Treatment Period II, whereas if terminated of study occurred before 2nd randomization, the patient will be considered to have terminated the study in Treatment Period I.
- Completed the Study: Conversely, a patient will be considered to have completed the study if it is recorded that the patient completed the EOS visit ('Yes' box checked) on the 'Study Termination' page of the eCRF.

The number and percentage of patients who discontinued the study drug in each period will be presented by primary reason for study drug discontinuation and treatment group. The number and percentage of patients who were terminated from the study in each period will also be displayed by reasons for study termination and treatment group. Summaries will be provided for the ITT Set and for the ITT-Treatment Period II subset by treatment group. The reasons for study drug discontinuation will be displayed using the following categories and ordering:

- Inadequate efficacy (including disease progression) in the judgement of the investigator
- Adverse Event
- Significant protocol deviation(s).
- Lost to follow-up.
- Investigator's decision.
- Withdrawal by subject
- Pregnancy
- Other

Reasons for study termination will be displayed using the following categories and ordering:

- Withdrawal by subject
- Lost to follow-up
- Adverse Event
- Other

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

7. DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1. Demographics and Stratification Details

The following demographic measures and baseline characteristics will be summarized for the ITT Set and ITT-Treatment Period II subset: age (years); gender (male, female); Female Fertility Status (pre-menarche, surgically sterilized, post-menopausal, potentially able to bear children); race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, not allowed by investigator country regulations, other); ethnicity (Hispanic or Latino, non-Hispanic or non-Latino, unknown); height (cm) at Screening; weight (kg) at Screening.

The stratification factors for the first randomization, body weight (<100 kg or ≥100kg) measured on Day 1, disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤ 5.1) and prior biologic use approved for RA treatment (yes or no) will be summarized for the ITT Set by treatment group. The stratification factor for the second randomization, disease activity by DAS28 (ESR) score at Week 20 (<2.6 vs. ≥2.6) will be summarized for the ITT-Treatment Period II subset. If there is a difference for data entered between IWRS and eCRF, the stratification factors will be summarized using the final data collected on the eCRF.

Demographics and stratification details will be listed for the ITT Set by treatment group.

7.2. Hepatitis B and C and Human Immunodeficiency Virus Test

At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (total or IgG) will be assessed in all patients as specified in Appendix 1.

If a patient has HBsAg (negative), HBsAb (negative or positive), and HBcAb (positive), a HBV DNA test will be performed at Screening. For patients who are enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, HBV DNA will be performed at the Week 24 and EOS visits.

Hepatitis C antibody and HIV will be assessed at Screening in all patients. If hepatitis C or HIV test result is positive, the patient will be excluded from the study.

Hepatitis B/C and HIV test results at baseline will be summarized by treatment group for the ITT Set. If confirmatory test is conducted, the result of the confirmatory test will be used for the summary. All collected results will be listed for the ITT Set by treatment group.

7.3. Medical History

Medical history is captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA version 24.1 or higher). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) for the ITT Set and ITT-Treatment Period II subset. The total number of medical history and the number and percentage of patients with at least one medical history will also be presented in the table by treatment group. Medical history will also be listed for the ITT Set by treatment group.

7.4. Rheumatoid Arthritis History

Rheumatoid arthritis (RA) history is captured at Screening and is based on the Rheumatoid Arthritis Classification Criteria 2010 (Aletaha *et al.*, 2010). The summary for each RA criterion and time since RA diagnosis will be tabulated for the ITT Set and ITT-Treatment Period II subset by treatment group.

Time (years) since RA diagnosis will be calculated as [(date of the first study drug administration – date of RA diagnosis)/365.25]. If an incomplete date of RA diagnosis is recorded for a patient, the date will be imputed using the latest possible date as below.

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

If the imputed date is later than the first administration date of study drug, it will be imputed using the first administration date of study drug. If the whole date is missing, time since RA diagnosis will not be calculated. RA history will also be listed for the ITT Set by treatment group. Time (years) since RA diagnosis will be displayed to two decimal places.

7.5. American College of Rheumatology (ACR) revised criteria

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

Table 1 American College of Rheumatology Revised Criteria of Functional Status

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

Note: Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.
Reference: Hochberg *et al*., 1992.

ACR revised criteria assessment data will be tabulated for the ITT Set and ITT-Treatment Period II subset by treatment group. All collected results will also be listed for the ITT Set by treatment group.

7.6. Rheumatoid Factor (RF) and Anti-Cyclic Citrullinated Peptide (Anti-CCP)

Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (Anti-CCP) will be assessed at Screening. RF and Anti-CCP will be summarized displaying descriptive statistics and listed for the ITT Set and ITT-Treatment Period II subset by treatment group.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS visit (Week 52), will be recorded in both the source documents and the eCRF. Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug will be recorded until EOS visit in both the source documents and the eCRF. All medications will be coded according to the World Health Organization drug dictionary (WHO Drug Dictionary September 2021 or later version).

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

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

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

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

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

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

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

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

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

- Example 1:
  Medication start: UNJUN2021
  Medication stop: 20OCT2021
  Date of first study drug administration: 16OCT2021
  Medication start imputed: 01JUN2021
- Example 2:
  Medication start: UNOCT2021
  Medication stop: 20OCT2021
  Date of first study drug administration: 16OCT2021
  Medication start imputed: 16OCT2021
- Example 3:
  Medication start: UNOCT2021
  Medication stop: 20OCT2021
  Date of first study drug administration: 24OCT2021
  Medication start imputed: 20OCT2021

A prior medication is defined as following, and all other medications will be defined as concomitant medication.

- A medication having actual/imputed stop date of medication before date of the first study drug administration, or
- A medication checked as yes to "If stop date is unknown, was this drug stopped before the first administration of study drug (Day 1)?" on eCRF.

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

The prior medications will be summarized by treatment group, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and PT along with the total number of prior medications and the number and percentage of patients with at least one prior medication. The summary of prior medications will be conducted on the Safety Set by treatment groups. When ATC Level 2 for drug class is not available, Level 1 will be used instead. Similar table will be provided separately for:

- Prior biologics for RA (Safety Set) by medical review
- Concomitant medications in Treatment Period I (Safety Set)
- Concomitant medications in Treatment Period II (Safety-Treatment Period II subset)
- Concomitant medications in Overall Period (Safety Set)
- Rescue therapy in Treatment Period I (Safety Set)
- Rescue therapy in Treatment Period II (Safety-Treatment Period II subset)
- Rescue therapy in Overall Period (Safety Set)

Note: Concomitant medications will be summarized, including medications collected after study drug discontinuation regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation.

All prior and concomitant medications will be listed separately by treatment group for the ITT Set. Information of rescue therapy and prior biologics will also be provided.

8.1.1. Co-administration of Methotrexate and Folic Acid

Data on co-administration of methotrexate and folic acid will be collected separately from all other medications. The same rules for date imputation will apply. The number of patients with administration of methotrexate or folic acid will be summarized. The methotrexate dose (mg/week) at the first study drug administration of each treatment period, at Week 12 and at Week 24 will also be summarized using descriptive statistics.

All summaries for co-administration of methotrexate and folic acid will be based on the Safety Set for Treatment Period I and the Safety-Treatment Period II subset for Treatment Period II and presented by treatment group.

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

8.2. Exposure to Study Drug

The number and percentage of patients with dose administered will be summarized by treatment group at each scheduled dose week, along with the number and percentage of patients by planned dose per body weight (mg/kg). Descriptive statistics of actual dose per weight (mg/kg) will be summarized by treatment group and visit. If the body weight is 100kg or more, the actual dose per weight (mg/kg) will be calculated based on 800 mg (maximum dose per protocol). For patients who are not administered study drug, the number and percentage of patients with each reason why the dose was not administered will be displayed by visit. In addition, descriptive statistics for the total number of doses received and total amount of study drug received will be summarized by treatment group for Treatment Period I on the Safety Set, and Treatment Period II on the Safety-Treatment Period II subset.

A listing will be provided by treatment group for the ITT Set showing the details of study drug administration. This will include all data collected. The prescribed dose per weight (mg/kg) and actual dose per weight (mg/kg) will be displayed to two decimal places in the listing.

9. EFFICACY ANALYSIS

Change from baseline in DAS28 (ESR) at Week 24 is the primary efficacy endpoint. The primary efficacy analysis will be conducted on the ITT Set, and a supportive analysis for the primary efficacy endpoint will be conducted using the PPS. Sensitivity analysis using tipping point approach will be conducted on the ITT Set.

The efficacy endpoint applies treatment policy estimand. For treatment policy estimand, all available data will be included in the efficacy analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation. Estimand attributes for primary efficacy analysis are described in Table 2.

Table 2 Estimand Attributes for Primary Efficacy Analysis

Primary Estimand	
Treatment Condition	Assigned treatment (CT-P47 or reference drug [RoActemra]) by randomization during Treatment Period. Rescue therapy and prohibited medications (Section 5.8, Section 5.9 of the protocol, each) will be considered.
Population	Target population: Patients with moderate to severe RA satisfying the inclusion and exclusion criteria, as defined in Section 4.1 of the protocol. Analysis population: All patients in ITT Set#
Endpoint	Change from baseline in DAS28 (ESR) at Week 24
Intercurrent event and strategy	Study drug discontinuation, switch to rescue therapy or protocol violation will be considered as intercurrent event. (Additional intercurrent event will be discussed during the blinded DRM if necessary.) The efficacy endpoint applies treatment policy strategy. Under the treatment policy, whether an intercurrent event has occurred or not is irrelevant, the data will be collected and analyzed regardless. Therefore, intercurrent events will not be considered in the primary efficacy analysis.
Population-level summary	Mean difference of the primary endpoint between treatment groups (CT-P47 minus RoActemra) with Multiple Imputation (MI) under the Missing At Random (MAR) assumption for missing data handling
Supplementary Estimands for Primary Efficacy Analysis	
All attributes as in primary estimand with the following difference. Analysis population: All patients in PP Set#.	
Sensitivity Estimand for Primary Efficacy Analysis	
A tipping point analysis under the Missing Not At Random (MNAR) assumption will be conducted to assess the robustness of the primary efficacy analysis or the impact of missing data. All estimand attributes as in primary estimand, will be applied.	

#: Specific definitions for analysis set are described in Section 5.4.

All other efficacy endpoints will be summarized for Overall Period on the ITT Set, Treatment Period I on the PPS, and Treatment Period II on the ITT-Treatment Period II subset, unless otherwise specified. All efficacy listings will be based on the ITT Set.

9.1. Disease Activity Score 28 (DAS28)

DAS28 (ESR) for the primary efficacy endpoint, will be derived according to Section 9.1.4 and analyzed according to Section 9.1.4.1. Section 9.1.1 through Section 9.1.3 describe the components required for DAS28 calculation. When the DAS28 (ESR) assessment at Week 20 for the 2nd randomization is not performed, the DAS28 (ESR) result at Week 24 will be used for the 2nd randomization.

9.1.1. Number of Tender/Swollen Joints

The number of tender and swollen joints will be assessed with a total of 28 joints for tenderness and 28 joints for swelling. However, any joint injected with intra-articular corticosteroids or that has undergone any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will be excluded from assessment. The prorated tender joints will be calculated as (the number of tender joints / the number of evaluable joints) × 28, and it will be used in summary table and calculation of DAS28, Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) scores and ACR/EULAR Remission (Boolean-based definition). The same method will be applied to the number of swollen joints.

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

patient and visit, showing number of tender and swollen joints by category. The prorated tender/swollen joint counts will be displayed to two decimal places.

9.1.2. Visual Analogue Scale (VAS)

The VAS range is from 0 to 100 mm, with higher scores indicating poorer status or more severe pain (therefore an improvement in status or pain is reflected by a decrease in VAS). A VAS is used to record the Patient's Global Assessment of Disease Activity, the Patient's Assessment of pain and the Physician's Global Assessment of Disease Activity at each scheduled visit.

For these scales, descriptive statistics for actual value and change from baseline will be presented at each scheduled visit using the VAS standardized result automatically calculated in the eCRF system based on the VAS result (mm) and the total length of VAS scale on the questionnaire. A listing will also be provided showing VAS measurements along with the change from baseline.

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

The descriptive statistics for actual value and change from baseline will be presented for both CRP and ESR by treatment group at each scheduled visit. CRP and ESR will be listed along with the other DAS28 components on ITT Set.

9.1.4. Disease Activity Score 28 (DAS28)

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

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

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

Where:

- TJC28 = Tender Joint Count (0-28)
- SJC28 = Swollen Joint Count (0-28)
- ESR = ESR measurement (mm/h)
- CRP = CRP measurement (mg/L)
- GH = patient's global disease activity measured on VAS (0-100 mm)

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

9.1.4.1. Primary Analysis

The difference of mean change from baseline of DAS28 (ESR) at Week 24 will be analyzed on the ITT Set using an ANCOVA model with Multiple imputation (MI) under the Missing At Random (MAR) assumption for missing data handling. Missing values will be imputed using regression method with treatment, body weight (<100 kg or ≥100 kg) measured on Day 1 and

baseline DAS28 (ESR) score and prior biologic use approved for RA treatment (yes or no) as covariates. The 100 imputed datasets will be created. These multiple imputed datasets are then analyzed by using ANCOVA with treatment as a fixed effect and body weight (<100 kg or ≥100 kg) measured on Day 1, baseline DAS28 (ESR) score and prior biologic use approved for RA treatment (yes or no) as covariates. The results from each set of imputed datasets will then be pooled using PROC MIANALYZE procedure in SAS®, aggregating the results for the final statistical inference using Rubin's method.

Pooled least squares mean and corresponding standard error (SE) of the mean change from baseline in DAS28 (ESR) at Week 24 will be presented for each treatment group. A point estimate and two-sided 90% confidence interval (CI) for the difference between the 2 treatment groups (CT-P47 and RoActemra) will also be provided. Therapeutic equivalence of treatment difference in the change from baseline of DAS28 (ESR) at Week 24 will be concluded if the 90% CIs for the treatment difference is entirely within -0.6 to 0.5.

In addition, a supportive analysis for the primary efficacy endpoint will be conducted on the PPS. However due to the definition of PPS (as defined in Section 5.4.3), MI cannot be performed under PPS, so in the case of supportive analysis, only ANCOVA will be performed without MI.

9.1.4.2. Sensitivity Analysis

A tipping point analysis under the Missing Not At Random (MNAR) assumption will be conducted for the primary efficacy endpoint in the ITT Set in order to assess the robustness of the primary efficacy analysis or the impact of missing data. Tipping point analyses are conducted under MNAR (Missing Not at Random) assumption shifting gradually from the imputed values by treatment groups. A 90% CI for the treatment difference will be obtained from ANCOVA under these scenarios, and the scenario which the confidence interval no longer be included in the equivalent margin of -0.6 to 0.5 will be displayed. All the scenarios and corresponding CIs will be provided.

9.2. ACR20, ACR50, ACR70 Criteria and Hybrid ACR

9.2.1. Number of Tender/Swollen Joints

The number of tender joints and number of swollen joints will be assessed, with a total of 68 joints assessed for tenderness, and 66 joints assessed for swelling. This assessment is performed independently of the assessment of 28 tender/swollen joints for the DAS28. Similar to the number of tender/swollen joints for the DAS28, the number of tender joints counted among the evaluable joints will be adjusted to (the number of tender joints / the number of evaluable joints) × 68, and it will be used in summary table and evaluation of ACR response. The same method with the exception of multiplying by 66 instead of 68 will be applied to the number of swollen joints. Descriptive statistics for actual value and change from baseline for both the number of tender joints and the number of swollen joints will be presented at each scheduled visit. A listing will be provided by patient and visit, showing the number of tender and swollen joints, along with the change from baseline and percent change from baseline. The prorated tender/swollen joint counts will be displayed to two decimal places.

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

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

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

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

There are 3 steps to scoring the HAQ:

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

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

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

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

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

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

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

9.2.3. ACR20, ACR50 and ACR70 Criteria

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

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

- At least 20% decrease from baseline in the number of tender and swollen joints, and
- At least 20% decrease from baseline on three of the following:
  - Patient's assessment of pain (VAS, 0-100 mm)
  - Patient's global assessment of disease activity (VAS, 0-100 mm)
  - Physician's global assessment of disease activity (VAS, 0-100 mm)
  - HAQ estimate of physical ability
  - Serum CRP (mg/dL) concentration or ESR (mm/h)

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

The following categories of patients are considered non-responders:

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

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

The proportion of patients achieving clinical response according to the criteria for ACR20, ACR50 and ACR70 will be summarized at each scheduled visit. The denominator will be the number of patients within each treatment group for the analysis set of interest. A listing will be provided by treatment group and visit, showing ACR20, ACR50 and ACR70 responder status at each visit.

9.2.4. Hybrid ACR

The hybrid ACR is an outcome measure that combines ACR20, ACR50, and ACR70 and a continuous score of the mean improvement in core set measures (tender joint count, swollen

joint count, physician's global assessment of disease activity, patient's global assessment of disease activity, patient's assessment of pain, HAQ and CRP [or ESR]).

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

The steps to calculate the hybrid ACR are as follows:

(1) For each core set measure, calculate improvement percentage as 100×(baseline score – post-baseline score)/(baseline score).
(2) If a core set measure worsened by >100%, that improvement percentage is set to -100%.
(3) Mean % change is the average of the improvement percentage for all core set measures.
(4) The hybrid ACR score is determined from the following table. ACR20, ACR50, or ACR70 status of the patient (left column) is taken, along with the mean % change in core set items calculated in step (3); the hybrid ACR score is where they intersect in the table.

Table 4 Scoring Method for the Hybrid ACR

ACR Status	Mean % Change in Core Set Measures			
	<20	≥20, <50	≥50, <70	≥70
Not ACR20	Mean % change	19.99	19.99	19.99
ACR20 but not ACR50	20	Mean % change	49.99	49.99
ACR50 but not ACR70	50	50	Mean % change	69.99
ACR70	70	70	70	Mean % change

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

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

9.3. EULAR Response Criteria

The European Alliance of Associations for Rheumatology (EULAR) response criteria categorize the DAS28 response (i.e., good, moderate, or none) based on changes in DAS28 from baseline.

Table 5 European Alliance of Associations for Rheumatology Criteria

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

Abbreviations: DAS28, disease activity score 28.
Reference: Fransen and van Riel 2005

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

9.4. Clinical Disease Activity Index and Simplified Disease Activity Index

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

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

Where:

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

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

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

9.5. ACR/EULAR Remission (Boolean-based definition)

ACR/EULAR remission will be evaluated using the Boolean-based definition. Patient must satisfy all of the following:

- Tender joint count ≤ 1 (of 28 assessed)
- Swollen joint count ≤ 1 (of 28 assessed)
- CRP ≤ 1 mg/dL
- Patient’s global assessment of disease activity (VAS) ≤ 1 (when converted to 0-10 cm)

Note: Prior to calculation of the ACR/EULAR remission, the PGA on VAS results should be converted from ‘mm’ to ‘cm’.

Frequencies and percentages of ACR/EULAR remission will be presented at each scheduled visit. The ACR/EULAR remission categories will be listed in the DAS28 listing.

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

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

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

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

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

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

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

9.7. Joint Damage Progression

Joint damage progression based on radiographic evaluations (1 image of both the right and left hands and both the right and left feet, a total of 4 images) will be assessed by the change in the total Sharp score using the modified total Sharp scoring (mTSS) system (Plant *et al.*, 1994; Sharp *et al.*, 1971; Sharp *et al.*, 1985) at each scheduled visit.

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

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

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

The maximum erosion score is 170 for hands and 60 for feet, and the maximum JSN score is 128 for hands and 40 for feet. The total sharp score is the sum of the erosion score (from 0 to 230 for both hands and feet) and the JSN score (from 0 to 168 for both hands and feet), thus it ranges from 0 to 398. At least two independent readers will produce scores at each visit for each patient. Cases that require adjudication will be identified once the two primary independent readings are completed.

Descriptive statistics for actual value and change from baseline will be presented for total sharp score by treatment group and visit. The summary will be only conducted for Overall Period for final CSR. Raw scores for each joint will be listed by treatment group, visit. In addition, total scores, subtotal scores and change from baseline will be listed on the ITT Set.

9.8. Joint Surgery

A listing will be produced displaying patients undergoing any surgical 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 24.1 or the higher version) and the procedure date along with flag for patients who receive joint surgery or synovectomy before Week 24 without study drug discontinuation.

10. PHARMACOKINETIC ANALYSIS

All pharmacokinetic (PK) analyses for Treatment Period I will be performed on PK Set and data for Treatment Period II will be summarized on the PK-Treatment II subset by treatment group.

Blood samples for PK analysis will be collected prior to dosing at the scheduled time points specified in Appendix 1. If the PK blood sample is unable to be analyzed or is missing, extra blood samples collected for immunogenicity assessment at the same time point can be used for PK assessment.

Below the lower limit of quantification (BLQ) values that occur prior to first study drug administration will be treated as zero (0), and all other BLQ values will be treated as missing.

Serum concentrations will be summarized by treatment group at each time point, using descriptive statistics (n, mean, SD, CV%, geometric mean, minimum, median and maximum). If the minimum value from the data is zero, then the geometric mean will not be calculated.

Individual serum concentrations, scheduled visit and actual serum collection time will be presented in a data listing in the PK Set. All concentrations on the BLQ will be indicated in the data listing.

11. SAFETY ANALYSIS

Safety data for Treatment Period I will be summarized on the Safety set, safety data for Treatment Period II will be summarized on the Safety-Treatment Period II subset by each treatment group, and all safety data will be listed for the Safety Set unless otherwise stated. The safety endpoints will be evaluated under a treatment policy estimand, and for AESI, evaluation will be under both 'treatment policy estimand' and 'while on treatment' estimand. For the treatment policy estimand, all available data will be included in the safety analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation. For the 'while on treatment' estimand, only collected data until a fixed timepoint after permanent treatment discontinuation will be included. The fixed timepoint is defined as the earliest of the following events.

- 28 days after last study drug administration
- Start date of rescue therapy
- Date of EOS (Week 52)

- Start date of any other intercurrent event: Intercurrent event is defined as events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest. Intercurrent event will be discussed during the blinded DRM.

11.1. Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a patient associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product. This includes any event that is new in onset or has aggravated in intensity or frequency compared with baseline. All AEs will be coded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher and will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug. This includes any occurrence that is new or aggravated in intensity or frequency from the baseline condition.

For the purpose of inclusion in TEAE tables, incomplete AE start and stop dates will be imputed as follows:

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

- Missing day (e.g. XXAPR2022): Assume the last day of the month. (e.g. 30APR2022)
- Missing day and month (e.g. XXXXX2022): Assume December 31st. (e.g. 31DEC2022)
- Missing day, month and year (e.g. XXXXXXXXX): Leave it as Missing.

In case of death, if the imputed stop date is after the date of death, the stop date will be imputed as the date of death.If the start date of an AE is partial or missing the following rules will be

applied. If the stop date of the AE is partial, imputed stop date will be used instead of reported stop date.

- If the day of an Adverse Event is missing (e.g. XXAPR2022), the month and year of the partial date will be compared to the date of the first study drug administration.
  - 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 study drug administration, and (ii) the end date of the AE.
  - If the month and year are not equal, the AE start date will be imputed as the first day of the month (e.g. 01APR2022).
- If the day and month is missing (e.g. XXXXX2022), the year of the partial date will be compared to the date of the first study drug administration.
  - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first study drug administration, and (ii) the end date of the AE.
  - If the year is not equal, start date will be imputed as the 1st of January of the partial date year (e.g. 01JAN2022).
- 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 study drug administration, and (ii) the end date of the AE.

TEAEs will be summarized for Treatment Period I on the Safety Set, Treatment Period II on Safety-Treatment Period II subset, and Overall Period on Safety Set. TEAEs for Treatment Period I and Treatment Period II will be classified as follows:

- Treatment Period I: TEAEs with an actual/imputed start date prior to the first study drug administration in Treatment Period II, or TEAEs for those patients who did not administer study drug during Treatment Period II will be included.
- Treatment Period II: TEAEs with an actual/imputed start date on or after the date of first study drug administration in Treatment Period II will be included.

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

All AEs will be listed for Safety Set including the following information: SOC, PT and Verbatim term; start and stop date/time; treatment period (Treatment period I, Treatment Period II), time to occurrence [calculated as (AE start date – first date of study drug administration +1)] (only for TEAE); AE duration [calculated as (AE stop date – AE start date +1)];TEAE flag, intensity (CTCAE Grade 1 to 5); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); relationship with study drug (unrelated, possible, probable, definite); action taken with study drug (dose not changed, drug interrupted, dose decreased, drug withdrawn); any treatment received (no, medication, non-medication treatment, both medication and non-medication treatment); Serious Adverse Event (SAE) flag and adverse event of special interest (AESI) flags; While on treatment flag. If the start or stop date of AE is incomplete or unknown, time to occurrence and AE duration will not be calculated.

11.1.1. Incidence of Treatment-Emergent Adverse Events

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

In addition, TEAEs with PT reported for at least 3% of incidence rate in any treatment group will be summarized separately.

11.1.2. Deaths

All patients who have a serious adverse event (SAE) with serious criteria of "Death" will be presented in a listing and the following variables will be included; date of first/last administration, date of last visit, date of death, time to death from first/last administration, days on study, treatment period (Treatment period I, Treatment Period II), TEAE flag, SOC/PT, cause of death, whether an autopsy was performed (yes, no), whether a death certificate was completed (yes, no), relationship to the study drug. Time (days) to death from the first/last administration will be calculated as (date of death – date of first/last administration + 1).

11.1.3. Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose: result 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.

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

All SAEs will be listed including a subset of the variables detailed in Section 11.1. Serious criteria and SAE description will be presented in an additional information listing.

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

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

11.1.5. Treatment-Emergent Adverse Events of Special Interest

The TEAEs of special interest are as following:

- Infection
  - AEs coded with a SOC of 'Infections an Infestations' will be included.
- Hypersensitivity, including anaphylaxis
  - TEAEs checked as Hypersensitivity/anaphylaxis in the eCRF will be included. Anaphylaxis will be reviewed by medically according to Sampson criteria (Sampson *et al.*, 2006).
- Hepatic event
  - SMQ Hepatic disorder (narrow)
- Hemorrhage (medically significant bleeding events)
  - SMQ Hemorrhage terms (narrow) (excluding laboratory terms).
- Gastrointestinal perforation
  - SMQ GI perforation (narrow) followed by medical review
- Malignancy
  - SMQ Malignant or unspecified tumours (narrow)
- Demyelinating disorder
  - SMQ Demyelination (narrow)

TEAEs of each special interest will be summarized in separate tables. These are displayed by treatment group, SOC, PT, relationship and intensity, displaying number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TEAESI over all SOCs will also be displayed, and incidence rate and its difference between treatments arms will be presented along with their 95% CIs.

TEAEs classified as hypersensitivity, including anaphylaxis will be presented in separate listings including a subset of the variables detailed in Section 11.1. Additional information about experienced signs and symptoms for TEAEs classified as hypersensitivity, including anaphylaxis will be presented in separate listing. AESIs will be flagged in listing for AEs.

Additionally, the summary will be repeated in a separate table for TEAESI under the 'while on treatment' estimand. AESIs under the 'while on treatment' estimand will be flagged in listing for AEs.

11.2. Clinical Laboratory Evaluations

Blood and urine samples for clinical laboratory assessments will be collected at each scheduled visit specified in Appendix 1.

The following clinical laboratory assessment will be performed:

Clinical chemistry: Total protein, serum bilirubin (total, direct), alanine aminotransferase (ALT), artate aminotransferase (AST), alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, magnesium, lactate dehydrogenase, total cholesterol,

triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, Creatine kinase, Creatine kinase-MB, CRP, uric acid and creatinine clearance (only at screening for inclusion).

Hematology: Hematocrit, hemoglobin, red blood cells, total and differential white blood cell count, ESR, ANC, and platelet count.

Urinalysis: Bilirubin, blood, color, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen.

Summary of laboratory parameters will be based on the results from the central laboratory, except for ESR where the results analyzed by the local laboratory will be used in the summary. However, the listing will display all results analyzed by the central and local laboratories on the Safety Set.

Actual value and change from baseline for numeric laboratory parameters will be summarized by treatment group, parameter and scheduled visit using descriptive statistics (n, mean, SD, median, minimum, and maximum).

For laboratory parameters, shift tables from baseline will be generated using "Normal" or "Abnormal" classification by each scheduled visit. The number and percentage of patients will be displayed for post-baseline visits by treatment group, laboratory category, test parameter and visit.

Some laboratory parameters will be labeled with a CTCAE term, and grading will be applied to post-baseline values where possible according to CTCAE v5.0. Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. If different grades share the same criteria due to exclusion of clinical input, lower grade will be used. The CTCAE terms and ranges for applicable parameters are listed in Appendix 2. The CTCAE grades for this analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a patient does not satisfy any CTCAE grade, it will be classified as "No Grade".

The number and percentage of patients by laboratory category, CTCAE term and CTCAE grade will be summarized using the most severe grade after first study drug administration for each treatment period and for Overall Period. The most severe grade will be selected for all postbaseline results including unscheduled visits and EOS. For the summary in Treatment Period I and Treatment Period II, following results will be used:

- Treatment Period I: All post-baseline collected on or after the first study drug administration in Treatment Period I, or post-baseline of those patients who did not administer study drug during Treatment Period II will be included.

- Treatment Period II: All post-baseline collected after the first study drug administration in Treatment Period II will be included.

Clinical chemistry, hematology and urinalysis data will be presented in separate listings along with interpretation (Normal, Abnormal, High or Low), if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters.

11.3. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart and respiratory rate and body temperature) and weight will be measured at each scheduled visit specified in Appendix 1.

Actual values and change from baseline for vital signs and weight, except for hypersensitivity monitoring results, will be summarized by treatment group at each visit using descriptive statistics (n, mean, SD, median, minimum and maximum). Individual vital sign measurements and body weight, except for hypersensitivity monitoring, will be presented in a data listing.

11.4. Hypersensitivity Monitoring

For hypersensitivity monitoring, additional vital signs (including systolic and diastolic blood pressure, heart and respiratory rate and body temperature) will be performed at the following time points as specified in Table 6.

Table 6 Schedule of Assessments for Hypersensitivity Monitoring

Time points	Window
Before beginning of the study drug administration	Within 15 minutes
1 hour after the end of the study drug administration	± 15 minutes

Clinically notable hypersensitivity results of each parameter will be summarized by treatment group at each time point. The criteria for clinically notable results are defined as below.

Table 7 Criteria for Clinically Notable Results

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

In addition, any type of ECG will be performed for hypersensitivity monitoring 1 hour (±15 minutes) after the end of the study drug administration.

Individual vital sign measurements and electrocardiograms (ECG) for hypersensitivity monitoring will be presented in a data listing. High and low flags will be included in this listing to show whether a hypersensitivity result is outside of the clinically notable ranges.

11.5. Electrocardiograms

Twelve-lead electrocardiograms (ECG) will be performed at each scheduled visit specified in Appendix 1 and if the patient have signs and symptoms of hypersensitivity or other cardiac origin during the study drug administration. Findings of 12-lead ECG will be classified as "Normal", "Abnormal, Not Clinically Significant" or "Abnormal, Clinically Significant".

Individual 12-lead ECG results except for hypersensitivity monitoring will be summarized using a frequency table by treatment group, and presented in a data listing.

11.6. Physical Examination

Physical examinations will be performed at each scheduled visit specified in Appendix 1. The following body systems will be examined:

- General Appearance
- Head and Neck
- Skin
- Cardiovascular System
- Respiratory System
- Abdominal System
- Neurological System
- Musculoskeletal System
- Lymphatic System

Findings of physical examination will be classified as "Normal", "Abnormal, not clinically significant" or "Abnormal, clinically significant".

A shift table from baseline visit to each scheduled post-baseline visit for each body system will be summarized by treatment group. Individual physical examination results will be presented in a data listing.

11.7. Tuberculosis Assessment

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

Results for IGRA will be classified as "Positive", "Indeterminate" or "Negative". If the result of IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening Period. The number and percentage of patients with IGRA results will be summarized for baseline (as defined in Section 5.5) and scheduled visit.

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

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

11.8. Pregnancy Test

Only female patients of childbearing potential with a negative serum pregnancy test results can be enrolled. Pregnancy tests consist of serum and urine pregnancy tests. Serum pregnancy test will be performed on female patients with childbearing potential who have not been surgically sterilized at Screening and EOS visit by central laboratory. Serum pregnancy test results will be classified as "Positive", or "Negative".

Urine pregnancy test will be performed at local laboratory during all study period except EOS visit. Urine pregnancy test results will be classified as "Positive" or "Negative". If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at central laboratory.

Serum and urine pregnancy test results will be summarized by using the number of female patients with childbearing potential as a denominator by treatment group, type of pregnancy test, at each scheduled visit, displaying the number and percentage of patients. Individual pregnancy test results will be presented in a data listing.

11.9. Soluble interleukin-6 receptor

Soluble interleukin-6 receptor (sIL-6R) will be collected at each scheduled visit specified in Appendix 1. Actual value and change from baseline will be summarized by treatment group and scheduled visit using descriptive statistics (n, mean, SD, median, minimum, and maximum). sIL-6R results for each patient will be presented in the listing.

11.10. Immunogenicity

Blood samples for immunogenicity assessments will be collected at each scheduled visit specified in Appendix 1. If the blood sample is unable to be analyzed or is missing, extra blood samples collected for PK assessment at the same time point can be used for the immunogenicity assessment. Additional immunogenicity test will be performed if a patient experiences any immune-related AEs.

The ADA assay will follow a three-tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. The result for the screening assay will be "Positive" or "Negative". Samples that are "Positive" in the screening assay will be subject to further testing in the confirmatory assay to determine if samples are true positive. The result for the confirmatory assay will be: "Positive", "Negative". "Positive" indicates a true positive result and will be labeled as "Positive" in outputs, and will be subject to titration assay. Patients with a "Negative" result for either screening or confirmatory assays will be considered negative for the overall ADA assessment.

Samples that are Positive in the ADA assay will be subject to neutralizing antibody (NAb) assessment to see if ADA in the sample has neutralizing activity. The result for the NAb screening assay will be: "Positive" or "Negative".

The summary of immunogenicity will only be conducted for Overall Period on the Safety Set. The number and percentage of patients for ADA final result and NAb result will be presented by treatment group and test at each scheduled visit. Actual value for ADA titration will be summarized at each scheduled visit using descriptive statistics. For the summary, original results containing inequality sign will be considered as '0', which means that no titer detected within each dilution factor. The immunogenicity results for each patient will be presented in a data listing.

In addition, the number of patients and percentages with positive ADA and NAb Conversion will be summarized including all scheduled and unscheduled visits (including EOS) for Treatment Period I and Overall Period on the Safety Set, and Treatment Period II on the Safety-Treatment Period II subset. The rule of ADA and NAb conversion is as follow:

1) Treatment Period I

- ADA Conversion in Treatment Period I is defined as patients who reported at least one ADA positive result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II in patients who
    - Have at least one ADA result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II and
    - Do not have any ADA positive result before first study drug administration in Treatment Period I.
- NAb Conversion in Treatment Period I is defined as patients who reported at least one NAb positive result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II in patients who
    - Have at least one ADA result after first study drug administration in Treatment Period I and before the first study drug administration in Treatment Period II, and
    - Do not have any NAb positive result before first study drug administration in Treatment Period I.

2) Treatment Period II

- ADA Conversion in Treatment Period II is defined as patients who reported at least one ADA positive result after first study drug administration in Treatment Period II in patients who
    - Have at least one ADA result after first study drug administration in Treatment Period II and
    - Do not have any ADA positive result before first study drug administration in Treatment Period II.
- NAb Conversion in Treatment Period II is defined as patients who reported at least one NAb positive result after first study drug administration in Treatment Period II in patients who
    - Have at least one ADA result after first study drug administration in Treatment Period II, and
    - Do not have any NAb positive result before first study drug administration in Treatment Period II.

3) Overall Period

- ADA Conversion in Overall Period is defined as patients who reported at least one ADA positive result after first study drug administration in Treatment Period I in patients who
    - Have at least one ADA result after first study drug administration in Treatment Period I and
    - Do not have any ADA positive result before first study drug administration in Treatment Period I.

- NAb Conversion in Overall Period is defined as patients who reported at least one NAb positive result after first study drug administration in Treatment Period I in patients who
    - Have at least one ADA result after first study drug administration in Treatment Period I, and
    - Do not have any NAb positive result before first study drug administration in Treatment Period I.

12. Changes in the Planned Analysis

12.1. Changes in the Protocol

1) Number of Multiple Imputation (MI) Iterations

According to study protocol, planned number of MI iterations was 10. However, the number of MI iterations is increased to 100 because more reliable estimation is possible as the number of iterations increases.

2) Covariate for Primary Efficacy Endpoint

In the protocol, stratification factors were covariates of the primary efficacy analysis, but one of the stratification factors "Disease Activity by DAS28 (ESR) score at Screening (>5.1 or ≤ 5.1) (categorical value) is changed to "Baseline DAS28 (ESR) score (continuous value)" according to the CHMP guideline "Guideline on adjustment for baseline covariates in clinical trials (EMA/CHMP/295050/2013)".

13. Reference List

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14. APPENDICES

Appendix 1: Schedule of Assessments

Procedure	Screening	Study Period													
		Treatment Period I						Treatment Period II							EOS[1]
		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	
Study visit (Week)	**–6**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit (Day)	**–42 to –1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Visit Window (days)[2]			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Screening/Baseline assessments															
Informed consent	X														
Demographics, height	X														
Medical history[3]	X														
Inclusion/exclusion criteria	X	X[4]													
Hepatitis B test[5]	X							(X[4])							(X)
Hepatitis C and HIV-test[6]	X														
Serum pregnancy test[7]	X														X
Chest X-ray[8]	X														X
Interferon-γ release assay[9]	X							X[4]							X
Rheumatoid factor	X														
Anti-CCP	X														
Randomization[10]		X[4]						X[4]							
Study drug administration[11]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Efficacy assessments															
Swollen joint count[12] (28 joints/66 joints)	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Tender joint count[12] (28 joints/68 joints)	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
CRP[13]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
ESR (local)[13]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
VAS global assessment of disease activity (patient/physician) scores	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
VAS pain score	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Health assessment questionnaire	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
QoL (SF-36) assessment	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Hand and foot x-ray[14]	X														X

Procedure	Screening	Study Period													
		Treatment Period I						Treatment Period II							EOS[1]
		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 6	Dose 7	Dose 8	Dose 9	Dose 10	Dose 11	Dose 12	Dose 13	
Study visit (Week)	**–6**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**
Study visit (Day)	**–42 to –1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**365**
Visit Window (days)[2]			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
PK/Immunogenicity assessments															
Pharmacokinetic blood sampling[15]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Immunogenicity blood sampling[16]		X[4]	X[4]	X[4]	X[4]	X[4]		X[4]		X[4]		X[4]		X[4]	X
Safety and other assessments															
Vital signs, body weight	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Physical examination	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Clinical chemistry, hematology, urinalysis[17]	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Soluble interleukin-6 receptor		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Urine pregnancy test[7]		X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	
12-lead ECG[18]	X	X[4]													X
Hypersensitivity monitoring[19]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Prior, concomitant medications[20]	X														
TB clinical monitoring[21]	X														
AEs[22]	X														

Abbreviations: AE, adverse event(s); ANC, absolute neutrophil count; Anti-CCP, anti-cyclic citrullinated peptide antibody; CRP, C-reactive protein; DNA, DeoxyriboNucleic Acid; ECG, electrocardiogram; eCRF, electronic case report forms; EOS, end-of-study; ESR, erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IGRA, Interferon-Gamma Release Assays; ICF, informed consent form; IM, intramuscular; VAS, visual analogue scale; PK pharmacokinetic; QoL, quality of life; Q4W, every 4 week; SC, subcutaneous; TB, tuberculosis.

1. An EOS visit will occur at Week 52 for all patients who completed or discontinued study drug.
2. A dose visit window of 3 days is allowed based on the Day 1 visit throughout the study period, including EOS visit. Details of dose delay/skip criteria is described in Section 5.6 of the protocol (CT-P47 3.1).
3. Rheumatoid arthritis history including 2010 ACR/EULAR classification criteria and ACR global functional status at Screening will also be collected.
4. Procedures will be performed at the study center prior to the study drug administration.
5. At Screening, HBsAg, HBsAb, and HBcAb must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive), and HBcAb (positive), a HBV DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. For patients who are enrolled based on the HBV DNA test, testing of HBsAg, HBsAb, HBV DNA, ALT, AST, and total bilirubin will be performed at the Week 24 and EOS visits. Hepatitis B analysis will be performed at the central laboratory.
6. If hepatitis C or HIV test result is positive, the patient will be excluded from the study. Hepatitis C and HIV analysis will be performed at the central laboratory.

7. For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted at Screening and EOS visit by central laboratory and a urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on each scheduled visit or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory. For patient who early discontinued study drug, urine pregnancy test is unnecessary after the discontinuation.
8. A chest X-ray (both posterior-anterior and lateral views) is not required at Screening if a chest X-ray from within the 42 days prior to the first administration of the study drug (Day 1) is available.
9. The IGRA testing will be performed at the central laboratory. No further IGRA testing is required during the study period for patients who have at least 1 positive result for IGRA test and have completed the prophylaxis at least for required duration by country specific legislation.
10. Patients will be randomly assigned to receive either CT-P47 or RoActemra prior to dosing on Day 1 (Week 0) (first randomization). Patients will be randomized again prior to dosing on Week 24 (second randomization).
11. Methotrexate (10 to 25 mg/week, oral or parenteral [IM or SC] dose, and dose and route must be maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose) will be administered throughout the study treatment, unless dose modification is required due to laboratory abnormalities as per Section 5.2.2 of the protocol (CT-P47 3.1).
12. An independent joint count assessor will be assigned to each study center. If possible, it is recommended that the joint count assessments are performed independently by the same person, at each study center throughout the entire study period.
13. Both CRP and ESR are considered as efficacy and safety (clinical laboratory test) endpoints.
14. One image of each hand and each foot (both the right and left hands and feet, a total of 4 images) for analysis of efficacy will be obtained at the scheduled times. The baseline radiographs will be assessed within 42 days prior to the first administration of the study drug (Day 1). Joint damage progression as determined by radiography will be assessed using the modified total Sharp scoring system by the central independent reviewer.
15. Blood samples for PK analysis will be collected at predose (prior to the beginning of study drug administration) for all PK sampling time points up to and including Week 48. For EOS visit, PK samples will be obtained anytime during the day. For patients who early discontinued the study drug, PK sampling will only be collected until the next scheduled visit and further PK sampling is unnecessary.
16. Blood samples for immunogenicity analysis will be drawn prior to dosing of study drug at the same time as the clinical laboratory test where applicable. Analysis will be performed at the central laboratory. Additional immunogenicity will be assessed when immune-related AEs occur. For patients who early discontinued the study drug, immunogenicity sampling will only be collected until the next scheduled immunogenicity sampling visit and further immunogenicity sampling is unnecessary.
17. Clinical laboratory (clinical chemistry, hematology and urinalysis) test samples will be analyzed at the central laboratory. Refer to Section 5.2.2 of the protocol (CT-P47 3.1) for guidelines for dosage modification and treatment interruption or discontinuation for laboratory abnormalities in liver enzymes (ALT and AST), absolute neutrophil count, or platelet counts. The laboratory results from previous visit will be used to determine if dose modification or discontinuation is needed. If the investigator confirms that the previous laboratory results of liver enzymes, ANC or platelet are within abnormal range, additional sample should be collected in advance (<7 days prior to the next dose administration as unscheduled visit) to facilitate rapid clinical decision making.

Clinical chemistry	Total protein, serum bilirubin (total, direct), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, magnesium, lactate dehydrogenase, total cholesterol, triglyceride, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, Creatine kinase, Creatine kinase-MB, C-reactive protein, uric acid, and creatinine clearance (only at screening for inclusion)
Hematology	Hematocrit, hemoglobin, red blood cells, total and differential white blood cell count, erythrocyte sedimentation rate, absolute neutrophil count (ANC), and platelet count
Urinalysis	Bilirubin, blood, color, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen

18. All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in supine position. If patients have signs and symptoms of hypersensitivity or other cardiac origin, a 12-lead ECG could be performed at any time during the study period by investigator's discretion. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the investigator's discretion.
19. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature will be monitored for hypersensitivity reactions before beginning of the study drug administration [within 15 minutes] and at 1 hour (±15 minutes) after the end of study drug administration. In addition, any type of ECG will be performed for hypersensitivity monitoring 1 hour (±15 minutes) after the end of the study drug administration. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator will be available. For patient who early discontinued study drug, monitoring of hypersensitivity is unnecessary after the discontinuation.
20. Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS visit (Week 52), will be recorded in both the source documents and the eCRF. Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug will be recorded until EOS visit in both the source documents and the eCRF.
21. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. The IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
22. Adverse events will be assessed from the date the ICF is signed until the EOS visit.

Note 1. The patients who early discontinued from the study drug will also visit the study center until Week 52 by regular scheduled time interval for efficacy and safety assessments (except for hypersensitivity monitoring and urine pregnancy), even if they change their RA medication (including those prohibited by the protocol). Blood samples for PK and immunogenicity analysis will only be collected until the next scheduled visit (from the last study drug administration) and further sampling is unnecessary. However, any assessment(s) that could jeopardize the patients' safety could be skipped, as per investigator judgement.
Note 2. If a study center is not equipped to perform the specified tests, this will be discussed and arranged with the sponsor or the sponsor's designee.
Note 3. Refer to Section 1.6.1.2 of the protocols (CT-P47 3.1) for COVID-19 mitigation plans.

Appendix 2: Table of CTCAE v5.0 Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Blood bilirubin increased	Serum Bilirubin (Total) *	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Alanine aminotransferase increased	Alanine aminotransferase (ALT) *	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	Aspartate aminotransferase (AST) *	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline Phosphatase *	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
GGT increased	γ-Glutamyl Transferase *	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Creatinine increased	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
CPK increased	Creatine Kinase	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
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	
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L;	>155 - 160 mmol/L;	>160 mmol/L;
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 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;
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; #	<3.0 - 2.5 mmol/L;	<2.5 mmol/L;
Hypercalcemia	Calcium	High	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; @	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; @	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; @	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; @
Hypocalcemia	Calcium	Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; @	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; @	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; @	Corrected serum calcium of <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;

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Hypermagnesemia	Magnesium	High	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L		>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L;
Hypomagnesemia	Magnesium	Low	<LLN-1.2 mg/dL; <LLN-0.5 mmol/L	<1.2-0.9 mg/dL; <0.5-0.4 mmol/L	<0.9-0.7 mg/dL; <0.4-0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L
Blood lactate dehydrogenase increased	Lactate Dehydrogenase	High	>ULN			
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Hypertriglyceridemia	Triglyceride	High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L;
Hyperuricemia	Uric acid	High	>ULN			
Leukocytosis	Total White Blood Cell Count	High			>100,000/mm3	
White blood cell decreased	Total White Blood Cell Count	Low	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L
Neutrophil count decreased	Absolute Neutrophil Count	Low	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Eosinophilia	Eosinophil Count	High	>ULN and >Baseline			
Lymphocyte count decreased	Lymphocyte Count	Low	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
Lymphocyte count increased	Lymphocyte Count	High		>4000/mm3 - 20,000/mm3	>20,000/mm3	
Platelet count decreased	Platelet Count	Low	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	
Glucosuria	Urine Glucose	N/A	Present			

Note: LLN = lower limit of normal, ULN = upper limit of normal. The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by the central laboratory.
* indicates that baseline results will be considered abnormal only when the baseline result is abnormal and high, otherwise normal.
# indicates that this grade will not be used because this grade shares the same criteria due to exclusion of clinical input.
@ indicates that corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0-serum albumin [g/dL]), where 4.0 represents the average albumin level. The LLN and ULN values of total calcium will be used.