CLINICAL STUDY PROTOCOL

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

Protocol Number CT-P47 3.1

EudraCT Number:	2022-001066-36
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Protocol Version and Date:	Version 1.1, including country specific A.0, 07 July 2022

CONFIDENTIAL

Protocol Approval

Study Title: 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

Protocol Number: CT-P47 3.1

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Protocol accepted and approved by:

[redacted]

CELLTRION, Inc.
23, Academy-ro,
Yeonsu-gu, Incheon,
22014, Republic of Korea

[redacted]

Declaration of Investigator

I have read and understood all sections of the protocol entitled "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" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 1.1, including country specific A.0, dated 07 July 2022, the International Council for Harmonisation harmonised guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a sub-investigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from CELLTRION, Inc.

Signature of Principal Investigator Date

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number: CT-P47 3.1

Title: 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

Study Phase: Phase 3

Study Centers: Approximately 22 study centers in Poland

Test Drug, Dose and Regimen: CT-P47, 8 mg/kg (not exceeding 800 mg/dose) by intravenous (IV) infusion every 4 weeks (Q4W), co-administered with methotrexate (MTX) between 10 to 25 mg/week, oral or parenteral dose (dose and route must be maintained from the beginning to the end of the study) and folic acid (≥5 mg/week, oral dose)

Reference Drug, Dose and Regimen: EU-approved RoActemra, 8 mg/kg (not exceeding 800 mg/dose) by IV infusion Q4W, co-administered with MTX between 10 to 25 mg/week, oral or parenteral dose (dose and route must be maintained from the beginning to the end of the study) and folic acid (≥5 mg/week, oral dose)

Objectives:

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.

Secondary Objective

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

Main selection criteria: Male or female patient with moderate to severe active rheumatoid arthritis (RA) diagnosed according to the 2010 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) classification criteria (Aletaha et al., 2010) for at least 24 weeks, who have inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs), will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female aged 18 to 75 years old, both inclusive.
2. Patient has had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria (Aletaha et al., 2010) for at least 24 weeks prior to the first administration of the study drug (Day 1).
3. Patient must have moderate to severe disease activity as defined by all of the following at Screening:
   - 6 or more swollen joints (of 66 assessed)
   - 6 or more tender joints (of 68 assessed)
   - either an ESR ≥28 mm/hour or a serum C-reactive protein (CRP) concentration ≥1.0 mg/dL (≥10 mg/L)
   - DAS28 (ESR or CRP) ≥3.2
4. Patient who has been receiving oral or parenteral MTX for at least 12 weeks and who has been on a stable dose and route of MTX between 10 to 25 mg/week for at least 8 weeks prior to the first administration of the study drug (Day 1).
5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
   - Serum creatinine ≤1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (SI [Système International d'Unités] units: 0.84 mL/s)
   - Serum alanine aminotransferase ≤2.0 × ULN

- Serum aspartate aminotransferase ≤2.0 × ULN
- Serum total bilirubin ≤1.5 × ULN

6. Patient has the following hematology laboratory test results at Screening:
   - Absolute neutrophil count ≥2,000/mm^3 ($2.0\times10^3/\mu L$)
   - Platelet count ≥100,000/mm^3 ($100.0\times10^3/\mu L$)
7. Patient and their partner of childbearing potential must agree to use following highly effective method of contraception consistent with local regulations throughout the study and for 6 months after the last dose of assigned treatment. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active (i.e., a man is fertile after puberty unless permanently sterile by bilateral orchidectomy or a woman is fertile, following menarche and until becoming postmenopausal unless permanently sterile).
   - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
   - Intrauterine device or system
   - True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.
   - Double contraceptive methods (e.g., male condom in addition to use of hormonal or barrier method in female); for male patient with his female partner of childbearing potential only.

   If patient or their partner has been surgically sterilized for less than 24 weeks prior to the date of informed consent, they must agree to use any medically acceptable methods of contraception. Postmenopausal females must have experienced their last menstrual period more than 1 year prior to the date of informed consent without an alternative medical cause to be classified as not of childbearing potential.
8. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, has the ability to cooperate with the investigator and is given ample time and opportunity to read and understand verbal and/or written instructions, and signs the written informed consent form with date prior to participation in the study.

Exclusion Criteria:

A patient meeting any of the following criteria will be excluded from the study:

1. Patient who has previously received investigational or licensed product; targeted synthetic DMARD(s) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or an interleukin-6 (IL-6) inhibitor for any purposes.
2. Patient who has previously received more than 1 biologic agents approved for the treatment of RA.

   Note. Patient with 1 biologic agent for the treatment of RA can be enrolled after sufficient wash-out period of at least 3 months or 5 half-lives (whichever is longer) prior to the first administration of the study drug (Day 1), except for etanercept and anakinra where only a 1 month washout prior to the first administration of study drug (Day 1) is necessary. Patients who have been treated with rituximab or a biosimilar of rituximab will not be allowed to enroll in the study.
3. Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products.
4. Patient who currently has, or has a history of, any of the following infections:
   - A known infection with hepatitis B (active or carrier of hepatitis B) or hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past hepatitis B virus is allowed if resolved (confirmed by negative HBsAg and HBV DNA).
   - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1)
   - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1)
   - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). However, a patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.

- Other serious infections within 24 weeks prior to the first administration of the study drug (Day 1)

5. Patient who currently has, or has a history of, any of the following tuberculosis (TB):
   - Patient who has current or a history of active TB. Patient who has any evidence of history of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.
   - Patient who has signs or symptoms suggestive of active TB.
   - Patient who has had exposure to a person with active TB such as first-degree family members or co-workers within 16 weeks prior to the first administration of the study drug (Day 1).
   - Patient who has a past diagnosis of latent TB unless they have documentation of completing TB prophylaxis, or have received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
   - Patient who has a current diagnosis of latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest X-ray) at Screening without a history of active TB or latent TB. However, a patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
   - Patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening. If the result of IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening Period. Depending on the result of retest, the enrollment will be determined as follows:
     - If the repeated IGRA result is negative, the patient can be enrolled.
     - If the repeated IGRA result is positive, the patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
     - If the repeated IGRA result is again indeterminate, the patient cannot be enrolled.
6. Patient who has a medical condition including one or more of the following:
   - Current uncontrolled diabetes mellitus, even after insulin treatment
   - Current uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg)
   - Any other current inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or fibromyalgia, that may confound the evaluation of the effect of the study drug
   - Current significant systemic RA involvement (e.g., Sjögren's syndrome, vasculitis, pulmonary fibrosis), which would put the patient at risk if they are enrolled
   - Current or history of diverticulitis, chronic ulcerative lower gastrointestinal tract disease or any other gastrointestinal condition that may predispose to perforation.
   - A known malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
   - Current or past history of severe uncontrolled cardiac disease (unstable angina, New York Heart Association [NYHA] Class III or IV heart failure or clinically significant electrocardiogram [ECG] abnormalities judged by the investigator) including cardiovascular disorders or myocardial infarction within 24 weeks prior to the first administration of the study drug (Day 1)
   - History of organ transplantation, including corneal graft/transplantation
   - Any current respiratory disease that can be judged as clinically significant at the investigator's discretion, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion
   - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome

- Any other current or history of serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results
- History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion

7. Patient who has received or plans to receive any of the following prohibited medications or treatment:
    - Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1). A patient is permitted to receive one injection of intra-articular corticosteroid (≤40 mg of methylprednisolone or equivalent) from Week 36 (after all Week 36 assessments have been performed) and until the end of the study. A patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and non-steroidal anti-inflammatory drug, if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1) and the same dose must be maintained until 24 weeks after the first administration of the study drug (Day 1). In addition, a patient is permitted to receive low-potency topical, inhaled, otic, and ophthalmic glucocorticoid preparations provided, if the preparations are administered per the instructions on the product label.
    - Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days must wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug (Day 1)
    - Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer
    - Alkylating agents within 1 year prior to the first administration of the study drug (Day 1)
    - Herbal treatment within 2 weeks prior to the first administration of the study drug (Day 1)
    - Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 1), or any planned live or live-attenuated vaccination during the study period
    - Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 1) or planned within 36 weeks after the first administration of the study drug (Day 1)
8. Severe physical incapacitation (severely limited in ability to perform routine self-care, has RA ACR global functional status Class IV [Hochberg et al., 1992], or who cannot benefit from medication).
9. Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed within 6 months of the last dose of study drug. Male patient who is planning to donate sperm or father a child within 6 months of the last dose of study drug.
10. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 1 years from Screening.
11. Patient is vulnerable (e.g., employee of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).
12. Patient who, in the opinion of the investigator, should not participate in the study.

Study Design:

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 IV Q4W in combination with MTX (between 10 to 25 mg/week, oral or parenteral [intramuscular or 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 first randomization to treatment assignment will be stratified by the followings:

- 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)

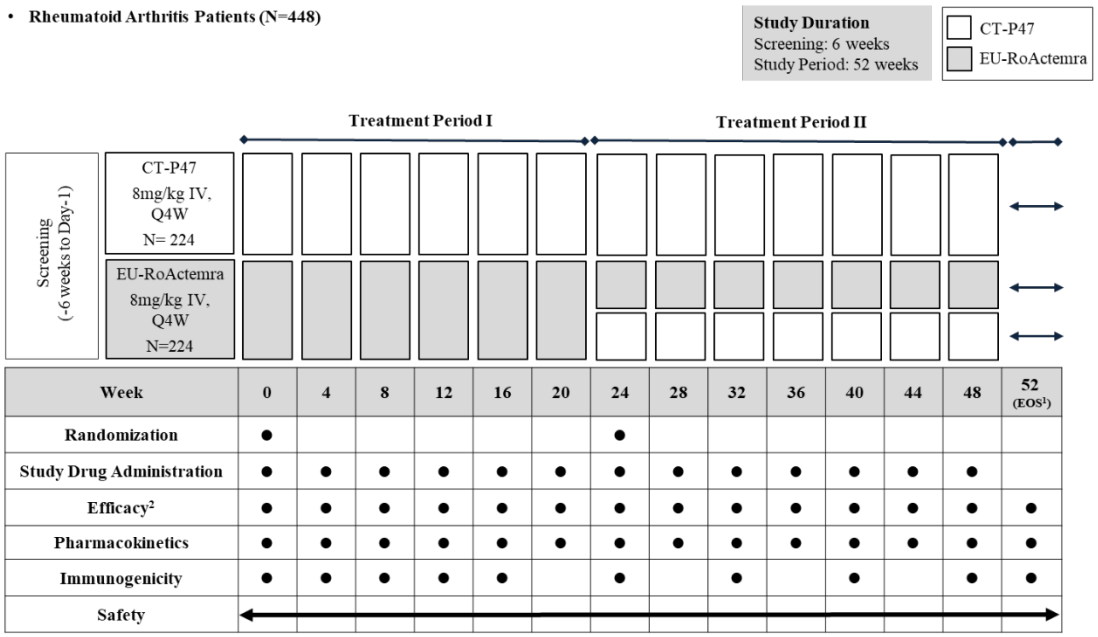
Patients will receive CT-P47 or RoActemra Q4W up to Week 20. Prior to dosing at Week 24, patients in the RoActemra treatment group will be randomly assigned in a ratio of 1:1 to either continue with RoActemra (Cohort 2) or undergo transition to CT-P47 (Cohort 3). All patients who are initially assigned 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

The study design and patient assessment overview is presented in Figure S1.

Figure S1 Study Design Overview



Week	0	4	8	12	16	20	24	28	32	36	40	44	48	52 (EOS[1])
Randomization	●						●							
Study Drug Administration	●	●	●	●	●	●	●	●	●	●	●	●	●	
Efficacy[2]	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Pharmacokinetics	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Immunogenicity	●	●	●	●	●		●		●		●		●	●
Safety	←	←	←	←	←	←	←	←	←	←	←	←	←	→

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.

After database lock for data up to 32 weeks for all patients, the study will be unblinded for reporting purposes and efficacy, PK, and safety endpoints will be evaluated by the pre-defined unblinded sponsor

and Contract Research Organization (CRO) teams. The investigators, patients, and other sponsor and CRO teams will remain blinded until the end of the study.

Study Schedule: The study will include a Screening Period, Treatment Period (I and II), and End-of-Study (EOS) visit.

Screening Period:
Screening will take place between Day –42 and Day –1 (6 weeks), prior to the first study drug administration.

Treatment Period:

- 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])

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. The patient will receive either CT-P47 or RoActemra, as per first and second randomization, by IV infusion Q4W, co-administered with MTX between 10 to 25 mg/week, oral or parenteral dose (intramuscular [IM] or SC; dose and route must be maintained from beginning to EOS) and folic acid (≥5 mg/week, oral dose). Patients will comply with all appropriate visits and assessments. At each visit, the patient will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of 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 RA medication (including those prohibited by the protocol).

Efficacy Assessments:

Primary Endpoint

- Mean change from baseline of DAS28 (ESR) at Week 24

Secondary Endpoints

The following secondary efficacy endpoints will be assessed up to Week 52:

- ACR20, ACR50 and ACR70
- Individual components of the ACR
- Hybrid ACR response
- DAS28 (CRP)
- DAS28 (ESR) (except for Week 24)
- Individual components of the DAS28
- EULAR response
- Simplified disease activity index (SDAI) and clinical disease activity index (CDAI)
- ACR/EULAR remission (Boolean-based definition)

- 36-item short form health survey (SF-36)
- Joint damage progression based on radiographic evaluations

Pharmacokinetic Assessment:

Secondary Endpoint

- Serum tocilizumab concentration at each time point will be assessed up to Week 52

Safety Assessments:

Safety assessments will be performed on AEs (including serious AEs), AEs of special interest (AESI) (infection, hypersensitivity including anaphylaxis, hepatic event, haemorrhage, gastrointestinal perforation, malignancy, and demyelinating disorder), immunogenicity, hypersensitivity monitoring (via monitoring of vital signs, includes BP, heart and respiratory rates, and body temperature), vital sign and weight measurement, ECGs, physical examination findings, IGRA, chest X-ray, hepatitis B and hepatitis C and HIV status, pregnancy testing, clinical laboratory analyses, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study.

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 was 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.

Statistical Analysis:

The statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute, Inc., Cary, North Carolina). The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to database lock. The data documented in this study and the clinical parameters measured will be described using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for quantitative variables and frequency counts and percentages for qualitative variables.

Definition of Analysis Set:

- **Intent-to-treat (ITT) Set:** The ITT Set is defined as all patients randomly assigned to receive study drugs (CT-P47 or RoActemra)
- **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.
- **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 endpoint. 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 efficacy primary endpoint before unblinding.
- **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.
- **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.
- **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).

- **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.

Efficacy Analysis

- **Primary endpoint:** The difference of mean change from baseline of DAS28 (ESR) score at Week 24 will be analyzed 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, disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤5.1), and prior biologic use approved for RA treatment (yes or no) as covariates. The multiple imputed datasets are then analyzed by using ANCOVA with treatment as a fixed effect using covariates as above. Final determination of covariates and details will be described in the SAP. The two-sided 90% confidence interval (CI) for the difference between the 2 treatment groups (CT-P47 and RoActemra) will be produced. Therapeutic equivalence of treatment difference in the change from baseline of DAS28 (ESR) at Week 24 by the ANCOVA analysis will be concluded if the 90% CIs for the treatment difference is entirely within –0.6 to 0.5.

  The primary population of primary endpoint is ITT Set evaluated under a treatment policy estimand. For the treatment policy estimand, all available data will be included in the primary analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation. A supportive analysis for the primary efficacy endpoint will be conducted using the PPS. Additionally, the sensitivity analysis to evaluate the impact of missing data will be conducted on the ITT Set.
- **Secondary endpoints:** The secondary efficacy endpoints will be descriptively summarized using the ITT Set and PPS and data for Treatment Period II will be summarized on the ITT-Treatment Period II subset, unless otherwise specified.

Pharmacokinetic Analysis

Serum concentrations for Treatment Period I will be summarized on PK Set and data for Treatment Period II will be summarized on PK-Treatment Period II subset, unless otherwise specified. Serum concentrations will be summarized using quantitative descriptive statistics (including geometric mean and percent coefficient of variation [CV%], as appropriate).

Safety Analysis

Adverse events will be coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Prior and concomitant medication will be coded to drug class and PT using the World Health Organization (WHO) drug dictionary. All safety data including immunogenicity will be listed and summarized by treatment groups as appropriate for the Safety Set and data for Treatment Period II will be summarized on Safety–Treatment Period II subset, unless otherwise specified. 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.

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
bDMARD	Biological disease-modifying antirheumatic drug
BP	Blood pressure
CDAI	Clinical disease activity index
CEE	Central and Eastern Europe
CFR	Code of Federal Regulations
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	Curriculum vitae
CV%	Percent coefficient of variation
DAS28	Disease Activity Score 28
DMARD	Disease-modifying antirheumatic drug
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOS	End-of-study
EPAR	European public assessment report
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

Abbreviation	Definition
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent ethics committee
IGRA	Interferon-gamma release assays
IL	Interleukin
IL-6R	Interleukin-6 receptor
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
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SDAI	Simplified disease activity index
SI	Système International d'Unités
SF-36	36-item short form health survey
sIL-6R	Soluble interleukin-6 receptor
SJC	Swollen joint count
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event

Abbreviation	Definition
TJC	Tender joint count
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WHO	World Health Organizations

1 Introduction

1.1 Background

Rheumatoid arthritis (RA) is the most common autoimmune inflammatory arthritis in adults, occurring in approximately 0.5 to 1.0% of the global population (Silman and Pearson, 2002; Singh et al., 2015). It is characterized by synovial inflammation and hyperplasia, autoantibody production, cartilage and bone destruction, and systemic features (Mcinnes and Schett, 2011). It has a significant negative impact on the ability to perform daily activities and health-related quality of life, and it increases mortality (Singh et al., 2015). The goals of RA treatment are to improve patients' quality of life by reducing symptoms, reducing functional limitations, preventing joint damage, and decreasing complications of the disease. The mainstays of treatment have been conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate (MTX) and sulfasalazine. An array of targeted biologic therapies have now been approved to treat RA (ACR, 2018).

Interleukin (IL)-6 (IL-6) is a pleiotropic cytokine that is over-expressed in synovial tissue in patients with RA, with raised concentrations in serum and synovial fluid. IL-6 affects the function of neutrophils, T cells, B cells, monocytes, and osteoclasts cells that are highly activated in RA and is the major inducer of the hepatic acute phase response, which is also a key feature of RA that is correlated with disease activity and joint destruction (Smolen et al., 2008). An interleukin-6 receptor (IL-6R) inhibitor biological DMARD (bDMARD) approved for the treatment of RA includes tocilizumab and sarilumab (Smolen et al., 2020; Fraenkel et al., 2021).

Tocilizumab is a recombinant humanized immunoglobulin (Ig) G1 monoclonal antibody (mAb) directed against the IL-6R that binds specifically to both soluble and membrane-bound IL-6R, thereby inhibiting IL-6-mediated signaling (RoActemra EPAR, 2018). Tocilizumab was originally approved as RoActemra in the European Union (EU) in January 2009 and as Actemra in the United States (US) in January 2010. Tocilizumab is available in 2 different pharmaceutical forms to allow either administration by intravenous (IV) infusion or by subcutaneous (SC) injection. Both pharmaceutical forms of tocilizumab are approved in both the EU and US, for the treatment of RA in adults, for the treatment of polyarticular juvenile idiopathic arthritis in patients 2 years of age and older, and for the treatment of systemic juvenile idiopathic polyarthritis in patients 2 years of age and older. The SC formulation of tocilizumab is also approved for the treatment of giant cell arteritis in adult patients and systemic sclerosis-associated interstitial lung disease (US only). The IV formulation of tocilizumab is also approved for the treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release

syndrome in adults and pediatric patients 2 years of age and older (RoActemra SmPC, 2022; Actemra USPI, 2022).

1.2 CT-P47

CT-P47, containing the active ingredient tocilizumab, is a recombinant humanized Ig G1 mAb directed against the IL-6R that binds specifically to both soluble and membrane-bound IL-6R, thereby inhibiting IL-6-mediated signaling.

CT-P47 is being developed by CELLTRION, Inc (hereafter, the sponsor) as a proposed biosimilar to the reference products, EU-approved RoActemra and US-licensed Actemra (hereafter referred to as RoActemra and Actemra, respectively). CT-P47 is manufactured using a Chinese hamster ovary cell line. The primary amino acid sequences of tocilizumab in CT-P47 are identical to those of the reference products.

CT-P47 will be supplied as a sterile, preservative-free, colorless to pale yellowish solution at a concentration of 20 mg/mL in 400 mg (20 mL) vials for IV infusion. The CT-P47 drug product will have the same pharmaceutical liquid formulation form and strength as the reference products for IV infusion and is intended to have a highly similar quality profile to the reference products.

The sponsor plans to seek approval for all indications for which the reference products has been approved by demonstrating similarity of CT-P47 with the reference products through an extensive array of quality, nonclinical, and clinical comparability assessments.

1.3 Pre-clinical Studies

Detailed information regarding the non-clinical pharmacology and toxicology of CT-P47 can be found in the investigator's brochure (IB).

1.4 Clinical Studies

The PK and safety of CT-P47 will be evaluated in two phase 1 clinical studies; Study CT-P47 1.1 will compare CT-P47 and RoActemra SC in healthy subjects and CT-P47 1.2 will compare CT-P47, RoActemra, and Actemra IV in healthy subjects. The study results are not yet available.

The efficacy and safety of the reference products (RoActemra or Actemra) administered by IV infusion in RA patients were assessed in several randomized clinical trials. Of these, a brief description of the 5 pivotal double-blind, randomized, parallel group phase 3 studies is provided below.

Study WA17822 (OPTION) assessed the therapeutic effects of tocilizumab in 623 RA patients. The patients were randomized to receive tocilizumab 8mg/kg (n=205), tocilizumab 4mg/kg (n=214), or placebo (n=204) intravenously every 4 weeks (Q4W), with MTX at stable doses (10-25 mg/week). At Week 24, American College of Rheumatology 20% improvement (ACR20) responses were seen in more patients receiving tocilizumab than in those receiving placebo (59% patients in the 8mg/kg group, 48% in the 4mg/kg group, and 26% in the placebo group). The study demonstrated that tocilizumab could be an effective therapeutic approach in patients with moderate to severe active RA (Smolen et al., 2008).

Study WA18062 (RADIATE) evaluated efficacy and safety of tocilizumab in patients with RA refractory to tumor necrosis factor (TNF) antagonist therapy. A total of 499 patients were randomly assigned to receive tocilizumab 8mg/kg (n=170), tocilizumab 4mg/kg (n=161), or placebo (n=158) intravenously Q4W with stable MTX (10-25 mg/week) for 24 weeks. ACR20 was achieved at 24 weeks by 50.0%, 30.4% and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively. Disease activity score 28 (DAS28) remission (DAS28 <2.6) rates at Week 24 were clearly dose related, being achieved by 30.1%, 7.6% and 1.6% of 8 mg/kg, 4 mg/kg and control groups. Tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and had a manageable safety profile (Emery et al., 2008).

Study WA18063 (TOWARD) examined efficacy and safety of tocilizumab combined with conventional DMARDs in patients with RA. A total of 1,220 patients were randomized (2:1 ratio) and the patients remained on stable doses of DMARDs and received tocilizumab 8mg/kg (n=805) or placebo (n=415) every 4 weeks. At Week 24, the proportion of patients achieving ACR20 response was greater in the tocilizumab plus DMARD group than in the placebo group (61% versus 25%). Tocilizumab combined with any of the DMARDs evaluated was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents (Genovese et al., 2008).

Study WA17824 (AMBITION) evaluated the efficacy and safety of tocilizumab monotherapy versus MTX in patients with RA for whom previous treatment with MTX/biological agents had not failed. This study randomized 673 patients to either tocilizumab 8mg/kg every 4 weeks (n=288), or MTX starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks (n=284), or placebo for 8 weeks followed by tocilizumab 8mg/kg (n=101). The intention-to-treat analysis demonstrated that tocilizumab was better than MTX treatment with a higher ACR20 response (69.9 vs 52.5%), and DAS28 <2.6 rate (33.6 vs 12.1%) at Week 24 (Jones et al., 2010).

Study WA17823 (LITHE) assessed the efficacy and safety of tocilizumab plus MTX versus MTX alone in preventing structural joint damage and improving physical function and disease activity in patients with RA and inadequate responses to MTX. A total of 1,196 patients were randomized to receive tocilizumab 8 mg/kg (n=398), 4 mg/kg (n=399), or placebo (n=393) every 4 weeks plus MTX (10-25 mg/week). Mean change in the total Genant-modified Sharp score was 0.29 and 0.34 with tocilizumab 8 mg/kg plus MTX and 4 mg/kg plus MTX, respectively, versus 1.13 with placebo plus MTX. Analysis of variance of the area under the curve for change from baseline in the disability index of the Health Assessment Questionnaire (HAQ) showed greater decreases with tocilizumab 8 mg/kg and 4 mg/kg (-144.1 and -128.4 units, respectively) than with placebo (-58.1 units). Proportions of patients with ACR20, 50, and 70 and with DAS28 remission were higher in those receiving 8 mg/kg tocilizumab than in those receiving placebo. The safety profile of tocilizumab was consistent with the profiles in previous studies (Kremer et al., 2011).

1.5 Study Rationale

CT-P47 is currently being developed by Sponsor, and is intended to be developed as a biosimilar to RoActemra and Actemra. For a biosimilar to be approved, it must be proven that there are no clinically meaningful differences between the two products. The stepwise ‘totality of evidence’ approach adopted by regulatory authorities for biosimilars means that the type of clinical studies needed varies on a case-by-case basis. However, statistically proven equivalence between biosimilar and reference product in both pharmacokinetics (PK) and efficacy are usually required, as is a demonstration of acceptable safety and immunogenicity. Therefore, the PK profile of both IV and SC formulations of CT-P47 and the reference products will be compared to demonstrate PK equivalence in two phase 1 studies in healthy volunteers, respectively.

In conjunction with IV and SC phase 1 studies, this study will evaluate the similarity in efficacy, PK, safety, and immunogenicity using IV formulation in patients with moderate to severe active RA. CT-P47 or RoActemra 8 mg/kg (not exceeding 800 mg/dose) will be administered Q4W for up to 48 weeks. The proposed dosing regimen is in line with the approved labeling for RoActemra (RoActemra SmPC, 2022; Actemra USPI, 2022). The route of IV administration has been chosen for this study based on comparable efficacy, safety, and immunogenicity results between the SC and IV administration of tocilizumab demonstrated from extensive clinical experiences.

Comparable efficacy was demonstrated between tocilizumab 162 mg administered SC weekly and 8 mg/kg administered IV Q4W in patients with RA. The safety profiles were similar, with the exception of a higher incidence of injection site reaction, which were

more common with SC administration (Burmester et al., 2014). Low and comparable immunogenicity of SC and IV administration has been observed for tocilizumab (RoActemra EPAR, 2014). Anti-drug antibody (ADA) positivity rates in patients administered tocilizumab SC and IV were 1.2% and 1.5%, respectively, based on a pooled analysis data from 8,974 patients in 5 tocilizumab SC and 8 tocilizumab IV phase 3 studies, indicating overall low risk of tocilizumab immunogenicity. The development of ADA did not correlate with PK or safety events, including hypersensitivity or injection-site reactions, and no patients who developed ADAs had loss of efficacy (Burmester et al., 2017).

International regulations (EMA, 2010; FDA, 2015) suggest that proposed biosimilars should be tested in a population representative of approved therapeutic indications of the reference product and sufficiently sensitive for detecting potential differences between the biosimilar and the reference product. Consequently, RA has been selected as indication for the comparative clinical trial, due to the relatively high magnitude of the treatment effect observed in the tocilizumab clinical studies in this indication and approved standard doses; thus, facilitating the detection of potential differences between CT-P47 and the reference products.

1.6 Benefit and Risk Assessment

RoActemra has been studied extensively and has been shown to be effective at reducing symptoms in patients with RA (RoActemra SmPC, 2022; Actemra USPI, 2022).

Taking into account the results of the analytical similarity, pharmacological, and toxicological profiles of CT-P47 in non-clinical studies, the clinical findings for CT-P47 are expected to be in line with those of RoActemra/Actemra, specifically in terms of clinical pharmacology, efficacy, and safety.

The design of this study contains adequate measures to mitigate risks and adequate safety monitoring to protect the patients. Nonresponders from Week 16 and thereafter, will be offered to receive a rescue therapy at the discretion of the investigator (see Section 5.8). An independent data monitoring committee (IDMC) appointed to the study will provide an additional level of risk mitigation. The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P47 administration.

Based upon the clinical evidence (Section 1.4) as well as the proven safety profile of RoActemra, the benefits of the conduct of the proposed clinical study outweigh the associated risks.

1.6.1 Risk Assessment During COVID-19 Pandemic

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified during an outbreak of atypical viral pneumonia cases of unknown cause in the People's Republic of China in December 2019 and the disease caused by SARS-CoV-2 has been designated as coronavirus disease 2019 (COVID-19). On 11 March 2020, World Health Organization (WHO) declared the SARS-CoV-2 infection outbreak a global pandemic as there are now in excess of 6 million deaths have been reported globally (WHO COVID-19 Dashboard, 2022).

Due to the global impact of the COVID-19 pandemic, the sponsor is taking proactive measures to guarantee that all site staff and patients involved in trial are secure and the patients remain in the study until their last visit, with continuation of treatment during study period.

1.6.1.1 Benefit and Risk Assessment on Study Population

To date, there is no evidence that patients with RA face more risk of contracting COVID-19 than individuals without RA, nor that they have a worse prognosis when they contract it. Patients with RA should in general be advised to comply with the same preventive and control measures prescribed by the health authorities in their countries. Patients with RA who do not have suspected or confirmed COVID-19 should be advised to continue their treatment unchanged, namely NSAIDs, glucocorticoids, synthetic DMARDs, bDMARDs, osteoporosis medications and analgesics, among others during the COVID-19 outbreak (Landewé et al., 2020).

Basically, the quarantine of COVID-19 should be carried out based on the SOP of each site and local regulatory guidelines. Taking this into account, the risk of COVID-19 infection for each patient is not expected to increase by participating in this study. Yet due to the possibility of increasing the safety risk by being involved in the study, a systematic risk assessment will be conducted during the study by the sponsor through a sufficient discussion with the Investigators and IDMC.

1.6.1.2 Mitigation Plans

Investigational Medical Product Management

To better cope with the sudden imposition of movement restriction and/or increase shipment lead time due to frequent flight cancellation and limited staff at customs, sufficient investigational medicinal product (IMP) will be supplied to cover patient visit for longer period. Inter-country study drug transfer using regional airways will be considered in case intercontinental flights are repeatedly cancelled. In addition, sponsor

will prepare site-to-site transfer of study drug from nearby clinical sites in case agile resupply is required (e.g., patients are enrolled in a site more than anticipated but additional supplied IMP could not be sufficient).

COVID-19 vaccination during the study period

According to the ACR guidance for COVID-19 vaccination in patients with rheumatic and musculoskeletal diseases (Curtis et al., 2021), no modification is required in the use and timing of treatment with IL-6R inhibitors. However, patients receiving MTX is advised to hold MTX for 1 week after each of the 2 mRNA vaccine dose with the exception for those with well-controlled disease, or to withhold MTX for 2 weeks after single-dose COVID-19 vaccination, for those with well-controlled disease.

Patients will be allowed to receive an authorized COVID-19 vaccine of non-live attenuated types (e.g., mRNA, viral vector) at least >7 days apart from the previous and next study drug administration. Dose modification of MTX will be at the discretion of the investigator and in accordance with local regulatory requirements.

Rescheduling of Visit and Study Drug Administration Schedule of Patients

The COVID-19 screening tests will be performed locally based on each site and/or local regulatory guidelines upon the investigator's discretion throughout the study period. If COVID-19 is confirmed positive during the Screening period, the patient should not be enrolled in this study until confirmation of complete recover from COVID-19 as per site and/or local regulatory guidelines. Although patients can be screened only once in normal circumstance as specified in Section 4.2.1, additional rescreening can be performed only in limited cases considering COVID-19. If COVID-19 is confirmed after randomization, the investigators will discuss a case-by-case about the position of patient with the sponsor. In case of patient who has contact with COVID-19 patients within 14 days from any site visit, investigator will reconsider the enrollment or visit schedule following the site and/local regulatory guidelines

Investigators will promptly notify to the sponsor if any unfavorable situation is occurred in relation to local COVID-19 status (e.g., site shut down, lock down of city, cohort isolation, etc.). For sites where the patients are unable to travel or use public transportation, the sponsor will support the patients with alternative transportation or reimbursement for travel to ensure the visits can be made within the window or the visit can be proceeded at the earliest. Pre-approval is required for reimbursement.

The patients require face-to-face interactions for study drug administration. Therefore, in the event patients cannot visit the study center on the scheduled day for administration,

the treatment schedule will be adjusted following Section 5.6. However, if study drug administration cannot be done within an allowed visit window or missed dose is expected, whether to continue with the subsequent study drug will be discussed with the sponsor, ensuring the compliance with the trial protocol to such an extent that an ongoing benefit-risk assessment for the clinical trial and patients is still possible.

Even if study visit cannot be made, possible data will be collected via phone call and during the next visit, if applicable. Investigator will keep following up with patients regarding any safety issues by phone call before the patients visit the site.

Although the COVID-19 pandemic situation is likely to introduce more protocol deviations than normal circumstance, protocol deviations will be managed in accordance with the standard procedures. The number and type of deviations will be monitored periodically to assess whether a protocol amendment or other modifications are needed.

Site Monitoring and Audit

In case where a monitoring visit cannot be made because of the situation of COVID-19, centralized monitoring will be performed by the sponsor and/or contract research organization (CRO) as alternatives particularly considering the situation of the site, for the sites where the first patient is randomized but the first monitoring visit is not performed. Manual data review on electronic case report form (eCRF) will be performed and if any mistakes or deviations are observed, proper guidance will be provided to avoid them in the future on the site. Sponsor and/or CRO will review the data entered in CRF continuously and ensure raising queries and support the sites as necessary. If necessary, sponsor will create and review a report based on the eCRF data to check whether visits, assessments and administrations of study drug are in progress according to protocol and the same will be shared with CRO for site management.

Audits are needed as part of implementing quality assurance throughout the study period in order to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. In case where an audit cannot be made due to COVID-19 pandemic situation, sponsor will postpone audits or consider the remote audits after careful consideration of COVID-19 pandemic situation according to Guidance on the management of clinical trials during the COVID-19 Pandemic (EMA, 2021). Audits will be conducted only when permitted under national, local and/or organizational social distancing restrictions.

Handling of Missing Data

To assess any possible risks on data collection, data will be routinely reviewed according to Centralized monitoring plan and Risk based monitoring plan. After data collection, missing data on the primary analysis due to COVID-19 will be handled equally as specified in Section 7.4.1 as other missing cases. However, if a different approach is required for missing data due to COVID-19, it will be discussed at the masked data review meeting in a case-by-case manner and method of handling missing data will be specified in the SAP.

2 Study Objectives

2.1 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 DAS28 (Erythrocyte-Sedimentation Rate [ESR]) at Week 24.

2.2 Secondary Objective

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

3 Investigational Plan

3.1 Study Design

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 IV Q4W in combination with MTX (between 10 to 25 mg/week, oral or parenteral; intramuscular [IM] or 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 3-1.

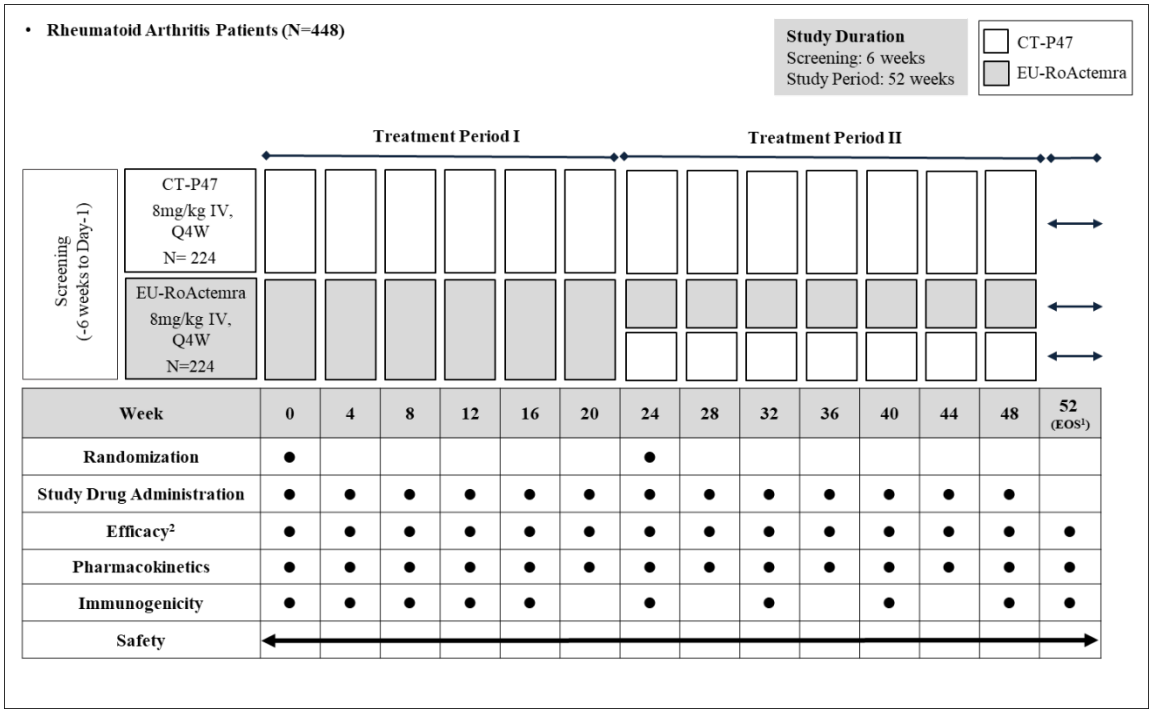


Figure 3-1 Study Design Overview

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.

3.1.1 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.

3.1.2 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 beginning to 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 (Table 11-1). 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).

3.1.3 End-of-Study 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 RA medication (including those prohibited by the protocol).

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

It is expected that approximately 448 patients will be enrolled at approximately 22 study centers in Poland. Male or female patients with moderate to severe active RA diagnosed according to the 2010 ACR/European Alliance of Associations for Rheumatology (EULAR) classification criteria (Aletaha et al., 2010) for at least 24 weeks, who have inadequate response to one or more DMARDs, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Patient is male or female aged 18 to 75 years old, both inclusive.
2. Patient has had a diagnosis of RA according to the 2010 ACR/EULAR classification criteria (Aletaha et al., 2010) for at least 24 weeks prior to the first administration of the study drug (Day 1).
3. Patient must have moderate to severe disease activity as defined by all of the following at Screening:
   - 6 or more swollen joints (of 66 assessed)
   - 6 or more tender joints (of 68 assessed)
   - either an ESR ≥28 mm/hour or a serum C-reactive protein (CRP) concentration ≥1.0 mg/dL (≥10 mg/L)
   - DAS28 (ESR or CRP) ≥3.2
4. Patient who has been receiving oral or parenteral MTX for at least 12 weeks and who has been on a stable dose and route of MTX between 10 to 25 mg/week for at least 8 weeks prior to the first administration of the study drug (Day 1).
5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
   - Serum creatinine ≤1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula) (SI [Système International d'Unités] units: 0.84 mL/s)
   - Serum alanine aminotransferase (ALT) ≤2.0 × ULN
   - Serum aspartate aminotransferase (AST) ≤2.0 × ULN
   - Serum total bilirubin ≤1.5 × ULN

6. Patient has the following hematology laboratory test results at Screening:
   - Absolute neutrophil count (ANC) ≥2,000/mm^3 ($2.0\times10^3/\mu L$)
   - Platelet count ≥100,000/mm^3 ($100.0\times10^3/\mu L$)
7. Patient and their partner of childbearing potential must agree to use following highly effective method of contraception consistent with local regulations throughout the study and for 6 months after the last dose of assigned treatment. A man or woman is of childbearing potential if, in the opinion of the investigator, he or she is biologically capable of having children and is sexually active (i.e., a man is fertile after puberty unless permanently sterile by bilateral orchidectomy or a woman is fertile, following menarche and until becoming postmenopausal unless permanently sterile).
   - Combined (estrogen and progestogen containing) or progestogen-only hormonal contraceptives associated with inhibition of ovulation
   - Intrauterine device or system
   - True abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to investigational drug, and withdrawal are not acceptable methods of contraception.
   - Double contraceptive methods (e.g., male condom in addition to use of hormonal or barrier method in female); for male patient with his female partner of childbearing potential only.

   If patient or their partner has been surgically sterilized for less than 24 weeks prior to the date of informed consent, they must agree to use any medically acceptable methods of contraception. Postmenopausal females must have experienced their last menstrual period more than 1 year prior to the date of informed consent without an alternative medical cause to be classified as not of childbearing potential.
8. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, has the ability to cooperate with the investigator and is given ample time and opportunity to read and understand verbal and/or written instructions, and signs the written informed consent form with date prior to participation in the study.

4.1.2 Exclusion Criteria

A patient meeting any of the following criteria will be excluded from the study:

1. Patient who has previously received investigational or licensed product; targeted synthetic DMARD(s) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or an IL-6 inhibitor for any purposes.
2. Patient who has previously received more than 1 biologic agents approved for the treatment of RA.

   Note. Patient with 1 biologic agent for the treatment of RA can be enrolled after sufficient wash-out period of at least 3 months or 5 half-lives (whichever is longer) prior to the first administration of the study drug (Day 1), except for etanercept and anakinra where only a 1 month washout prior to the first administration of study drug (Day 1) is necessary. Patients who have been treated with rituximab or a biosimilar of rituximab will not be allowed to enroll in the study.
3. Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products.
4. Patient who currently has, or has a history of, any of the following infections:
   - A known infection with hepatitis B (active or carrier of hepatitis B) or hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past hepatitis B virus is allowed if resolved (confirmed by negative HBsAg and HBV DNA).
   - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1)
   - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1)
   - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). However, a patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.
   - Other serious infections within 24 weeks prior to the first administration of the study drug (Day 1)
5. Patient who currently has, or has a history of, any of the following tuberculosis (TB):

- Patient who has current or a history of active TB. Patient who has any evidence of history of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.
- Patient who has signs or symptoms suggestive of active TB.
- Patient who has had exposure to a person with active TB such as first-degree family members or co-workers within 16 weeks prior to the first administration of the study drug (Day 1).
- Patient who has a past diagnosis of latent TB unless they have documentation of completing TB prophylaxis, or have received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
- Patient who has a current diagnosis of latent TB (defined as a positive result of interferon-γ release assay [IGRA] with a negative examination of chest X-ray) at Screening without a history of active TB or latent TB. However, a patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
- Patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening. If the result of IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening Period. Depending on the result of retest, the enrollment will be determined as follows:
  - If the repeated IGRA result is negative, the patient can be enrolled.
  - If the repeated IGRA result is positive, the patient who has received at least the first 3 weeks of country-specific TB prophylaxis prior to the first administration of the study drug (Day 1) and intends to complete its entire course can be enrolled.
  - If the repeated IGRA result is again indeterminate, the patient cannot be enrolled.

6. Patient who has a medical condition including one or more of the following:
   - Current uncontrolled diabetes mellitus, even after insulin treatment
   - Current uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg)

- Any other current inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or fibromyalgia, that may confound the evaluation of the effect of the study drug
- Current significant systemic RA involvement (e.g., Sjögren's syndrome, vasculitis, pulmonary fibrosis), which would put the patient at risk if they are enrolled
- Current or history of diverticulitis, chronic ulcerative lower gastrointestinal tract disease or any other gastrointestinal condition that may predispose to perforation. A known malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
- Current or past history of severe uncontrolled cardiac disease (unstable angina, New York Heart Association [NYHA] Class III or IV heart failure, or clinically significant electrocardiogram [ECG] abnormalities judged by the investigator) including cardiovascular disorders or myocardial infarction within 24 weeks prior to the first administration of the study drug (Day 1)
- History of organ transplantation, including corneal graft/transplantation
- Any current respiratory disease that can be judged as clinically significant at the investigator's discretion, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion
- Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome
- Any other current or history of serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results
- History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion

7. Patient who has received or plans to receive any of the following prohibited medications or treatment:

- Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1). A patient is permitted to receive one injection of intra-articular corticosteroid (≤40 mg of methylprednisolone or equivalent) from Week 36 (after all Week 36 assessments have been performed) and until the end of the study. A patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and NSAID, if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1) and the same dose must be maintained until 24 weeks after the first administration of the study drug (Day 1). In addition, a patient is permitted to receive low-potency topical, inhaled, otic, and ophthalmic glucocorticoid preparations provided, if the preparations are administered per the instructions on the product label.
- Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days must wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug (Day 1)
- Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer
- Alkylating agents within 1 year prior to the first administration of the study drug (Day 1)
- Herbal treatment within 2 weeks prior to the first administration of the study drug (Day 1)
- Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 1), or any planned live or live-attenuated vaccination during the study period
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 1) or planned within 36 weeks after the first administration of the study drug (Day 1)

8. Severe physical incapacitation (severely limited in ability to perform routine self-care, has RA ACR global functional status Class IV [Hochberg et al., 1992], or who cannot benefit from medication).

9. Female patient who is currently pregnant or breastfeeding, or plans to become pregnant or breastfeed within 6 months of the last dose of study drug. Male patient who is planning to donate sperm or father a child within 6 months of the last dose of study drug.
10. Patient who currently abuses alcohol or drugs or has a history of alcohol or drug abuse within 1 years from Screening.
11. Patient is vulnerable (e.g., employee of the study center or any other individuals involved with the conduct of the study, or immediate family members of such individuals, persons kept in prison, or other institutionalized persons by law enforcement).
12. Patient who, in the opinion of the investigator, should not participate in the study.

4.2 Study Drug Discontinuation and Study Termination

Patients are free to withdraw consent for treatment or participation in the study at any time for any reason. The investigator may also discontinue the study drug at any time in the interest of patient safety. Study drug discontinuation should not be considered as study termination. The primary reasons for the study drug discontinuation and study termination must be recorded in the patient's medical record and in the eCRF, with any comments (spontaneous or elicited) or complaints made by the patient. Reasons for study drug discontinuation include the following:

- Patient has any AE that would compromise his or her safety if he or she continues the study drug.

  Note. Patient experiences abnormal laboratory results (who meet discontinuation condition), or anaphylaxis or other serious treatment-related hypersensitivity reactions as described in Section 5.2.2.

- Patient shows inadequate efficacy or disease progression in the judgement of the investigator.
- Patient has a significant protocol deviation(s).
- Patient is pregnant.
- Investigator's decision.
- Patient withdraws consent for treatment: Patients will continue off treatment in the study until EOS or until withdraws consent for participation.

- Patient dies
- Patient is lost to follow-up

If the patient does not visit the study center without contacting and is not responsive to the telephone contact by the site, the site will try to contact to patient's family member(s) by telephone, using contact information available on file at the site. The contact information will only be collected if the patient and patient's family member(s) agreed in advance. For all patients who discontinue study drug early, every effort should be made to complete regularly scheduled visits for efficacy and safety assessments, even if they change their RA medication (including those prohibited by the protocol). If a patient cannot or is unwilling to attend any visit(s), a safety follow-up will be conducted by telephone according to the study visit schedule.

Reasons for study termination include the following:

- Patient withdraws consent or refuses to procedures/observations.
- Patient is lost to follow-up.
- Patient dies.

If necessary, the investigator may discuss with sponsor or its designee any patient's reason for study drug discontinuation or study termination. The sponsor may be contacted if clarification is required on a case-by-case basis. All patients who terminated from the study will retain their patient number.

4.2.1 Recruitment of Additional Patients

Patients who receive study drug and terminate prior to study completion will not be replaced. Patients who are failed at Screening, for any reason, can be rescreened only once. If there is unusual situation that justifies consideration for additional rescreening, the investigator is recommended to discuss with the sponsor. Rescreened patient will be assigned with new patient identification number.

4.3 Premature Termination of the Study

The sponsor reserves the right to terminate the study at any time for reasonable medical and/or administrative reasons. As far as possible, this should occur after mutual consultation.

During the study period, IDMC members will review and evaluate accumulating data including safety according to Section 9.4.1. IDMC members will recommend trial continuation or stop considering the safety of study patients and/or unfavorable results.

If the study is terminated prematurely by the sponsor, all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the independent ethics committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Groups

An interactive web response system (IWRS) will be used for the randomization. Biostatistician will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes.

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 followings;

- 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

The details of stratification factors will be described in the randomization specification document, which will be provided in a separate document.

5.2 Treatments Administered

Patients will receive either CT-P47 or RoActemra 8 mg/kg (not exceeding 800 mg/dose) by IV infusion Q4W. The study drug should be diluted to a final volume of 100 ml with sterile, non-pyrogenic sodium chloride 9 mg/ml (0.9%) solution and infused over 1 hour (+15 minutes). Patients will be dosed at specific time points as detailed in the schedule of events (Table 11-1).

5.2.1 Co-administration of Methotrexate and Folic Acid

All patients should have been receiving oral or parenteral (IM or SC) MTX at a dose of between 10 to 25 mg/week, for at least 12 weeks and have been on a stable dose and route of MTX for at least 8 weeks prior to the first administration of the study drug (Day 1). The same dose and route should be maintained throughout the study.

Methotrexate with folic acid is co-administered to minimize or prevent AEs related to MTX side effects. Patients are required to take folic acid (≥5 mg/week, oral dose) throughout the duration of the study (Whittle and Hughes, 2004).

Methotrexate and folic acid should be given according to a weekly schedule on the day recommended by the investigator and details will be recorded in the source documents and the eCRF.

5.2.2 Dosage Modification and Treatment Interruption or Discontinuation

For patients who experienced anaphylaxis or other serious treatment-related hypersensitivity reaction, study drug must be stopped immediately and discontinue study drug. If patients develop laboratory abnormalities in liver enzyme (ALT and/or AST), ANC, or platelet, or develops a serious infection, an opportunistic infection, or sepsis, the dose of concomitant DMARDs should be modified or dosing stopped and/or study drug (CT-P47 or RoActemra) dosing modified until the clinical situation has been evaluated and controlled. The window for dose delay should be followed according to Section 5.6.

5.2.2.1 Elevated Liver Enzyme (ALT and/or AST)

Laboratory Value	Action
>1 to 3 × Upper Limit of Normal (ULN)	Dose modify concomitant MTX if appropriate. For persistent increases in this range (e.g., if lab abnormality occurs at ≥2 consecutive visits or by investigator's decision), reduce dose to 4 mg/kg or hold CT-P47 or RoActemra until ALT or AST have normalized. Restart with 4 mg/kg or 8 mg/kg, as clinically appropriate.
>3 to 5 × ULN	Interrupt CT-P47 or RoActemra dosing until <3 × ULN and follow recommendations above for >1 to 3 × ULN. For persistent increases >3 × ULN (confirmed by repeat testing) (e.g., if lab abnormality occurs at ≥2 consecutive visits or by investigator's decision), discontinue CT-P47 or RoActemra.
>5 × ULN	Discontinue CT-P47 or RoActemra.

References: RoActemra SmPC, 2022; Actemra USPI, 2022.

5.2.2.2 Low Absolute Neutrophil count

Laboratory Value (cells x 10^9/L)	**Action**
ANC >1	Maintain dose.
ANC 0.5 to 1	Interrupt CT-P47 or RoActemra dosing. When ANC increases >1 × 10^9/L, resume CT-P47 or RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
ANC <0.5	Discontinue CT-P47 or RoActemra.

References: RoActemra SmPC, 2022; Actemra USPI, 2022.

5.2.2.3 Low Platelet Count

Laboratory Value (cells x 10^3/µL)	**Action**
Platelet 50 to 100	Interrupt CT-P47 or RoActemra dosing. When platelet count >100 × 10^3/µL, resume CT-P47 or RoActemra at 4 mg/kg and increase to 8 mg/kg as clinically appropriate.
Platelet <50	Discontinue CT-P47 or RoActemra.

References: RoActemra SmPC, 2022; Actemra USPI, 2022.

5.3 Identity of Investigational Product

CT-P47 is a humanized mAb that is being developed as a proposed biosimilar medicinal product to RoActemra and Actemra.

The International Non-proprietary Name of the commercially available reference material (RoActemra/Actemra) is tocilizumab and the Anatomical Therapeutic Chemical Classification System code is L04AC07.

The reference product, RoActemra, is supplied as a sterile concentrate for solution for IV infusion. RoActemra is a clear to opalescent, colorless to pale yellow solution (RoActemra SmPC, 2022).

CT-P47 drug product will be supplied as a sterile, preservative-free, colorless to pale yellowish solution with a pH 5.5-6.5. CT-P47 for IV use in clinical study is formulated at 400 mg/20 mL in single-dose vial.

The following drug supplies will be used in the study:

Product	Supplied as:
CT-P47	Vial containing 20 mL (400 mg/20 mL) concentrate of CT-P47 for solution for infusion
RoActemra	Vial containing 20 mL (400 mg/20 mL) concentrate of tocilizumab for solution for infusion

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging, Labelling, and Storage

The appropriate number of study drug will be allocated to each patient via the IWRS system at each visit.

A label will be attached to the outside of each patient kit, as well as to the immediate container. The text will be compliant with local regulatory requirements and may include some of the following information:

- Protocol number
- Patient number
- Contents
- Lot number
- Randomization code/kit number
- Investigator’s name
- Storage instructions
- Caution statement (for study use only)
- Sponsor’s contact name and address
- Expiry date

All study drug supplies must be stored in a secured area (e.g., a locked cabinet), protected from light. Both CT-P47 and RoActemra must be kept at a controlled refrigerated temperature between 2°C and 8°C (36°F to 46°F) and it must not be frozen.

5.4.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result

recorded in the drug accountability form maintained at the study center. The study drug accountability will be verified by the monitor during on-site monitoring visits. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

The investigator agrees not to supply the study drug to any person other than sub-investigators, designated staff, and the patients participating in the study. Study drug may not be relabeled or reassigned for use by other patients unless approved by sponsor.

During the study, unused study drug vials should be returned to the depot of origin. Accountability of the product must be completed at the site level and discrepancies, if any, need to be resolved prior to return. Only if it is written in standard operating procedures or documentation in place, the used vials can be destroyed locally. The list of destroyed vials must be recorded. The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with sponsor.

Details in study drugs accountability and destruction will be followed according to the pharmacy manual.

5.5 Blinding

This study will be double-blind.

5.5.1 Breaking the Blind

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 sponsor and EastHORN blinded teams until all patients have completed the study and the database has been finalized for study termination.

5.6 Treatment Compliance

CT-P47 and RoActemra will be diluted by a designated staff, and will be supplied to the treating staff or designee in the blinded manner. The study drug should be administered as a 1-hour infusion (+15 minutes). The start and end time of the infusion as well as any deviations from the planned infusion time will be recorded in both the source documents and the eCRF.

Every effort will be made to encourage patients' compliance with the study visits during study period. Particularly, patients are encouraged to visit study center at Week 20 within visit window for efficacy assessment which will be used for second randomization process at Week 24. If patient is unable to visit the study center at all at Week 20 for efficacy assessment, the investigator should contact the sponsor for further discussion.

A dose visit window of ±3 days is allowed from Dose 2 (Week 4) to Dose 13 (last dose at Week 48). If the dose visit window exceeds >3 days but ≤13 days from the scheduled visit date due to lab abnormality (Section 5.2.2) or other safety concerns for dosing by the investigators' discretion, it should be considered as 'dose delay' and the subsequent visit schedule should be readjusted to every 4 weeks from the time of last study drug administration. However, for other cases (e.g., patient's personal reasons), original scheduled visit (Table 11-1) should be followed for the subsequent visits. If the dose visit window exceeds >13 days from the scheduled visit date (e.g., dosing interval is over 6-week) regardless of the reasons, it should be considered as 'dose skip' and the next dose should be administered as soon as possible. The subsequent visit schedule should be readjusted to every 4 weeks from the time of last study drug administration. For study visits at which the study drug dosing is held, all other study assessments should be performed as per study schedule, if possible.

5.7 Prior, Concomitant, and Subsequent Therapy

Aside from MTX and folic acid, which should be administered throughout the study as described in Section 5.2.1, a patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and NSAID, if they have received a stable dose for at least 4 weeks prior to the first administration of the

study drug (Day 1) and the same dose must be maintained until 24 weeks after the first administration of the study drug (Day 1). Any changes before Week 24, in terms of dose, need to be reported to and discussed with the medical monitors of sponsor or its designee in advance. In addition, patients are permitted to receive low-potency topical, inhaled, otic, and ophthalmic glucocorticoid preparations provided, if the preparations are administered per the instructions on the product label.

Killed vaccinations are acceptable during the study.

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 the patient's eCRF.

Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug until the EOS visit, will be recorded in the patient's eCRF. However, in order to check eligibility, prior medications will be reviewed from date specified in Section 4.1.2. This will include all prescription drugs, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

5.8 Rescue Therapy

For the duration of the study, 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 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 information about the rescue therapy use will be reported in the patient's eCRF.

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.

5.9 Prohibited Therapy

The following medications, treatments, or procedures during the study period are prohibited. Patients who have received or plan to receive these prohibited medications or treatments will not be enrolled in the study (Section 4.1.2). Patients who receive any prohibited therapy during the Screening period should be considered a screen failure. Intake of any of the following prohibited therapy by the patients after randomization will be considered as protocol deviation (except patient receives prohibited medication for rescue therapy specified in Section 5.8).

- Any biologic agents approved for the treatment of RA or IL-6 inhibitor for any purposes
- Conventional DMARDs other than MTX or targeted synthetic DMARDs

  Intra-articular corticosteroids (From Week 36 [after all Week 36 assessments have been performed], one injection of ≤ 40 mg of methylprednisolone or equivalent is allowed until the end of the study)
- Any other investigational device or medical product
- Alkylating agents
- Herbal treatments
- Live or live-attenuated vaccine. Inactivated vaccines are acceptable during the study.

  Note. Authorized COVID-19 vaccines of non live-attenuated types are allowed (e.g., mRNA, viral vector), if patients receive COVID-19 vaccine at least >7 days apart from the previous and next study drug administration (refer to Section 1.6.1.2).
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) are not allowed until 36 weeks after the first administration of the study drug (Day 1)

6 Study Assessments and Procedures

Prior to performing any study procedures, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered prior to signing the ICF. The investigator must address all questions raised by the patient. The investigator or designee will also sign the ICF.

All patients will return to the study center by regular scheduled time intervals for clinical assessments and blood samplings. Patients will undergo the procedures at the time points specified in the schedule of events (Table 11-1).

6.1 Demographics, Baseline, and Background Characteristics

At screening, medical history (general medical history and medication history), demographic data (age, gender, ethnicity, and race), and height will be collected and reported in the eCRF.

Blood samples for rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) will be collected only at screening, at the same time as the clinical laboratory blood samples. The blood samples will be tested in the central laboratory.

6.2 Efficacy Assessments

Efficacy will be assessed by the evaluation of the DAS28 (DAS28 [ESR], DAS28 [CRP], and individual components) score, ACR criteria (individual components, ACR20, ACR50, and ACR70, and hybrid ACR response), EULAR response criteria, simplified disease activity index (SDAI), clinical disease activity index (CDAI), ACR/EULAR remission (Boolean-based definition), quality of life (SF-36), and joint damage progression at the time points specified in the schedule of events (Table 11-1).

6.2.1 Joint Count Assessment

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. 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 not be included in the joint count from all subsequent assessments. For assessment, the independent joint assessor will be informed about the history of the patient's joint surgery with the name of the surgery, date, and location. Standardized training will be provided to all joint count assessors and evidence of such training will be recorded in the joint assessor's training records.

6.2.2 Disease Activity Score Using 28 Joint Counts

Disease Activity Score using 28 joint counts (ESR) and DAS28 (CRP) will be evaluated at time points specified in the schedule of events (Table 11-1). The core set of variables for DAS28 for this study include the following:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 for swelling
- Patient's global assessment of disease activity measured using visual analogue scale (VAS) (Appendix 11.3)
- ESR
- CRP

6.2.3 American College of Rheumatology Criteria and Individual Components

The ACR criteria are a series of individual assessments used for the calculation of ACR20, ACR50, ACR70, and hybrid ACR response (American College of Rheumatology Committee to Reevaluate Improvement Criteria, 2007). The ACR core set of variables (individual components) for this study include the following:

- Number of tender and swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling
- Patient's and physician's global assessment of disease activity measured on VAS (Appendices 11.3 and 11.4)
- Patient's assessment of pain measured on VAS (Appendix 11.5)
- Health Assessment Questionnaire (HAQ) estimate of physical ability (Appendix 11.6)
- ESR
- CRP

6.2.4 Simplified Disease Activity Index and Clinical Disease Activity Index

Simplified and clinical disease activity will be measured using SDAI and CDAI (Aletaha and Smolen, 2009). The core set of variables for SDAI and CDAI for this study include the following:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 joints assessed for swelling
- Patient's global assessment of disease activity (VAS) (Appendix 11.3)
- Evaluator/physician global assessment of disease activity (VAS) (Appendix 11.4)
- CRP (for SDAI only)

6.2.5 ACR/EULAR remission (Boolean-based definition)

ACR/EULAR remission will be evaluated using the Boolean-based definition. The variables include the following:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 joints assessed for swelling
- CRP
- Patient's global assessment of disease activity (VAS) (Appendix 11.3)

6.2.6 Quality of Life

Quality of life will be assessed using the 36-item short form health survey (SF-36) questionnaire at the time points specified in the schedule of events (Table 11-1).

6.2.7 Joint Damage Progression

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 time points specified in the schedule of events (Table 11-1). Joint damage, progression as determined by radiography, will be assessed in the central laboratory by the change in total Sharp score using the modified total Sharp scoring system (Plant et al., 1994; Sharp et al., 1971; Sharp et al., 1985) and the blind regarding the time point at which the displayed images will be obtained. The baseline radiographs will be assessed within 42 days prior to the first administration of the study drug (Day 1).

6.3 Pharmacokinetic Assessments

For all patients, blood samples for the determination of serum concentration of study drug will be collected prior to dosing at the time points specified in the schedule of events (Table 11-1). If the 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 the PK assessment. The PK of CT-P47 and RoActemra will be assessed using a validated method for serum concentration. It will be specified in a separate validation document.

Sample analysis will be performed at the bioanalytical laboratory.

6.4 Safety Assessments

Safety assessments will include the followings, at time points specified in the schedule of events (Table 11-1): AEs, clinical laboratory testing, and other safety assessments.

6.4.1 Adverse Events

Patients will be instructed to contact the investigator immediately if any symptoms develop from the time the ICF is signed until the end of the patient's participation in the study. The investigator is responsible for reporting all AEs that are observed and/or reported by the patient during the study through the eCRF.

6.4.1.1 Definitions of Adverse Events

An 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 severity or frequency compared with baseline.

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 severity or frequency after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they fulfill the following:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention

- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)

- Are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact

If the patient's RA worsens temporarily, disease aggravation will be captured as the (S)AE(s) term. However, if disease has worsened continuously in the judgment of the investigator (e.g., worsened for >8 weeks), this will be considered disease progression and not disease aggravation; disease progression will not be captured as an (S)AE. If disease progression is decided by the investigator, the patient will be discontinued from the study drug by investigator's judgement and the disease aggravation reported in the previous visit will be deleted in the eCRF.

Medical interventions such as surgery, diagnostic procedures, and therapeutic procedures are not AEs but the action taken to treat the medical condition. They should be recorded as treatment(s) of the AEs. The event term of primary cause should be recorded and reported in the eCRF instead of the term of surgery, diagnostic procedure, or therapeutic procedure.

6.4.1.1.1 Adverse Events of Special Interest

An adverse event of special interest (AESI) is an AE that is designated to be of special interest and will be reported by the study center following the same process as for AEs:

- Infection
- Hypersensitivity, including anaphylaxis
- Hepatic event
- Hemorrhage (medically significant bleeding events)
- Gastrointestinal perforation
- Malignancy
- Demyelinating disorder

6.4.1.1.2 Serious Adverse Events

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

- Results in death

- Is immediately life threatening: Refers to an AE in which the patient was at immediate risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Adverse events associated with hospitalization or prolongations of hospitalization are considered SAEs. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, from medical floor to a coronary care unit, from neurological floor to a TB unit).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is **not** in itself an SAE. Examples include the following:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment laboratory abnormality)
- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly physical examination)
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol)
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE

- Hospitalization purely for convenience (e.g., for easier performance of study assessments)

- Pre-planned treatments or surgical procedures; these should be noted in the baseline documentation for the entire protocol and/or for the individual patient

6.4.1.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as an event of which the nature or severity is not consistent with the applicable Reference Safety Information (e.g., IB). Assessment of expectedness will be made with the use of the IB. Therefore, if a treatment-related SAE occurs and it was not mentioned in the applicable Reference Safety Information of the product information, it will be reported as a SUSAR.

6.4.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the patient signs the ICF until the end of the patient's participation in the study. Adverse events of special interest will be closely monitored by the investigator.

Throughout the study, patients will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs identified from any study data (e.g., laboratory values, physical examination findings, ECG changes) or other data collected that are relevant to patient safety will be documented on the AE page in the eCRF.

6.4.1.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page in the eCRF. Information to be collected includes drug treatment, dose, event term, time of onset, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, action taken with study drug, any required treatment or evaluations, and outcome.

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, or reactions to concurrent medications must also be reported.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not considered as an AE. However, if a preexisting condition deteriorates at any time during the study, this is considered an AE and must be reported.

The investigator's assessment of an AE's severity and relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 6.4.1.5 and 6.4.1.6, respectively.

Adverse events (and SAEs) should be reported until the EOS visit regardless of the relationship to the study drug.

6.4.1.4 Reporting Serious Adverse Events

Any AE considered serious by the investigator or which meets SAE criteria (Section 6.4.1.1.2) must be reported to EastHORN immediately (within 24 hours after the study center staff first notices about the event).

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and email it to EastHORN within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. If the patient is hospitalized during an SAE or because of an SAE, a copy of the hospital discharge summary will be e-mailed to EastHORN as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or sub-investigator.

The following contact information is to be used for SAE reporting in case reporting via remote data capture system is not available:

EastHORN Pharmacovigilance Department

SAE E-mail: safety.22101@easthorn.eu
SAE Fax (to be used only if e-mail is inaccessible): +420 244 462 271

Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), the FDA's Code of Federal Regulations (CFR) (21 CFR part 312.32), International Council for Hamonisation (ICH) guidelines, and/or local regulatory requirements.

6.4.1.5 Assessment of Severity

The severity of an AE will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. For assessing severity for AEs that are not specifically listed in the CTCAE v5.0, the following general guideline will be used (a semicolon indicates "or" within each description):

Grade 1: Mild AE (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)

Grade 2: Moderate AE (minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.)

Grade 3: Severe or medically significant but not immediately life threatening (hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living)

Grade 4: Life-threatening consequences (urgent intervention indicated)

Grade 5: Death related to AE

The investigator will assess of the maximum intensity that occurred over the duration of the event. However, if an existing AE before study drug administration exacerbates after study drug administration or if an AE changes from a nonserious to a serious event, a new AE needs to be reported separately. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.1.6 Assessment of Causality

The causality or relatedness of an AE refers to whether or not the investigator deems the AE to be related to the study drug. The investigator's assessment of an AE's relationship to the study drug is part of the source documentation process and should be reported in the eCRF, regardless of the suggested causality.

The causal relationship of an AE to the study drug will be characterized using the following classification:

Unrelated: There is no association between the study drug and the reported event.

Possible: Treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: A reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation of study drug.

Definite: A definite causal relationship exists between drug administration and the AE, and other conditions (e.g., concurrent illness, progression of disease state, concurrent medication reaction, etc.) do not appear to explain the event.

6.4.1.7 Follow-Up of Patients Reporting Adverse Events

All AEs will be followed until resolution or improvement to baseline, death, confirmed by the investigator that no further improvement could be expected, or until the end of the patient's participation in the study.

6.4.2 Clinical Laboratory Testing

The standard clinical laboratory analyses will be performed by the central laboratory according to validated methods and procedures, except for ESR (local laboratory using kits supplied centrally).

The following clinical laboratory assessments will be performed (Table 11-1):

Clinical chemistry	Total protein, serum bilirubin (total, direct), ALT, 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, ESR, and uric acid
Hematology	Hematocrit, hemoglobin, red blood cells, total and differential white blood cell count, ANC, and platelet count

Viral Serology	Anti-HIV (HIV-1 and HIV-2) antibodies, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) (total or IgG), hepatitis C antibody (HCAb)
Other	IGRA, soluble interleukin-6 receptor (sIL-6R)
Urinalysis	bilirubin, blood, color, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, and urobilinogen

Creatinine clearance (by Cockcroft-Gault formula) will be calculated using serum creatinine level only at Screening for inclusion.

During the study period, liver enzymes (ALT and AST), ANC and platelets will be closely monitored considering dose related laboratory abnormalities as specified in Section 5.2.2. 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. Test results will be recorded in the eCRF and source documents.

It is the investigator's responsibility to review all laboratory findings. Any value that falls outside of the normal reference range will be flagged for review and the investigator will indicate whether or not the value is deemed clinically significant. If any of the screening results are indicated as clinically significant, the patient will be considered ineligible and **not** be allowed into the study without permission of the sponsor. However, a retest during the screening period is permitted once by the investigator's judgment. Additional testing during the study may be performed if medically indicated. If a clinically significant abnormality is observed during the study, as defined in Section 6.4.1.1, this should be recorded as an AE and the patient will be followed up until the test have normalized or stabilized.

6.4.2.1 Hepatitis B and Hepatitis C and Human Immunodeficiency Virus

At Screening, HBsAg, HBsAb, and HBcAb (total or IgG) will be assessed in all patients as specified in Table 6-1.

Table 6-1 Eligibility based on Serologic Markers for Hepatitis B Infection

Test Results				Eligibility
HBsAg	**HBsAb**	**HBcAb**	**HBV DNA**	
+	+/–	+/–	Not applicable	Not eligible
–	+/–	+	+	Not eligible
			–	Eligible[1]
–	+/–	–	Not applicable	Eligible

Abbreviations: DNA, DeoxyriboNucleic Acid; EOS, end of study; HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

1. Testing of HBsAg, HBsAb, HBV DNA, ALT, AST, and total bilirubin will be performed at Week 24 and EOS visit.

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. If the patient develops hepatitis B reactivation, the patient will be discontinued from the study drug.

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 and HIV analysis will be performed at the central laboratory.

6.4.3 Other Safety Assessment

6.4.3.1 Immunogenicity Testing

The immunogenicity of CT-P47 and RoActemra will be assessed by ADA and neutralizing antibody (NAb) test in validated immunoassay. It will be specified in a separate validation document.

Blood samples for immunogenicity assessments of CT-P47 and RoActemra will be collected from all patients at the time points specified in the schedule of events (Table 11-1). The immunogenicity samples will be drawn at the same time as samples for PK and/or for clinical laboratory testing, where possible. 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 will be assessed when immune-related AEs (e.g., hypersensitivity) occur.

6.4.3.2 Hypersensitivity Monitoring

For hypersensitivity monitoring, vital signs (including systolic and diastolic BP, heart rate, respiratory rate, and body temperature) will be monitored before beginning of the study drug administration (within 15 minutes) and at 1 hour (±15 minutes) after the end of the study drug infusion.

In addition, any type of ECG will be performed for hypersensitivity monitoring 1 hour (±15 minutes) after the end of the study drug infusion. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator will be available. For patient who early discontinued study drug, monitoring of hypersensitivity is unnecessary after the discontinuation.

For patients who experience anaphylaxis or other serious treatment-related hypersensitivity reaction, study drug must be stopped immediately and the patient discontinued from the study drug.

Anaphylaxis will be identified according to Sampson criteria as following.

Anaphylactic reactions

Anaphylaxis will be identified according to Sampson criteria (Sampson et al., 2006). Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled.

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

   a. Adults: Systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline.

Details will be recorded in both the source documents and the eCRF.

6.4.3.3 Vital Signs and Weight

Vital signs will be measured at the time points indicated in the schedule of events (Table 11-1). The following vital signs will be measured:

- Blood pressure (systolic and diastolic [mmHg])
- Heart rate (beats per minute)
- Body temperature (°C)
- Respiratory rate (breaths per minute)

Blood pressure and HR will be measured using consistent methods for each patient and after the patient has been resting for at least 5 minutes. The same route of temperature recording should be used for each patient. All measurements will be documented at each visit, and the details will be recorded in both the source documents and the eCRF.

Vital sign measurements will also be monitored before and after study drug administration as part of hypersensitivity monitoring (Section 6.4.3.2).

Body weight (in kg, wearing only light clothes, no shoes) will be measured according to the schedule of events (Table 11-1) to determine dose of study drug.

6.4.3.4 Physical Examination

A physical examination will be performed at the time points indicated in the schedule of events (Table 11-1).

The physical examination includes an assessment of general appearance and a review of systems. Information about the physical examination will be recorded by the investigator, or delegated clinical staff member, in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Clinically significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded as such in the source documents and eCRF.

6.4.3.5 Pregnancy

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 urine pregnancy test will be used to confirm patients are not pregnant prior to dosing on each scheduled visit specified in the schedule of events (Table 11-1) or more frequently if required by country-specific legislation. Only patients with a negative serum pregnancy test results can be enrolled in the study (i.e., patients with inconclusive serum pregnancy test results at first result are not considered inclusion). 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.

In an event of unexpected pregnancy during study participation and for 6 months after the last dose of study drug, patients will be counselled to inform the investigator. If a female patient becomes pregnant, the study drug must be discontinued immediately. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to sponsor and EastHORN pharmacovigilance department within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to sponsor and EastHORN within 24 hours after acquisition of the consent for the pregnancy form.

Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained. Pregnancy alone will not be regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. Elective abortions without complications should not be handled as AEs, unless they are therapeutic abortions. Hospitalization for normal delivery of a healthy newborn should not be considered as SAE. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.4.1.4).

6.4.3.6 Electrocardiogram

12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in supine position at the time points indicated in the schedule of events (Table 11-1).

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. If, following ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patients will be referred to a cardiologist and the event will be recorded in the source documents and the eCRF. Regardless of the ECG result, further evaluation with a cardiologist can be performed at the discretion of the investigator.

In addition, any type of ECG will be performed for hypersensitivity monitoring 1 hour (±15 minutes) after the end of the study drug infusion (Section 6.4.3.2).

6.4.3.7 Tuberculosis Assessment

Patients who currently have, or have a history of, or experience any of TB related situation as specified in Section 4.1.2, will result in exclusion from the study.

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, as specified in the schedule of events (Table 11-1). Patients with active TB based on the imaging, microbiology results and/or the clinical signs and symptoms will be discontinued from the study drug or terminate the study at discretion of the investigator.

If the result of the IGRA is positive during the study, patients will be referred to the clinician immediately to investigate the presence of active TB based on medical history and any clinical signs and symptoms including chest X-ray result. Even in the absence of clinical suspicion for active TB, study drug administration will be temporarily stopped. It is recommended that study drug administration is resumed in patients who have received at least 3 weeks of country-specific TB therapy and who intend to complete the entire course of TB therapy. However, study drug administration can be resumed simultaneously with the start of country-specific TB therapy after discussion with the medical monitors of sponsor or its designee in advance.

If the patient is exposed to a person with active TB during the study period, an IGRA test will be done immediately and country-specific TB therapy will be initiated immediately regardless of the IGRA test result being negative or positive. The IGRA test will be repeated 8 weeks after the initial IGRA test and country-specific TB therapy can be discontinued if the repeated result is negative.

No further IGRA testing is required during the treatment period for the following patients:

- Patient who has a history of latent TB with sufficient documentation of complete TB prophylaxis.

- Patient who has confirmed latent TB at Screening and enrolled after at least 3 weeks of latent TB prophylaxis. This patient should have sufficient documentation of complete TB prophylaxis.
- Patient with a positive result of IGRA during the study.

6.4.3.7.1 Chest X-Ray

A chest X-ray (both posterior–anterior and lateral views) should be taken during Screening and read by a qualified radiologist or pulmonary physician to specifically look for evidence of current or previous active or latent TB. If a chest X-ray within 42 days prior to the first administration of the study drug (Day 1) is available, a chest X-ray is not required at Screening, and the result will be recorded in both the source documents and the eCRF.

Radiographic findings suggestive of healed TB or active TB may include but are not limited to pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations, and pleural effusions. Any abnormal X-ray changes should be discussed with the medical monitor prior to the first administration of the study drug (Day 1). The chest X-ray should be available to the investigator for review prior to the first administration of the study drug (Day 1) of the patient.

6.4.3.7.2 Interferon- γ Release Assay

An IGRA will be used to identify positive conversion of negative results for patients. Samples for this analysis will be obtained at the time points specified in the schedule of events (Table 11-1). The IGRA will be performed at the central laboratory.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual. The sample collection tube may be changed during the study and details will be provided in the laboratory manual.

6.6 Sample Labelling, Storage, and Shipment

6.6.1 Sample Labelling

Each sample tube will be clearly labelled with the following information: study number, patient number, tube identification, and scheduled sampling time point.

6.6.2 Sample Storage and Shipment

During the study, blood samples will be collected for PK, immunogenicity, and/or safety analyses.

Where appropriate, the serum should be transferred into a sufficient number of transfer tubes for transport to assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples.

Additionally, back-up samples for PK and/or immunogenicity will be retained at the central laboratory as a backup for up to 5 years after the end of the study in case additional analysis is required, however, samples can be destroyed at any time with sponsor's approval even within 5 years. If additional analysis for PK and/or immunogenicity is not required, the sample will be stored at Sponsor or a designated biobank for a further 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by sponsor to destroy the sample. Additional tests can be conducted at sponsor or the biobank if it is required from a regulatory or medical perspective. Details in storage and shipment will be followed according to the laboratory manual.

7 Statistical Considerations

The statistical analysis will be performed using SAS software Version 9.4 or later (SAS Institute Inc., Cary, North Carolina, USA). The statistical methods for this study will be described in a detailed SAP, which will be finalized prior to database lock. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the study report.

Continuous variables will be summarized by reporting the following descriptive statistics: the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category. Data will be listed in data listings.

7.1 Sample Size Calculation

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 was 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.

7.2 Analysis Sets

The following analysis sets will be used in the statistical analyses.

Intent-to-treat (ITT) Set: The ITT Set is defined as all patients randomly assigned to receive study drugs (CT-P47 or RoActemra)

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.

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 endpoint. 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 efficacy primary endpoint before unblinding.

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.

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.

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).

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.

7.3 Demographics, Baseline, and Background Characteristics

Demographics (including age, gender, ethnicity, and race) and baseline and background characteristics (including medical history, RA history, RF, and anti-CCP) will be presented in summary tables. Qualitative data (e.g., medical history) will be summarized in contingency tables, and quantitative data (e.g., age) will be summarized using quantitative descriptive statistics.

Listings will be provided by treatment group showing the demographics, baseline, and background characteristics in ITT set. In addition, a listing of patients whose trial participation is impacted by COVID-19 with details of the impact, will be prepared, if applicable.

7.4 Efficacy Analyses

7.4.1 Primary Efficacy Analysis

The difference of mean change from baseline of DAS28 (ESR) score at Week 24 will be analyzed 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, disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤5.1), and prior

biologic use approved for RA treatment (yes or no) as covariates. The 10 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, disease activity by DAS28 (ESR) score at Screening (>5.1 or ≤5.1), 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. Final determination of covariates and details will be described in the SAP. The two-sided 90% confidence interval (CI) for the difference between the 2 treatment groups (CT-P47 and RoActemra) will be produced. Therapeutic equivalence of treatment difference in the change from baseline of DAS28 (ESR) at Week 24 by the ANCOVA analysis will be concluded if the 90% CIs for the treatment difference is entirely within –0.6 to 0.5.

The primary population of primary endpoint is ITT Set evaluated under a treatment policy estimand. For the treatment policy estimand, all available data will be included in the primary analysis regardless of intercurrent events such as study drug discontinuation, switch to rescue therapy or protocol violation. A supportive analysis for the primary efficacy endpoint will be conducted using the PPS. Definition of each analysis set is described in Section 7.2. Additionally, the sensitivity analysis to evaluate the impact of missing data will be conducted on the ITT Set as described in Section 7.4.1.2.

7.4.1.1 DAS28 (ESR)

Disease activity score in 28 joints (ESR) (Appendix 11.8) will be assessed using the following equation:

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

Where:

- TJC28 = number of tender joints (0-28): tender joint count (TJC)
- SJC28 = number of swollen joints (0-28): swollen joint count (SJC)
- ESR = ESR measurement (mm/hour)
- GH = patient's global disease activity measured on 100 mm VAS (Appendix 11.3)

Descriptive statistics for actual value and change from baseline of DAS28 (ESR) will be summarized by treatment group.

7.4.1.2 Sensitivity Analysis for Primary Efficacy Endpoint

Sensitivity analysis using tipping point approach will be conducted for the primary efficacy endpoint in the ITT set. Tipping point analysis will be performed under the Missing Not At Random (MNAR) assumption. Imputed values by MI will be shifted gradually to make MNAR scenarios. 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 MNAR scenarios and corresponding CIs will be provided.

7.4.2 Secondary Efficacy Analysis

The secondary efficacy endpoints will be descriptively summarized using the ITT Set and PPS and data for Treatment Period II will be summarized on the ITT-Treatment Period II subset, unless otherwise specified. These will be summarized by treatment group as appropriate and listed. The following secondary efficacy endpoints will be assessed for all patients during the study:

- ACR20, ACR50 and ACR70
- Individual components of the ACR
- Hybrid ACR response
- DAS28 (CRP)
- DAS28 (ESR) (except for Week 24)
- Individual components of the DAS28
- EULAR response
- Simplified disease activity index (SDAI) and clinical disease activity index (CDAI)
- ACR/EULAR remission (Boolean-based definition)
- 36-item short form health survey (SF-36)
- Joint damage progression based on radiographic evaluations

7.4.2.1 ACR20, ACR50, ACR70 and Individual Components

A patient is defined as a responder according to ACR20/ACR50/ACR70 criteria if the following are fulfilled:

- A decrease of at least 20%/50%/70% in the number of tender joints (based on 68 joints)
- A decrease of at least 20%/50%/70% in the number of swollen joints (based on 66 joints), and
- A 20%/50%/70% improvement in at least 3 of the following:
    - Patient's assessment of pain on the VAS
    - Patient's global assessment of disease activity (VAS)
    - Physician's global assessment of disease activity (VAS)
    - HAQ estimate of physical ability
    - Serum CRP concentration or ESR

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).

The proportion of patients demonstrating ACR20, ACR50 and ACR70 will be summarized by treatment. Descriptive statistics for actual value and change from baseline of components of the ACR will be summarized by treatment group.

7.4.2.1.1 Health Assessment Questionnaire Disability Index

General health status will be assessed using the Health Assessment Questionnaire (HAQ) (Appendix 11.6). Descriptive statistics for actual value and change from baseline of HAQ index will be summarized by treatment group.

The following are the 8 categories within the HAQ:

- 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)

7.4.2.2 Hybrid ACR Response

The hybrid ACR is an outcome measure that combines the ACR20, the ACR50, the ACR70, and a continuous score of the mean improvement in core set measures (American College of Rheumatology Committee to Reevaluate Improvement Criteria, 2007). The hybrid ACR will be summarized by treatment using descriptive statistics. The possible scores are displayed in Table 7-1.

Table 7-1 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.

7.4.2.3 DAS28 (CRP)

See Section 7.4.1.1 for DAS28 (ESR).

Disease activity score in 28 joints (CRP) (Appendix 11.8) will be assessed using the following equation:

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

Where:

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

- CRP = CRP measurement (mg/L)
- GH = patient's global disease activity measured on 100 mm VAS (Appendix 11.3)

Descriptive statistics for actual value and change from baseline of DAS28 (CRP) and components of the DAS28 (ESR and CRP) will be summarized by treatment group.

7.4.2.4 EULAR Response Criteria

Response criteria according to EULAR are measured using DAS28 (ESR and CRP) according to Table 7-2. The proportion of patients achieving the EULAR response categories will be summarized by treatment group.

Table 7-2 EULAR Response 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 in 28 joints; EULAR, European Alliance of Associations for Rheumatology.
Reference: Fransen and van Riel, 2005.

7.4.2.5 Simplified Disease Activity Index and Clinical Disease Activity Index

Simplified and clinical disease activity will be measured using SDAI and CDAI calculated from the formulas presented in Table 7-3. Descriptive statistics for actual value and change from baseline of SDAI and CDAI will be summarized by treatment group.

Table 7-3 Calculation of Disease Activity Indices

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

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

7.4.2.6 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 scale)

7.4.2.7 Short-Form Health Survey

General health status will be assessed using the SF-36 version 2 (Appendix 11.7). The following 8 aspects of the health status will be assessed:

- General and mental health
- Physical function
- Social function
- Physical and emotional health
- Pain
- Vitality

The score on each subscale ranges from 0 (worst) to 100 (best). The individual aspects of the survey will be grouped into a physical component and a mental component summary score, each of which will be assigned a mean (±SD) score of 50 with an SD of 10 on the basis of an assessment of the general population without chronic conditions. Individual scores will be compared with the normalized scores for the general population. Descriptive statistics for actual value and change from baseline of SF-36 score will be summarized by treatment group.

7.4.2.8 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 system (Plant et al., 1994; Sharp et al., 1971; Sharp et al., 1985) at EOS visit. Descriptive statistics for actual value and change from baseline of joint damage progression will be summarized by treatment group.

7.5 Pharmacokinetic Analyses

Serum concentrations will be summarized using quantitative descriptive statistics (including geometric mean and percent coefficient of variation [CV%], as appropriate) by treatment group, study visit, and time point.

Serum concentrations for Treatment Period I will be summarized on PK Set and data for Treatment Period II will be summarized on PK-Treatment Period II subset, unless otherwise specified.

7.6 Safety Analyses

Safety analyses will be performed on the Safety Set and data for Treatment Period II will be performed on Safety-Treatment Period II subset, unless otherwise specified. 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.

7.6.1 Adverse Events

Adverse events will be graded for severity according to the CTCAE v5.0 and will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA. Safety analysis will focus on TEAEs, as described in Section 6.4.1.1.

The following TEAE summaries will be reported by SOC, PT, and treatment group, as appropriate:

- Number and percentage of patients reporting at least 1 TEAE
- Number and percentage of patients reporting at least 1 treatment-emergent SAE
- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with AESIs (infection, hypersensitivity including anaphylaxis, hepatic event, haemorrhage, gastrointestinal perforation, malignancy, and demyelinating disorder)

At each level of summarization for the number of patients with an event, a patient is counted only once if they reported one or more events and only the worst intensity will be counted at each level of summarization. All AE data will be presented in the data listings.

7.6.2 Clinical Laboratory Tests

Clinical laboratory tests will be summarized by treatment group at each scheduled collection time. Actual values and changes from baseline for clinical laboratory test results will be summarized by treatment arm at each time point using descriptive statistics. Shift tables will be generated for clinical laboratory test results. Individual clinical laboratory test results will also be presented in data listings.

7.6.3 Immunogenicity

The number and percentage of patients with ADA and NAb results will be listed and summarized by treatment group and visit.

7.6.4 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary. All prior and concomitant medications data will be listed and summarized by treatment group as appropriate.

7.6.5 Other Safety Analyses

Actual values and change from baseline for vital signs measurements will be summarized by treatment arm at each time point using descriptive statistics.

A shift table of physical examination from baseline to each scheduled post-baseline timepoint for each body system will be summarized by treatment arm.

Individual 12-lead ECG results will be summarized using a frequency table by treatment arm.

Individual 12-lead ECG results, physical examination findings, and vital sign measurements (including hypersensitivity monitoring) will be presented in data listings.

IGRA will be summarized and listed by treatment at each scheduled collection time.

All other safety data will be listed and summarized by treatment arm as appropriate.

7.7 Interim Analyses

No interim analyses are planned for this study.

7.8 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be implemented in this study will be documented and will comply with the current ICH Good Clinical Practice (GCP) guidelines on quality and risk management.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, review of protocol procedures with the investigator and associated staff prior to the study, periodic monitoring visits by sponsor or its designee, and direct transmission of clinical laboratory data from a central laboratory into the clinical database. The eCRF will be reviewed for accuracy and completeness by the monitor during on-site monitoring visits and after their return to sponsor or its designee; any discrepancies will be resolved with the investigator or designees, as appropriate. The data will be entered into the clinical study database and verified for accuracy.

Quality assurance staff from sponsor or its designee may visit the study center to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRF. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a licensing application. The investigator should immediately notify sponsor or its designee if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be changed based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IEC but will not result in protocol amendments.

8.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the regulatory authorities or the IEC.

The investigator, all employees, and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

8.2 Independent Ethics Committee

Regulations and the ICH guidelines require that approval be obtained from an IEC prior to participation of human patients in research studies. Prior to study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IEC. Documentation of all IEC approvals and of the IEC compliance with ICH harmonised tripartite guideline E6(R2): GCP will be maintained by the study center and will be available for review by the sponsor or its designee.

All IEC approvals should be signed by the IEC chairman or designee and must identify the IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for providing written summaries of the progress and status of the study at intervals not exceeding 1 year or otherwise specified by the IEC. The investigator must promptly supply the sponsor or its designee, the IEC, and, where applicable, the institution, with written reports on any changes significantly affecting the conduct of the study or increasing the risk to patients.

8.3 Patient Information and Consent

A written informed consent in compliance with the ICH E6(R2) guidelines shall be obtained from each patient prior to entering the study or performing any unusual or non-routine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to the study centers. If any institution-specific modifications to study-related procedures are proposed or made by the study center, the consent should be reviewed by the sponsor or its designee or both prior to IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IEC for review and approval prior to the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Prior to recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

In addition to the standard requirements that physicians are currently obliged to observe when providing information, the following points must also be covered:

- A description of the objectives of the study and how it will be organized
- The type of treatment
- Any potential negative effects attributable to the study drug
- The freedom to ask for further information at any time
- The patient’s right to withdraw from the clinical study at any time without giving reasons and without jeopardizing the patient’s further course of medical treatment
- The existence of patient insurance coverage and a summary of what is included in this coverage
- Adequate time and opportunity to satisfy questions will be given to the patients.

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the investigator or sub-investigator and the patient or patient’s legal representatives (according to the local regulations) prior to the beginning of the study. The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

To ensure medical confidentiality and data protection, the signed ICFs will be stored in the investigator's study file. The investigator will allow inspection of the forms by authorized representatives of the sponsor, IEC members, and regulatory authorities. The investigator will confirm, by signing and dating the eCRF, that informed consent has been obtained.

8.4 Study Reporting Requirements

By participating in this study, the principal investigator or sub-investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.4.1.4. In addition, the principal investigator or sub-investigator agrees to submit annual reports to his or her IEC as appropriate.

8.5 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor EastHORN is financially responsible for further testing or treatment of any medical condition that may be detected during the Screening process. In addition, in the absence of specific arrangements, neither the sponsor nor EastHORN is financially responsible for further treatment of the patient's disease.

8.6 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Curriculum vitae (CV) for the principal investigator and each sub-investigator. Current licensure must be noted on the CV. The CV will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating that they are accurate and current.

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center.

8.7 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R2). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. The analytical assays will be conducted according to the general principles of the Organization for Economic Cooperation and Development Principles of Good Laboratory Practice for testing of chemicals C(81)30(Final).

Prior to the study onset, the protocol, informed consent, advertisements to be used for patient recruitment and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IEC. Documentation of all IEC approvals and of the IEC compliance with the ICH E6(R2) guidelines will be maintained by the study center and will be available for review by the sponsor or its designee.

All IEC approvals will be signed by the IEC chairman or designee and must identify the IEC name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted.

The principal investigator or designated sub-investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IEC. The principal investigator or designated sub-investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or sub-investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or sub-investigator agrees to maintain source documentation (e.g., laboratory reports), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly. These source documents may include diaries, laboratory reports, ECG strips, etc.

The analysis data sets will be a combination of these data and data from other sources (e.g., laboratory data).

An eCRF is accessed through the appropriate system, which allows for on-site data entry and data management. Study center users can read from and write to the sponsor's database where the clinical data are collected. This provides immediate, direct data transfer to the database, as well as immediate detection of discrepancies, enabling study center coordinators to resolve and manage discrepancies in a timely manner.

Each study center staff involved with the study at each study center will have an individual logon and password that allow for record traceability. Thus, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records.

8.9 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R2) and all applicable guidelines and regulations.

8.10 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

8.11 Records Retention

All correspondence (e.g., with sponsor, IEC, or clinical research associates) relating to this clinical study will be kept in appropriate file folders. Records of patients, source documents, eCRF, and drug inventory sheets pertaining to the study must be kept on file.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If an investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person, who will accept the responsibility. Notice of transfer must be made to and agreed upon by the sponsor.

8.12 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and may work with the investigators to determine how the manuscript is written and edited, the number and order of authors based on SOPs of sponsor, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

9 Study Management

9.1 Sponsor

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9.2 Vendor Contact

EastHORN Clinical Services in CEE, Limited.
Zinonos Sozou 11, Office 303, 1075 Nicosia, Cyprus
Phone: +44 7801 058660

The names and addresses of the investigators and clinical study centers involved in the study are presented separately together with the investigators' signatures.

9.3 Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant. The following analytical facilities will be used:

Central Laboratories

Medicover Integrated Clinical Services
Palio Office Park, Building A, Marynarki Polskiej 197, 80-868 Gdańsk, Poland
Phone: +48 602 443 552

Laboratories for Pharmacokinetic and Immunogenicity Testing

Syneos Health, Inc.
Ligand Binding R&D, 301D College Road East, Princeton, NJ 08540
Phone: +1 609 951 0005

Laboratories for X-Ray Image analysis

Clario
211 Carnegie Center Drive, Princeton, NJ 08540
Phone: +1 609 936 2600

9.4 Monitoring

9.4.1 Independent Data Monitoring Committee

This study will be monitored by an independent data monitoring committee (IDMC) consisting of a PK specialist, statistician, independent physician, and an independent chairing physician. The IDMC will review and evaluate accumulating safety data to ensure the safety of study patients.

Additionally, study results when the clinical study report (CSR) is available will be reviewed by the IDMC.

Further details will be provided in the independent IDMC charter.

9.4.2 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study center at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. In case where a monitoring visit cannot be made because of the pandemic situation of COVID-19 the monitor will discuss with the sponsor, CRO, and the investigator for further plan, which is specified in Section 1.6.1.2.

All aspects of the study will be carefully monitored, by the sponsor or its designee, for compliance with applicable government regulation with respect to current ICH E6(R2) and current SOPs.

9.4.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and EastHORN of any audits scheduled by any regulatory authorities.

9.5 Management of Protocol Amendments and Deviations

9.5.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IEC for approval before patients are enrolled under an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from sponsor or its designee, and prior review, documented approval, and favorable opinion of the amendment from the relevant IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

9.5.2 Protocol Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IEC and agreed to by the investigator. A major deviation occurs when there is non-adherence to the protocol by the patient or investigator that may results in a significant impact on the completeness, accuracy, reliability of study data, or additional risk to the patient's rights, safety, and well-being. Major protocol deviations include the followings, and can lead to the patient being withdrawn from the study (Section 4.2) or exclusion from the statistical analysis according to SAP.

- Mis-randomization (defined as patients who received the opposite treatment to which they were assigned at any point during the study)
- Non-adherence to Inclusion or Exclusion criteria
- Significant ICH GCP non-compliance
- Receipt of prohibited therapy (Section 5.9)

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations will be defined prior to unblinding. Principal investigators will be notified in writing by the monitor of deviations. The IEC should be notified of all protocol deviations in a timely manner.

9.6 Study Termination

Although sponsor has every intention of completing the study, sponsor reserves the right to discontinue the study at any time for clinical or administrative reasons.

The completion of the study is defined as the date of final database is locked.

9.7 Clinical Study Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the CSRs are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

Sponsor plans to prepare 2 CSRs, but additional CSRs will be generated upon requirements for regulatory or academic purposes, including but not limited to the following:

- Data for each patient up to 32 weeks
- All data after completion of the study (up to Week 52)

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11 Appendices

11.1 Schedule of Event

Table 11-1 Schedule of Events

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; PK pharmacokinetic; QoL, quality of life; Q4W, every 4 week; SC, subcutaneous; TB, tuberculosis; VAS, visual analogue scale.

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.
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.
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 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, erythrocyte sedimentation rate, and uric acid
Hematology	Hematocrit, hemoglobin, red blood cells, total and differential white blood cell count, 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 infusion. In addition, any type of ECG will be performed for hypersensitivity monitoring 1 hour (±15 minutes) after the end of the study drug infusion. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator 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 for COVID-19 mitigation plans.

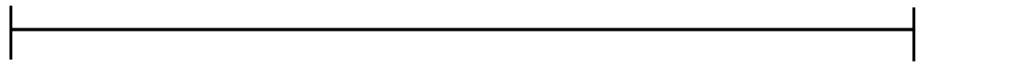
11.2 ACR Revised Criteria for Classification of Functional Status in RA

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.

11.3 VAS Patient's Global Assessment of Disease Activity

Patient's global assessment of disease activity is measured by the patient indicating the patient's current disease activity by marking one line (|) through the 100-mm line (0 mm equals very well and 100 mm equals very poor disease activity). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF. The converted score (in cm) for SDAI or CDAI will be calculated using 0.1 cm interval.

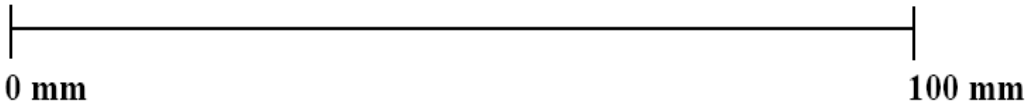


0 mm **100 mm**

Very well Very poor

11.4 VAS Physician Global Assessment of Disease Activity

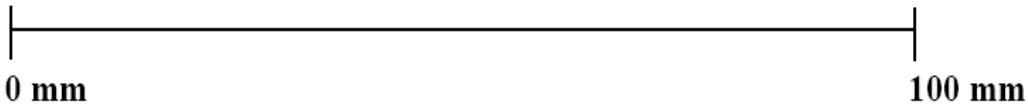
Physician's global assessment of disease activity is measured by the physician indicating the patient's current disease activity by marking one line (|) through the 100-mm line (0 mm equals very well and 100 mm equals very poor disease activity). This is an evaluation based on the patient's disease signs, functional capacity and physical examination, and should be independent of the patient's global assessment of disease activity. The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF. The converted score (in cm) for SDAI or CDAI will be calculated using 0.1 cm interval.



Very well Very poor

11.5 VAS Patient's Assessment of Pain

Patient assessment of pain is measured by the patient indicating the extent of their current pain by marking one line (|) through the 100-mm line (0 mm equals no pain and 100 mm equals most severe pain). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF.



No pain Most severe pain

11.6 Health Assessment Questionnaire and Scoring of the Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY#_____
QUESTDAT_____

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_____

PMSVIS_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do
DRESSING & GROOMING				
Are you able to:				
- Dress yourself, including tying shoelaces and doing buttons?	_____	_____	_____	_____
- Shampoo your hair?	_____	_____	_____	_____
ARISING				
Are you able to:				
- Stand up from a straight chair?	_____	_____	_____	_____
- Get in and out of bed?	_____	_____	_____	_____
EATING				
Are you able to:				
- Cut your meat?	_____	_____	_____	_____
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____
- Open a new milk carton?	_____	_____	_____	_____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	_____	_____	_____	_____
- Climb up five steps?	_____	_____	_____	_____

RASTUDY_____

QUESTNUM_____

DRESSNEW_____

RISENEW_____

EATNEW_____

WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____ Cane

_____ Walker

_____ Crutches

_____ Wheelchair

_____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)

_____ Built up or special utensils

_____ Special or built up chair

_____ Other (Specify:_____)

DRSGASST_____

RISEASST_____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____ Dressing and Grooming

_____ Arising

_____ Eating

_____ Walking

EATASST_____

WALKASST_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	_____	_____	_____	_____	
- Take a tub bath?	_____	_____	_____	_____	
- Get on and off the toilet?	_____	_____	_____	_____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	_____	_____	_____	_____	
- Bend down to pick up clothing from the floor?	_____	_____	_____	_____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	_____	_____	_____	_____	
- Open jars which have been previously opened?	_____	_____	_____	_____	
- Turn faucets on and off?	_____	_____	_____	_____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	_____	_____	_____	_____	
- Get in and out of a car?	_____	_____	_____	_____	
- Do chores such as vacuuming or yardwork?	_____	_____	_____	_____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

_____Raised toilet seat
_____Bathtub seat
_____Jar opener (for jars previously opened)
_____Bathtub bar
_____Long-handled appliances for reach
_____Long-handled appliances in bathroom
_____Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

_____Hygiene
_____Reach
_____Gripping and opening things
_____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

We are also interested in learning whether or not you are affected by pain because of your illness.

How much pain have you had because of your illness IN THE PAST WEEK:

PLACE A VERTICAL (I) MARK ON THE LINE TO INDICATE THE SEVERITY OF THE PAIN.

NO PAIN 0 ——————————— SEVERE PAIN 100

PAINSCAL_____

11.7 General Health Status (Medical Outcomes Study Short-Form Health Survey)

Study centers are using the validated questionnaire for their country; this appendix is included for information only and is not to be used as the official questionnaire to collect patient data.

For each of the following questions, please select the one response that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

2. Compared to one year ago, how would you rate your health in general now?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
○	○	○	○	○

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	○	○	○
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○	○	○
c. Lifting or carrying groceries	○	○	○
d. Climbing several flights of stairs	○	○	○
e. Climbing one flight of stairs	○	○	○
f. Bending, kneeling, or stooping	○	○	○
g. Walking more than a mile	○	○	○
h. Walking several hundred yards	○	○	○
i. Walking one hundred yards	○	○	○
j. Bathing or dressing yourself	○	○	○

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Were limited in the kind of work or other activities	○	○	○	○	○
d. Had difficulty performing the work or other activities (for example, it took extra effort)	○	○	○	○	○

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the amount of time you spent on work or other activities	○	○	○	○	○
b. Accomplished less than you would like	○	○	○	○	○
c. Did work or other activities less carefully than usual	○	○	○	○	○

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
○	○	○	○	○

7. How much bodily pain have you had during the past 4 weeks?

None	Very mild	Mild	Moderate	Severe	Very severe
○	○	○	○	○	○

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
○	○	○	○	○

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	○	○	○	○	○
b. Have you been very nervous?	○	○	○	○	○
c. Have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○
d. Have you felt calm and peaceful?	○	○	○	○	○
e. Did you have a lot of energy?	○	○	○	○	○
f. Have you felt downhearted and depressed?	○	○	○	○	○
g. Did you feel worn out?	○	○	○	○	○
h. Have you been happy?	○	○	○	○	○
i. Did you feel tired?	○	○	○	○	○

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
▼	▼	▼	▼	▼
○	○	○	○	○

11. How TRUE or FALSE is each of the following statements for you?

	Definitely true ▼	Mostly true ▼	Don't know ▼	Mostly false ▼	Definitely false ▼
a. I seem to get sick a little easier than other people	○	○	○	○	○
b. I am as healthy as anybody I know	○	○	○	○	○
c. I expect my health to get worse	○	○	○	○	○
d. My health is excellent	○	○	○	○	○

11.8 DAS28

The DAS28 score uses a calculation that requires the assessment of 28 joints for swelling and tenderness. The 28 joints are shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and the knees.

More information on DAS28 can be found at https://www.das-score.nl/en.

		Left Swollen	Tender	Right Swollen	Tender
Shoulder					
Elbow					
Wrist					
MCP	1				
	2				
	3				
	4				
	5				
PIP	1				

2				
3				
4				
5				
Knee				
Subtotal				
Total	Swollen		Tender	

Abbreviations: MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joints
Reference: DAS28.