CLINICAL STUDY PROTOCOL

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

PROTOCOL NUMBER CT-P10 3.2

Test Formulation:	CT-P10 (1000 mg) administered intravenously
Sponsor:	[redacted]
Sponsor Contact:	
SAE Reporting and Data Center:	
EudraCT No.:	2013-004555-21
Version and Date of Protocol:	Protocol Version 5.1, including Country-Specific Protocol Amendment 1 (US) – 01 April 2016

CONFIDENTIAL

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Protocol Approval

Study Title	A Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Pharmacokinetics, Efficacy and Safety between CT-P10, Rituxan and MabThera in Patients with Rheumatoid Arthritis
Protocol Number	CT-P10 3.2
Protocol Date	Protocol Version 5.1, including Country-Specific Protocol Amendment 1 (US) – 01 April 2016

Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understand all sections of the protocol entitled "A Randomized, Controlled, Double-Blind, Parallel-Group, Phase 3 Study to Compare the Pharmacokinetics, Efficacy and Safety between CT-P10, Rituxan and MabThera in Patients with Rheumatoid Arthritis" and the accompanying current investigator's brochure.

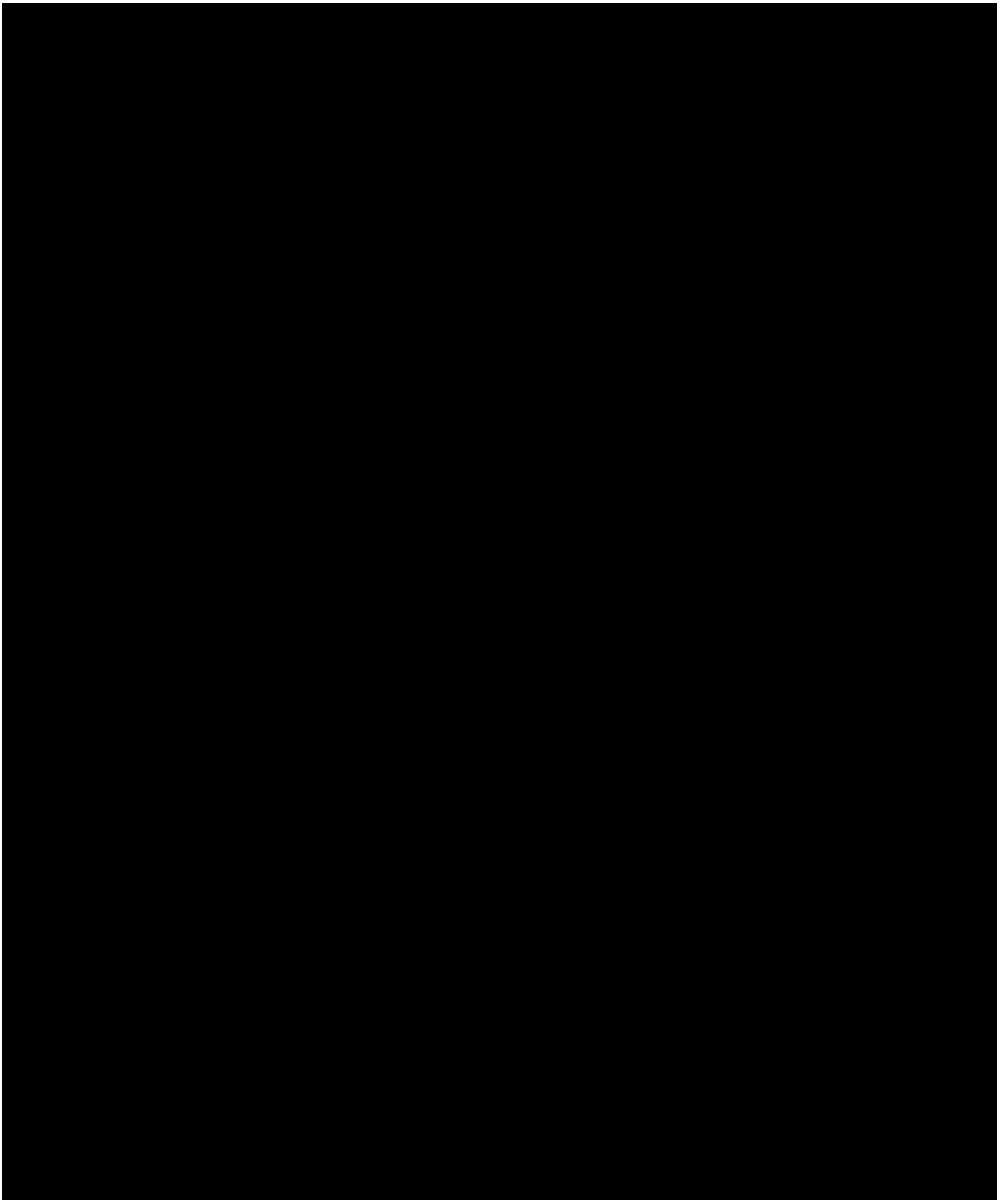
I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 5.1, including Country-Specific Protocol Amendment 1 – 01 April 2016, the International Conference on Harmonisation harmonised tripartite guideline E6 (R1): Good Clinical 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 subinvestigator.

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



Protocol Synopsis

Protocol Number: CT-P10 3.2

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

Clinical Phase: Phase 3

Study Design: Randomized, controlled, multicenter, 3-arm, double-blind, parallel-group, prospective, pharmacokinetic (PK), efficacy, pharmacodynamic (PD), and safety study.

Part 1: PK similarity

Part 2: Efficacy similarity

Planned Number of Centers/Countries: It is expected that up to approximately 110 study centers in Europe, Asia Pacific, and Latin America may be included in this study.

Test Formulation, Dose, and Regimen: CT-P10, 1000 mg by intravenous (IV) infusion. Each patient may receive 3 courses (2 courses in the Main Study Period and 1 course in the Extension Study Period) of treatment if the patient meets predefined safety criteria. Each course consists of 2 infusions with a 2-week interval between the first and second infusion. Methotrexate (MTX) (between 7.5 and 25 mg/week orally or parenterally [dose and route must be maintained from beginning to end of study]) and folic acid (≥5 mg/week) will be coadministered.

Reference Drug, Dose, and Regimen: Rituxan (United States-licensed) or MabThera (European Union-approved), 1000 mg IV infusion. Each patient may receive 3 courses (2 courses in the Main Study Period and 1 course in the Extension Study Period) of treatment if the patient meets predefined safety criteria. Each course consists of 2 infusions with a 2-week interval between the first and second infusions. Methotrexate (between 7.5 and 25 mg/week orally or parenterally [dose and route must be maintained from beginning to end of study]) and folic acid (≥5 mg/week) will be coadministered.

Objectives:

All patients from Part 1 of the study will be included in Part 2 of the study and undergo all assessments performed in Part 2.

The decision to enter Part 2 of the study will not be influenced by the results from Part 1.

Part 1

Primary objective:

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

Secondary objectives:

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

Part 2

Primary objective:

- To demonstrate that CT-P10 is similar to reference products (Rituxan and MabThera) in terms of efficacy as determined by clinical response according to change from Baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-reactive protein [CRP]) at Week 24.

Secondary objective:

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

Sample Size:

Part 1

The first 189 patients will be randomly assigned in a 1:1:1 ratio (approximately 63 patients per treatment group) to the CT-P10, Rituxan and MabThera treatment groups.

Part 2

Approximately 172 subsequent patients will be enrolled in a 1:1 ratio (approximately 86 patients per treatment group) to the CT-P10 or Rituxan treatment groups.

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

Main Selection Criteria: Male or female patients with a diagnosis of rheumatoid arthritis (RA) (as defined by the revised 1987 ACR classification criteria) for at least 6 months and active disease (as defined by the presence of 6 or more swollen joints and 6 or more tender joints), and serum C-reactive protein (CRP) ≥1.5 mg/dL (≥15 mg/L) or an erythrocyte sedimentation rate (ESR) ≥28 mm/hour 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 between 18 and 75 years old, inclusive.
2. Patient has a diagnosis of RA according to the revised 1987 ACR classification criteria for at least 6 months prior to randomization.
3. Patient has active disease as defined by the presence of 6 or more swollen joints (of 66 assessed) and 6 or more tender joints (of 68 assessed), and serum CRP ≥1.5 mg/dL (≥15 mg/L) or an ESR ≥28 mm/hour.
4. Patient has experienced an inadequate response to previous or current treatment with the antitumor necrosis factor (TNF) agents infliximab (≥3 mg/kg; at least 3 infusions for at least 3 months), golimumab (50 mg once a month for at least 12 to 14 weeks or 2 mg/kg IV infusion for at least 3 months), adalimumab (40 mg every other week for at least 3 months), or etanercept (25 mg twice weekly or 50 mg once weekly for at least 3 months), or was intolerant to at least 1 administration of these agents. Patients who discontinued etanercept for at least 4 weeks, infliximab or adalimumab for at least 8 weeks, or golimumab for at least 10 weeks prior to randomization are permitted to enter the study.

   Patients who received any other anti-TNF agents not in this list can be enrolled if the patient discontinued the treatment at least 4 weeks or 5 half-lives prior to randomization, whichever is longer.
5. Patient has a proper discontinuation period after treatment with interleukin-1 receptor (IL-1R) antagonist, interleukin-6 receptor (IL-6R) antibody, or abatacept. Patients who discontinued IL-1R antagonist for at least 4 weeks, abatacept for at least 8 weeks or IL-6R antibody for at least 17 weeks prior to randomization are permitted to enter the study.

   Patients who had any other biological drugs not in this list can be enrolled if the patient discontinued the treatment at least 4 weeks or 5 half-lives prior to randomization, whichever is longer.
6. Patient has received MTX treatment (7.5 to 25 mg/week orally or parenterally) for at least the past 12 weeks, with the last 4 weeks at a stable dose before Screening.
7. Patient has the following hematology laboratory test results at Screening:
   - Hemoglobin ≥8.0 g/dL
   - White blood cell count ≥3.5×10^3 cells/μL (SI [Système International d'Unités] units: ≥3.5×10^9 cells/L)
   - Neutrophil count ≥1.5×10^3 cells/μL (SI units: ≥1.5×10^9 cells/L)
   - Platelet count ≥75×10^3 cells/μL (SI units: ≥75×10^9 cells/L)
8. 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)

- Serum alanine aminotransferase <2.5 × ULN
- Serum aspartate aminotransferase <2.5 × ULN
- Serum total bilirubin <2 × ULN

9. Patient has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
10. Patient (or legal guardian, if applicable) has been informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, and provide signed and dated written informed consent before inclusion in the study.
11. For both male and female patients, the patient and their partners of childbearing potential either agree to practice total abstinence or use 2 of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilized):
    - Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
    - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
    - Intrauterine device

    Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use 2 medically acceptable methods of contraception or to practice total abstinence.

    Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

Exclusion Criteria:

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

1. Patient has taken more than 2 biologic agents.
2. Patient has previously been administered rituximab or participated in a rituximab biosimilar study.
3. Patient has allergies or hypersensitivity to murine, chimeric, human, or humanized proteins.
4. Patient has current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus-1 or -2 or who has a positive result to the screening test for these infections.
5. Patient has an infection requiring oral antibiotics 2 weeks before randomization, parenteral injection of antibiotics 4 weeks before randomization, other serious infection 6 months before randomization, a history of recurrent herpes zoster or other chronic or recurrent infection 6 weeks before randomization.
6. Patient has a past or current diagnosis of tuberculosis (TB), recent exposure to person with active TB, examination findings indicating the presence of TB, defined as a positive result for interferon-γ release assay, or other severe or chronic infection (such as sepsis, abscess or opportunistic infection, or invasive fungal infection such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of prophylaxis or complete resolution following treatment can be enrolled.
7. Patient is receiving any of the following medications or therapies:
    - Previous treatment within 6 months of IV gamma globulin or the Prosorba Column
    - Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to randomization or planned within 6 months after randomization
    - Intra-articular corticosteroids within 8 weeks prior to randomization. Patients are permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent), and nonsteroidal anti-inflammatory drug, if they have received a stable dose for at least 4 weeks prior to randomization. In addition, patients are permitted to receive low potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.
    - Disease-modifying antirheumatic drugs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine, within 4 weeks prior to randomization. Patients who discontinued leflunomide and

have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days must wait 4 weeks prior to randomization. Patients who discontinued leflunomide and did not have a cholestyramine discontinuation period must wait 12 weeks after last dose of leflunomide before randomization.

- Live or live-attenuated vaccine within 8 weeks prior to randomization, and killed vaccines within 4 weeks prior to randomization
- History of any biologic agent causing B-lymphocyte (B-cell) depletion or targeting B-cells

8. Patient has a medical condition including one or more of the following:
   - Uncontrolled diabetes mellitus, even after insulin treatment
   - Uncontrolled hypertension at the discretion of the investigator
   - Any other inflammatory or rheumatic disease, 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 study drug
   - History of any malignancy within the previous 5 years prior to date of informed consent except completely excised or cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
   - History of lymphoma, lymphoproliferative disease, or bone marrow hypoplasia
   - Patients with New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the previous 6 months prior to date of consent
   - History of organ transplantation, including corneal graft/transplantation
   - Severe physical incapacitation (unable to perform routine self-care), has RA ACR functional status class 4, or no expected benefit from medication
   - Any uncontrolled clinically significant respiratory disease (in the opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion
   - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barré syndrome
   - Any condition significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage) if it may interfere with the investigator's assessment of disease assessment scores including joint counts
   - Any other serious acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results, in the opinion of the investigator
9. Patient has current or past history of drug or alcohol abuse within 6 months of randomization.
10. Patient has had treatment with any other investigational device or medicinal product within 4 weeks of randomization or 5 half-lives, whichever is longer.
11. Patient is a female who is currently pregnant or breastfeeding or is planning to become pregnant or breastfeed within 12 months of the last dose of study drug.
12. Patient, in the opinion of their general practitioner or investigator, should not participate in the study.
13. Patient has a history of rheumatic autoimmune disease other than RA (except secondary Sjögren's syndrome) or significant systemic involvement secondary to RA (vasculitis, pulmonary fibrosis, or Felty's syndrome).

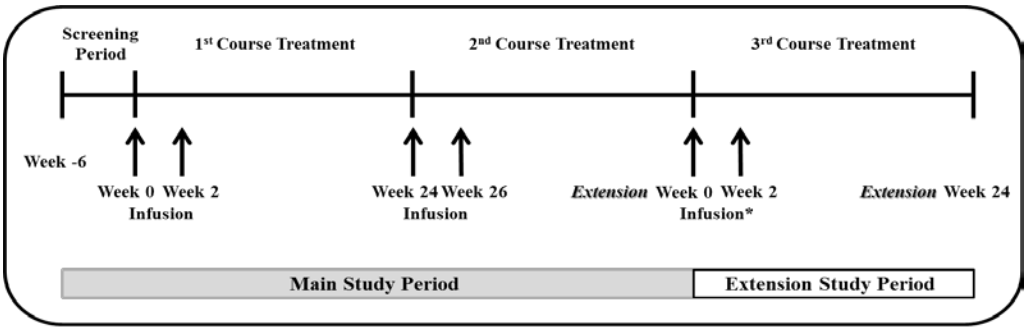
Study Design: This is a randomized, controlled, multicenter, 3-arm, parallel-group, double-blind, prospective, PK, efficacy, PD, and safety Phase 3 study. There will be up to 3 periods in this study:

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

The study duration will be up to 76 weeks after the Week 0 infusion. Extension Study Period will be initiated between Week 48 and Week 52 of the Entire Study Period. A schematic of the study design is presented in Figure S1. There will be additional follow-up visits for patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value until recovery is achieved for one of them.

The term "Extension" will be used for all the visits in the Extension Study Period (i.e. Extension Week X or Extension Day X). Otherwise, visits will simply be stated as Week X.

Figure S1 Study Schematic



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

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

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

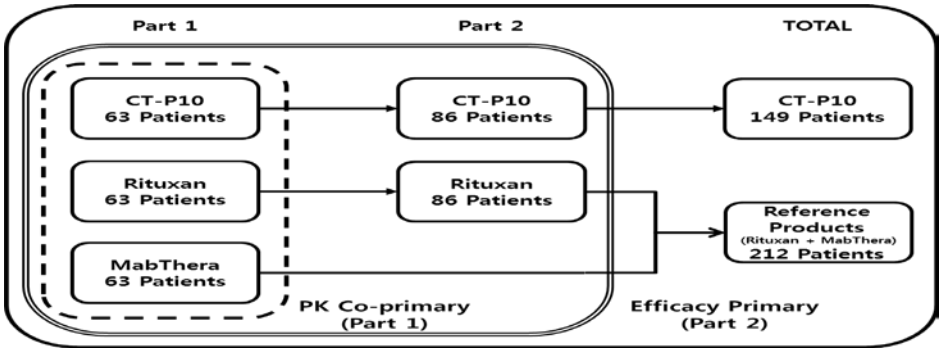
Note: Part 1 and Part 2 of the study will follow this study scheme.

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

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

Approximately 189 initial patients to be enrolled in the study will be assigned to Part 1 and all subsequent patients enrolled in the study will be assigned to Part 2. All patients from Part 1 of the study will be included in Part 2 of the study and undergo all assessments performed in Part 2. A schematic of study patient assignment for Part 1 and Part 2 is presented in Figure S2. Part 2 will run independently and in parallel with Part 1.

Figure S2 Study Schematic for the Main Study Period (up to Week 48)



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

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

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

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

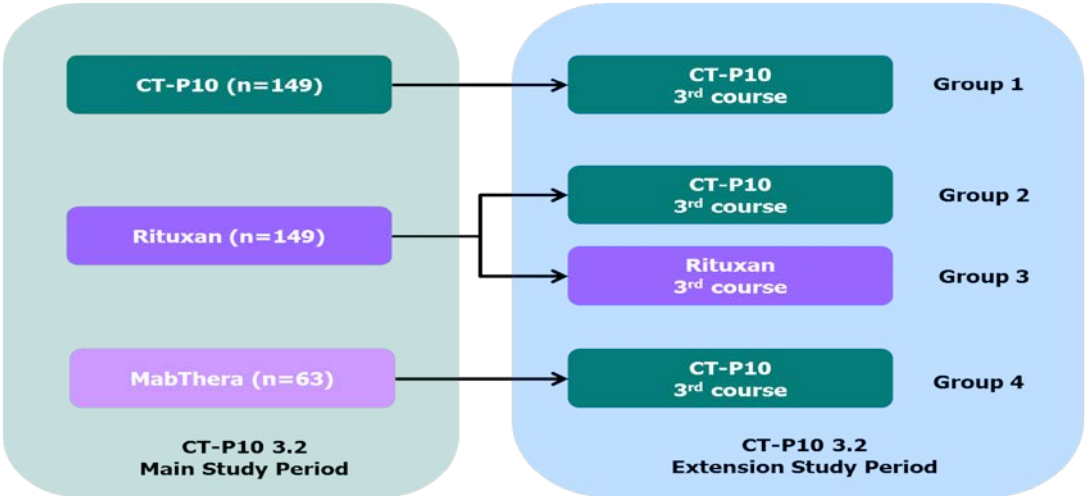
Note that patients, who have the End-of-Study (EOS) visit at Week 48, can participate in the Extension Study Period if the patients sign an informed consent form within 24 weeks from the EOS visit and do not have prohibited medications prior to entering the Extension Study Period.

All patients eligible for Extension Phase from Rituxan group will be randomized again at Extension Week 0. The randomization will be conducted and stratified by

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

To keep the blind during the study, stratification factors will be entered for all patients at Extension Week 0. In the case there were no EULAR-CRP response status available at week 40, the last EULAR-CRP response status assessment done between Weeks 40 and 48 will be used. Baseline values for assessment of EULAR-CRP will be the last value from screening to Day 0 (Week 0) of the study. A schematic of the study patient assignment for this randomization is presented in Figure S3.

Figure S3 Study Schematic



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

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

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

The third course of treatment will be initiated between Week 48 and Week 52 of the Entire Study Period if patients become eligible according to the predefined safety criteria for the course based on the results assessed

within 8 weeks from the Extension Week 0. A visit window is not permitted on the day of second infusion for the third course of treatment.

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

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

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

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

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

Pharmacokinetic Assessments: The PK analysis will be performed on the PK population. The following table summarizes the planned PK analysis.

	Part 1 (189 patients)			Part 2 (361 patients)	
	CT-P10 (63 patients)	Rituxan (63 patients)	MabThera (63 patients)	CT-P10 (149 patients[*])	Reference products (212 patients[#])
Primary	$AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and $C_{max,}$ over the first 24 weeks			Not applicable	
Secondary	$AUC_{0\text{-day14}}$, V_d, CL, $t_{1/2,}$ $C_{max,\ 1}$, $T_{max,}$ C_{min}, and C_{trough} over the first 24 weeks			C_{max}, $T_{max,}$ C_{min}, and C_{trough} over 48 weeks	

[*] Includes up to 63 patients from Part 1

[#] 149 patient from Rituxan group including 63 patients from Part 1 and up to 63 patients from MabThera group from Part 1

Serum blood samples will be obtained within 15 minutes prior to the beginning of the study drug infusion, within 15 minutes after the end of the study drug infusion, 1 hour (±15 minutes) after the end of the study drug infusion, and 24 hours (±2 hours) after the start of the study drug infusion and any time during the day according to the sampling scheme.

Part 1

Co-primary PK endpoints: The following PK parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as co-primary PK endpoints (over the first 24 weeks):

- $AUC_{0\text{-last}}$: area under the serum concentration-time curve covering both infusions, time to the last measurable concentration
- $AUC_{0\text{-}\infty}$: area under the serum concentration-time curve covering both infusion, time zero to infinity
- C_{max}: maximum concentration after the second infusion

Secondary PK endpoints: The following PK parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as secondary PK endpoints (over the first 24 weeks):

- $AUC_{0\text{-day14}}$: area under the serum concentration-time curve covering both infusion, time zero to day 14
- V_d: volume of distribution

- CL: total clearance
- $t_{1/2}$: terminal elimination half-life after the second infusion
- T_{max}: time to C_{max} after both the first and second infusions
- $C_{max, 1}$: maximum concentration after the first infusion
- C_{min}: concentration at Week 24
- C_{trough}: trough concentration prior to the second infusion

Part 2

Secondary PK endpoints: The following PK parameters for the study drug (CT-P10 and reference products) will be determined as secondary PK endpoints (up to Week 48 or over the first 24 weeks if second course of treatment is not administered)

- T_{max}: time to C_{max} after both the first and second infusions
- C_{max}: maximum concentration after both the first and second infusions
- C_{min}: concentration at Weeks 24 and 48
- C_{trough}: trough concentration prior to the second infusion

Efficacy Assessments:

Part 2

Primary endpoint: The following efficacy parameter for the study drugs (CT-P10 and reference products [Rituxan and MabThera]) will be determined as the primary efficacy endpoint:

- The change from Baseline in disease activity measured by DAS28 (CRP) at Week 24

Secondary endpoints: The following efficacy parameters for the study drug will be determined as secondary efficacy endpoints:

- American College of Rheumatology (ACR) definition of a 20% improvement criteria (ACR20), ACR 50% improvement criteria (ACR50) and ACR 70% improvement criteria (ACR70) at Week 24, Week 48, and Extension Week 24
- Individual components of the ACR criteria compared with Baseline at Week 24, Week 48, and Extension Week 24
- Time to onset of ACR20 response over 24 weeks
- Mean change from Baseline in disease activity measured by DAS28 (CRP) at Weeks 12 and 48 and Extension Week 24 and DAS28 (ESR) at Weeks 12, 24 and 48 and Extension Week 24
- Proportion of patients with a good response, defined according to the European League Against Rheumatism (EULAR) response criteria at Week 24, Week 48, and Extension Week 24
- Hybrid ACR response at Week 24, Week 48, and Extension Week 24
- Simplified disease activity index (SDAI) and clinical disease activity index (CDAI) at Week 24, Week 48, and Extension Week 24
- Joint damage progression based on radiographic evaluations, van der Heijde modification of the Sharp scoring system at Week 48, Extension Week 24 and the EOS visit
- Functional disability (Health Assessment Questionnaire [HAQ] disability index) at Week 24, Week 48, and Extension Week 24
- Health-related quality of life (Medical Outcomes Study Short-Form Health Survey [SF-36] health survey score) compared with Baseline at Week 24, Week 48, and Extension Week 24

Pharmacodynamic Assessments: The following PD parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as PD endpoints:

- B-cell kinetics over time including depletion and recovery
- CRP and ESR at Week 24, Week 48, and Extension Week 24
- Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) at Week 24, Week 48, and Extension Week 24

Biomarker Assessments (Optional): For patients who sign a separate informed consent form for the biomarker assessments, a blood sample for evaluation of FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected after randomization (before dosing on Day 0 of Week 0).

Safety Assessments: Safety will be assessed by immunogenicity testing, immunoglobulin (IgM, IgG and IgA) testing, hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates, and temperature) and ECGs, vital sign measurements, ECGs, signs and symptoms of TB monitored throughout the study, physical examination findings, adverse events (AEs), infections, infusion-related reactions, clinical laboratory analyses, pregnancy testing, and concomitant medications.

Data Analysis:

Statistical analysis: Randomization will be stratified by country, prior anti-TNF-alpha (anti-TNF-α) blocker status (inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative).

Patients from Rituxan and MabThera treatment groups will be combined as a reference products group for the Part 2 analyses up to Week 48.

At Extension Week 0, randomization will be conducted and stratified by the number of courses they are treated during the Main Study Period and the EULAR-CRP response status (responder vs non-responder) assessed at Week 40. In the case there were no EULAR-CRP response status available at week 40, the last EULAR-CRP response status assessment done between Weeks 40 and 48 will be used. Baseline values for assessment of EULAR-CRP will be the last value from screening to Day 0 (Week 0) of the study.

Pharmacokinetic analysis: For both primary and secondary PK analyses will be performed using data from the Main Study Period.

Co-primary PK endpoints: The primary PK analysis will assess the similarity of CT-P10, Rituxan and MabThera in terms of $AUC_{0\text{-last}}$ (over both infusions of the first course of treatment, from time zero to the last measurable concentration), $AUC_{0\text{-}\infty}$ (over both infusions of the first course of treatment, from time zero to infinity) and C_{max} (after the second infusion in the first course of treatment) as co-primary PK endpoints. The primary PK parameter estimates will be analyzed using an analysis of covariance (ANCOVA) with treatment as a fixed effect and country, gender, race, prior anti-TNF-alpha (anti-TNF-α) blocker status (inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region defined in the statistical analysis plan (SAP), for use as a covariate. Point estimates (geometric means and ratio of geometric means) will be calculated from back transforming the least squares means of the natural log-transformed values of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max}. $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} will be natural log-transformed prior to analysis, and 90% confidence intervals (CIs) for the ratio of the geometric means of the 2 treatments (CT-P10 versus Rituxan, CT-P10 versus MabThera, and Rituxan versus MabThera) will also be produced. Similarity will be demonstrated if the 90% confidence interval (CI) for the geometric mean ratio of CT-P10 to Rituxan and MabThera in $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} is within the bounds of 80% and 125%. $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} will be summarized by treatment. Summary statistics will include the n, mean, standard deviation (SD), median, minimum, maximum, geometric mean, and coefficient of variation (CV). In Part 1, based on overall 90% power, a type I error of 0.1, an interpatient CV in $AUC_{0\text{-last}}$ of 30%, 50 patients are needed in each treatment group being compared (50 patients in the CT-P10 treatment group, 50 patients in the Rituxan treatment group, and 50 patients in the MabThera treatment group; 150 patients in total). Allowing for a drop-out rate of 20%, 189 patients will be randomly assigned into the study in a 1:1:1 allocation.

Secondary PK endpoints: For patients in Part 1, the following secondary PK parameters will be considered: $AUC_{0\text{-day14}}$ (over both infusions of the first course of treatment, from time zero to day 14), V_d, CL, $t_{1/2}$ (after the second infusion in the first course of treatment), T_{max} (after both the first and second infusions in the first course of treatment), $C_{max,\ 1}$ (after the first infusion in the first course of treatment), C_{min} (at Week 24 in the first course of treatment), C_{trough} (prior to the second infusion in the first course of treatment).

For patients in Part 2, the following secondary PK parameters will be considered: T_{max} (after both the first and second infusions in the first and second courses of treatment), C_{max} (after the first and second infusions in the first and second courses of treatment), C_{min} (at Week 24), and C_{trough} (prior to the second infusion in the first and second courses of treatment).

These PK variables will be presented in listings and summarized in tables. The summary tables will display the following descriptive statistics: n, mean, median, SD, minimum, maximum, geometric mean, and CV.

The PK population is defined to be all patients who receive at least 2 doses (Week 0 and Week 2) of study drug (CT-P10, Rituxan or MabThera), who provide sufficient blood concentration data to compute the required PK variables, and who do not have any major protocol violation including a violation of the inclusion and exclusion of criteria. The PK population will be the primary population for the summary and analysis of PK data.

Efficacy analysis: For primary efficacy analysis will be performed using data from the Main Study Period.

Primary efficacy endpoint: The changes from baseline in disease activity measured by DAS28 (CRP) at Week 24. For Part 2, the sample size will be extended from that in Part 1 to 361 patients, 149 patients in the CT-P10 group and 212 patients from a reference products group (149 patients from Rituxan group and up to 63 patients from MabThera groups), including 3 × 63 patients from each of the three treatment groups from Part 1. In the sample size calculation, the common standard deviation of the mean change of DAS28 at Week 24 from baseline is assumed as 1.32 based on the CT-P10 1.1 study result for the therapeutic equivalence margin of ±0.50. This sample size of 133 and 189 evaluable patients in the CT-P10 and reference products groups, respectively, leads to approximately 90% power for the demonstration of similarity based on a two-sided 90% CI and the chosen margin. The drop-out rate has been hypothesized at 10% and it will be only applied to patients who will be enrolled for Part 2 since the drop-out rate for the patients from Part 1 is already considered, so the proposed total sample size of 361 patients (149 patients in the CT-P10 group and 212 patients in the reference products group [Rituxan and MabThera groups], including up to 63 patients per treatment group from Part 1) is expected to yield 322 evaluable patients (133 patients in the CT-P10 group and 189 patients in the reference products group [Rituxan and MabThera groups], including 56 patients per treatment group from Part 1). The primary analysis for DAS28 is an analysis of covariance (ANCOVA) comparing the change from baseline of DAS28 (CRP) after 24 weeks of treatment between two groups, CT-P10 and reference products, considering the treatment as a fixed effect and country, gender, race, prior anti-TNF-α blocker status (inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region defined in the SAP, for use as a covariate. Similarity for the change from baseline of DAS28 (CRP) at week 24 will be evaluated based on the two-sided 90% confidence interval obtained from the ANCOVA model for the difference of means of the change in DAS28 (CRP) between the two treatment groups. The equivalence margin for the 90% CI is defined as [-0.50, 0.50].

Secondary efficacy endpoints: The proportion of patients demonstrating ACR20, ACR50, and ACR70 (based on 1995 ACR criteria) will be summarized by treatment, at Week 24, Week 48, and Extension Week 24. The mean change in the components of the ACR criteria from Baseline will be summarized for ACR20, ACR50, ACR70, and hybrid ACR. Time to onset of the ACR20 response will also be summarized by treatment. The DAS28 data will be listed and summarized by treatment (including ESR and CRP levels). In addition, change from Baseline will also be summarized, by treatment, for assessments after the first infusion. The DAS-based EULAR response criteria will be summarized by treatment. Simplified and clinical disease activity will be measured using the SDAI and CDAI calculated from the appropriate formulas. Joint damage progression based on radiographic evaluations (1 image of both the right and left hands and both the right and left feet for a total of 4 images) will be assessed by the change in the van der Heijde modification of the Sharp scoring system at the Week48, Extension Week24 and the EOS Visit. The HAQ disability index and SF-36 data will be listed and summarized by treatment. Summaries will be included for the SF-36 physical component score and the mental component score.

The efficacy population is defined to be all patients who receive at least 1 dose of study drug (CT-P10, Rituxan or MabThera), who have at least 1 post-treatment efficacy result, and who do not have any major protocol violation including a violation of the inclusion and exclusion of criteria. The efficacy population will be the primary population for the summary of efficacy data.

The all-randomized population is defined to be all patients enrolled and randomly assigned to receive a dose of study drug, regardless of whether or not any study drug dosing was completed. All efficacy parameters will also be analyzed for the all-randomized population.

Pharmacodynamic analysis: All PD data will be listed and summarized by treatment, where appropriate. The comparison of the concentration of B-cell kinetics between CT-P10, Rituxan and MabThera will be performed

using ANCOVA, with treatment as a fixed effect and baseline values, country, gender, race, prior anti-TNF-α blocker status (inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region defined in the SAP, for use as a covariate. Point estimates and 95% CIs will be provided. Pharmacodynamic data will also be summarized using quantitative descriptive statistics (including geometric mean and CV, where appropriate).

The PD population is defined to be all patients who receive at least 1 dose of study drug (CT-P10, Rituxan or MabThera) and have at least 1 post-treatment PD result. The PD population will be the primary population for the summary of PD data.

Safety analysis: Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities. Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events v4.0. All safety data will be listed and summarized by treatment as appropriate.

The safety population is defined to be all patients who receive at least 1 dose (full or partial) of study drug (CT-P10, Rituxan or MabThera). The safety population will be the primary population for the summary of safety data.

List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	ACR 20% improvement criteria
ACR50	ACR 50% improvement criteria
ACR70	ACR 70% improvement criteria
AE	adverse event
ANCOVA	analysis of covariance
anti-CCP	Anti-cyclic citrullinated peptide
$AUC_{0\text{-day14}}$	area under the serum concentration-time curve from time zero to day 14
$AUC_{0\text{-}\infty}$	area under the serum concentration-time curve from time zero to infinity
$AUC_{0\text{-last}}$	area under the serum concentration-time curve from time zero to time of last quantifiable concentration
B-cell	B-lymphocyte
BLys	B-lymphocyte stimulatory protein
BQL	below quantification limit
CDAI	clinical disease activity index
CI	confidence interval
CL	total clearance
C_{max}	maximum serum concentration
C_{min}	minimum serum concentration
CRP	C-reactive protein
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough serum concentration
CV	coefficient of variation
DAS28	Disease Activity Score using 28 joint counts
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
EOS	end of study
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
HAQ	Health Assessment Questionnaire
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-1	interleukin-1
IL-1R	interleukin-1 receptor

Abbreviation	Definition
IL-6R	interleukin-6 receptor
IRB	institutional review board
IRR	infusion-related reaction
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive Web response system
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
PD	pharmacodynamic
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PT	preferred term
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDAI	simplified disease activity index
SF-36	Medical Outcomes Study Short-Form Health Survey
SI	Système International d'Unités
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
T-cell	T-lymphocyte
TB	tuberculosis
T_{max}	time to maximum serum concentration
TNF	tumor necrosis factor
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
US	United States
V_d	volume of distribution
VAS	visual analogue scale

1 Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that affects 0.8% to 1.0% of all populations. The etiology of RA is not fully understood although major progress has been made in our understanding of the disease.

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

About 80% of patients with RA present with rheumatoid factor (RF) (i.e., anti-immunoglobulin G [IgG]-Fc antibodies) in their serum, which is associated with a poor prognosis (McInnes 2001). Along with more recent discoveries of other autoantibodies, such as anticyclic citrullinated peptide (anti-CCP), the presence of autoantibodies strongly suggests that B-lymphocytes (B-cells) are involved in the pathogenesis of RA. Also, an observation more than 20 years ago of the presence of a considerable number of cells of the B-cell lineage in the rheumatoid synovium, including RF producing B-cells and plasma cells, supports this notion (Petersen et al 1984). Research in animal models has demonstrated the critical role of B-cells in disease development as animals lacking functional B-cells or receiving B-cell inhibitory signals are less likely to develop experimentally induced arthritis (Wang et al 2001).

Recent research established a clear role of cytokines, protein factors, and interaction of various cell populations (including T-lymphocytes [T-cells], B-cells, and fibroblasts) in the pathogenesis of the inflammatory lesion in the synovial membrane with consequent destruction of joint cartilage and bone. A recently discovered protein, B-lymphocyte stimulatory protein (BLys), is believed to contribute to B-cell recruitment and activation in RA. Elevated concentrations of BLys have been detected in the synovial fluid and serum of many patients with RA and in serum of patients with other inflammatory diseases (Tan et al 2003).

It has also been established that there is an intimate relationship among dendritic cells, macrophages, B-cells, and T-cells within the RA synovium. In particular, dendritic cells and macrophages are dependent on stimuli released by B-cells, and this may explain why

dendritic cell function may remain impaired beyond the recovery of B-cells following B-cell depletion (Toubi et al 2007; Youinou et al 2007). Cellular interactions, such as antigen processing and presentation, occur upstream of the proinflammatory cytokine response involving tumor necrosis factor (TNF)-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6. In addition, production of immunoglobulin M (IgM)-RF and IgG-RF by plasma cells in the rheumatoid synovium may act as a self-perpetuating stimulus for local B-cell proliferation and differentiation (Edwards 1999). Therefore, it appears increasingly evident that B-cells play a key pathogenetic role in the induction and maintenance of RA.

Clinical relevance of depleting B-cells in RA has been demonstrated by using a cytotoxic, chimeric anti-CD20 monoclonal antibody (Rituxan and MabThera) and these products have been approved for the treatment of patients with RA who have an inadequate response to TNF-α blocking agents. Also, previous studies on anti-TNF-α naïve patients with RA who did not benefit from methotrexate (MTX) therapy show that two-thirds of these patients obtained a clinical response following anti-CD20 therapy as measured by the American College of Rheumatology (ACR) 20% improvement criteria (ACR20) (Emery et al 2006). However, the adverse event (AE) profile included a high frequency of infusion-related events requiring premedication with intravenous (IV) steroids. One hypothesis is that rapid B-cell lysis is the driver for the observed infusion-related events. Development of human antichimeric antibodies has been observed in up to 25% of patients treated with a chimeric anti-CD20 antibody (Higashida et al 2005).

Following initial treatment, patients typically remain B-cell depleted for between 6 and 12 months, and some patients show no B-cell recovery for longer periods (MabThera 2015; Rituxan 2014). Currently, retreatment is given upon disease relapse, indicating that patients do not keep their initial clinical benefit over time. Also, in patients who initially do not respond to treatment, the prolonged B-cell depletion presents a risk without clinical benefit.

CT-P10 is being developed by CELLTRION, Inc. as a biosimilar candidate of Rituxan and MabThera, a compound with established efficacy in the treatment of active RA (MabThera 2015; Rituxan. 2014). Rituximab is approved as Rituxan in the United States and as MabThera in other countries. CT-P10 can offer a more affordable treatment for RA than the originator protein if similar efficacy and safety are demonstrated and allow increased access to this valuable drug with a proven mechanism of action in RA patients.

The pharmacokinetic (PK) profile is expected to be similar to that of Rituxan and MabThera. There will be 2 serum peaks of CT-P10 at the end of the IV infusions that will be

administered on Day 0 and Day 14: the peak concentrations will be approximately 400 μg/mL with a standard deviation (SD) of ±200 μg/mL. Serum levels will decrease slowly after maximum serum concentration (C_{max}) has been reached. The terminal elimination half-life ($t_{1/2}$) of CT-P10 is expected to be approximately 20 days (SD of ± several days).

This is a similarity study that consists of 3 parallel arms of Rituxan (US-licensed), MabThera (EU-approved), and CT-P10. All statistical assessments will be direct comparisons between the treatment groups at corresponding time points.

The PK sampling time design is based on mean MabThera $t_{1/2}$ of approximately 20.8 days in patients with RA (MabThera 2015) and on published PK studies (Breedveld et al 2007; Tran et al 2010). The area under the concentration-time curve from time zero to time of last quantifiable concentration ($AUC_{0\text{-last}}$), the area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}\infty}$) and C_{max} (after the second infusion) from the first course of treatment were selected as the co-primary PK endpoints.

1.1 Rationale for Study

CT-P10 is a monoclonal antibody currently being developed by CELLTRION, Inc., which is intended to be formulated as a biosimilar to Rituxan and MabThera. This randomized, controlled, multicenter, 3-arm, parallel-group, double-blind, prospective, Phase 3 study is designed to demonstrate similar pharmacokinetics in terms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} (after second infusion) between CT-P10, Rituxan and MabThera in patients with active RA concomitantly treated with MTX and folic acid during the first course of treatment (over the first 24 weeks).

For the treatment of a patient with RA who has experienced an inadequate response to previous or current treatment with the anti-TNF-α agents or was intolerant to at least 1 administration of these agents, the Summary of Product Characteristics for MabThera/Prescribing Information for Rituxan recommends 1000 mg by IV infusion. Each patient may receive 3 courses of treatment. Each course consists of 2 infusions with a 2-week interval between the first and second infusions.

Part 2 of the study is further designed to demonstrate that CT-P10 is similar to reference products (Rituxan and MabThera) in terms of efficacy at Week 24 and also to evaluate the additional Pharmacokinetics (up to Week 48), efficacy, pharmacodynamics, overall safety, and biomarkers of CT-P10 compared with reference products.

Patients from Rituxan and MabThera treatment groups will be combined as a reference products group for the Part 2 analyses up to Week 48.

The Extension Study Period will be composed of an additional course up to 24 weeks.

1.2 Benefits and Risks Assessments

In this study, all patients will receive at least 1 course of treatment consisting of 2 infusions of study drug (1000 mg CT-P10, Rituxan or MabThera) with a 2-week interval between the first and second infusions (i.e., on Day 0 [Week 0] and Day 14 [Week 2]). Subsequent courses of treatment also consisting of 2 infusions of study drug (1000 mg CT-P10, Rituxan or MabThera) with a 2-week interval between the first and second infusions may be administered at Week 24 for the second course and at Extension Week 0 for the third course, if patients meet the predefined safety criteria.

Infusions will begin slowly (50 mg/hour for the first infusion, 100 mg/hour for the second infusion) and increase following a predefined escalation scheme (based on infusion and/or hypersensitivity reaction) to a maximum of 400 mg/hour. The proposed dosing regimen is in line with the approved labeling for Rituxan and MabThera.

In view of the similar structure and biological activity, the overall safety profile of CT-P10 is expected to mirror that for Rituxan and MabThera. In RA, the most frequent adverse reaction considered to be due to receipt of Rituxan and MabThera was infusion-related reactions (IRRs). The overall incidence of IRRs in clinical studies was 23% with the first infusion and decreased with subsequent infusions. Serious IRRs were uncommon (0.5% of patients) and were predominantly seen during the initial course. In addition to adverse reactions seen in RA clinical studies for Rituxan and MabThera, progressive multifocal leukoencephalopathy and serum sickness-like reaction have been reported during postmarketing experience.

The proposed safety monitoring is deemed to be sufficient to monitor potential risks of CT-P10 administration. In view of the structural, biological, and toxicological similarity to Rituxan and MabThera, CT-P10 is expected to display the similar safety profile. Therefore, the incidence and severity of AEs, including serious AEs (SAEs), will be monitored and will be based on the safety profile for Rituxan and MabThera.

In conclusion, based upon the nonclinical and clinical evidence highlighted above as well as the proven safety profile of Rituxan and MabThera to CT-P10, the benefits of the conduct of the proposed clinical study outweigh the associated risks. Additionally, CT-P10 is being developed as a biosimilar candidate of Rituxan and MabThera, a compound with established

efficacy in its registered indications and CT-P10 is intended to offer a more affordable treatment than Rituxan and MabThera, if similar efficacy and safety can be demonstrated during the conduct of these key clinical studies.

2 Study Objectives

All patients from Part 1 of the study will be included in Part 2 of the study and undergo all assessments performed in Part 2.

2.1 Primary Objectives

2.1.1 Primary Objective: Part 1

The primary objective of Part 1 of the study is:

- To demonstrate similar pharmacokinetics in terms of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} (after the second infusion) of CT-P10 to Rituxan, CT-P10 to MabThera, and Rituxan to MabThera during the first course of treatment (over the first 24 weeks).

2.1.2 Primary Objective: Part 2

The primary objective of Part 2 of the study is:

- To demonstrate that CT-P10 is similar to reference products in terms of efficacy as determined by clinical response according to change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (C-reactive protein [CRP]) at Week 24.

2.2 Secondary Objectives

2.2.1 Secondary Objectives: Part 1

The secondary objectives of Part 1 of the study are:

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

2.2.2 Secondary Objective: Part 2

The secondary objective of Part 2 of the study is:

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

3 Investigational Plan

3.1 Study Design

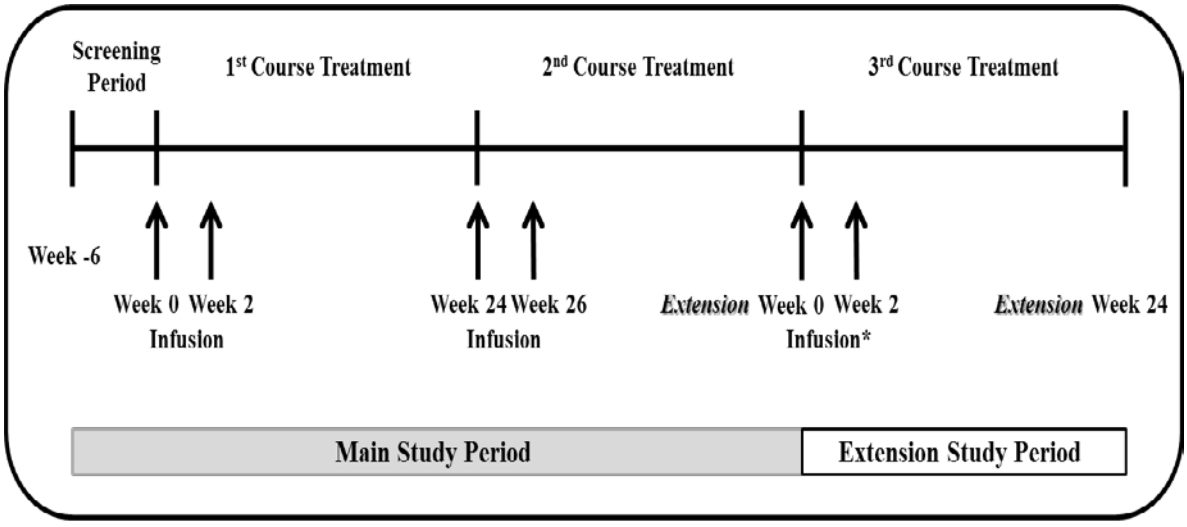
This is a randomized, controlled, multicenter, 3-arm, parallel-group, double-blind, prospective, PK, efficacy, PD, and safety Phase 3 study. There will be up to 3 periods in this study:

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

The study duration will be up to 76 weeks after the Week 0 infusion. Extension Study Period will be initiated between Week 48 and Week 52 of the Entire Study Period. A schematic of the study design is presented in Figure 1. There will be additional follow-up visits for patients with B-cell, IgM and IgG values below the lower limit or normal (LLN) or less than 50% of their baseline value until recovery is achieved for one of them.

The term "Extension" will be used for all the visits in the Extension Study Period (i.e. Extension Week X or Extension Day X). Otherwise, visits will simply be stated as Week X.

Figure 1 Study Schematic



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

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

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

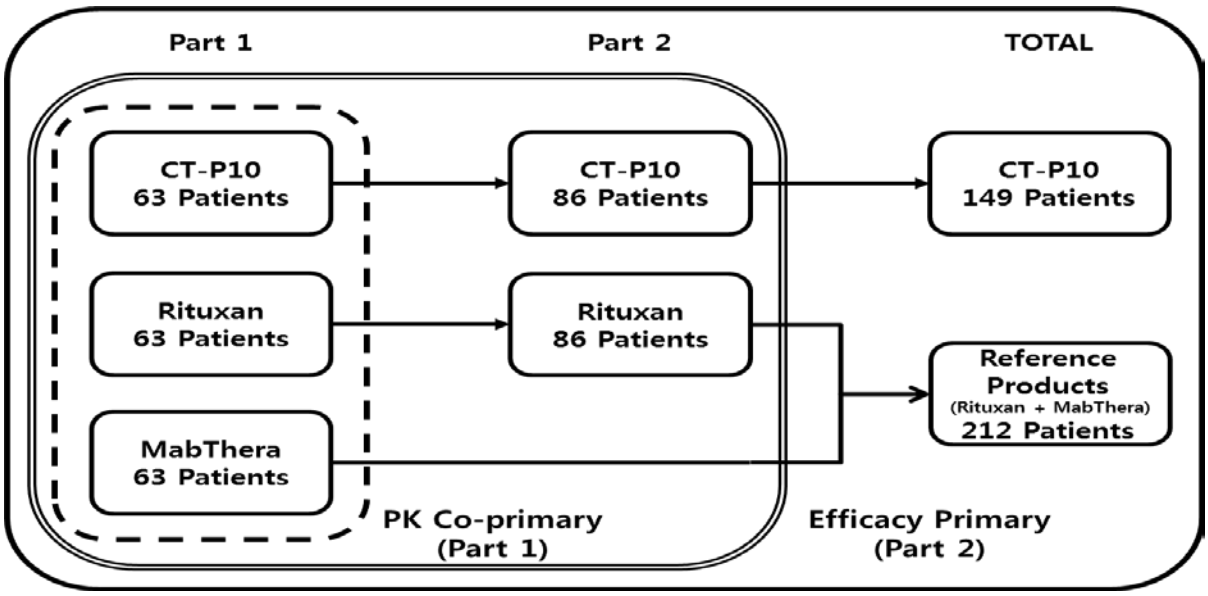
Note: Part 1 and Part 2 of the study will follow this study scheme.

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

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

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

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



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

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

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

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

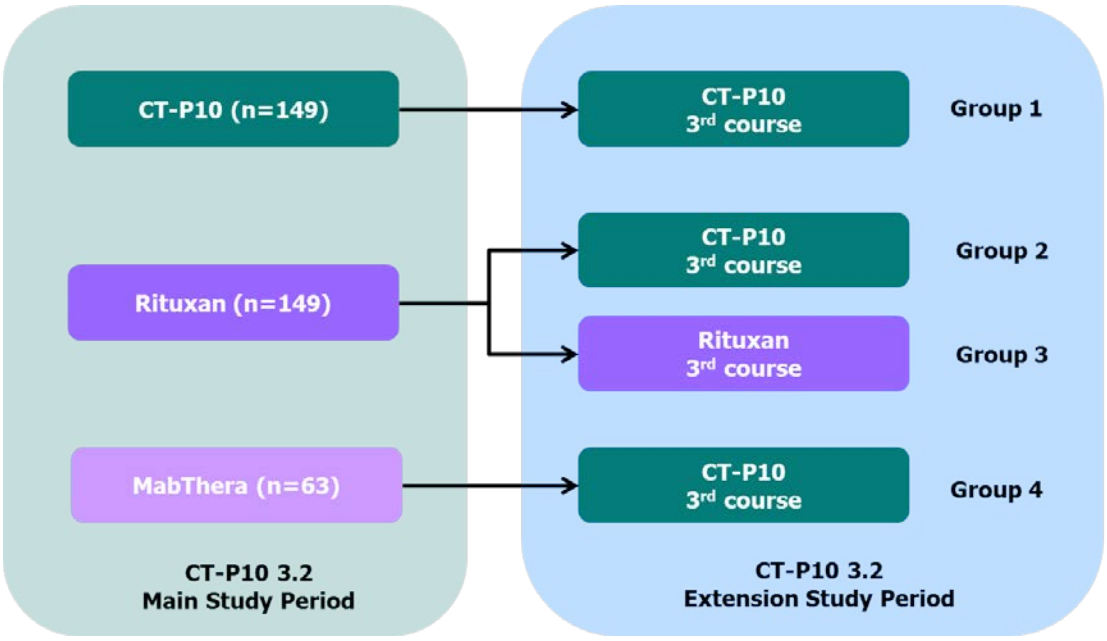
Note that patients, who have the End-of-Study (EOS) visit at Week 48, can participate in the Extension Study Period if the patients sign an informed consent form within 24 weeks from the EOS visit and do not have prohibited medications prior to entering the Extension Study Period.

All patients eligible for Extension Phase from Rituxan group will be randomized again at Extension Week 0. The randomization will be conducted and stratified by:

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

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

Figure 3 Study Schematic



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

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

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

The third course of treatment will be initiated between Week 48 and Week 52 of the Entire Study Period if patients become eligible according to the predefined safety criteria for the

course based on the results assessed within 8 weeks from the Extension Week 0. A visit window is not permitted on the day of second infusion for the third course of treatment (study drug may continue after discussion with the sponsor if a deviation occurs).

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

For patients who receive the third course of treatment at Week 48, the scheduled assessments and samplings should be performed according to the schedule of events and sampling schemes for the Extension Week 0 provided in the Table 6 and Table 9, respectively. Otherwise, all scheduled assessments for Week 48 should be performed separately from the Extension Week 0 according to the schedule of events (Table 6).

All patients will receive MTX and folic acid concomitantly. Each patient may receive 3 courses of treatment; the first course will be an infusion of study drug (CT-P10, Rituxan or MabThera) at Week 0 and Week 2. If patients meet the predefined safety criteria, patients are eligible to receive the additional course(s) of study drug (2 infusions in each course of 2-week interval) at the discretion of the investigator. For the second course of treatment in the Main Study Period, patients, who do not meet the predefined safety criteria, will not receive an additional course of treatment, but they will be followed according to the schedule of events (Table 5) for the Main Study Period.

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

Safety criteria for the any courses of treatment after the first course are predefined as:

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

For the Main Study Period, a schedule of events for patients who receive both first and second courses of treatment (from Screening to Week 48 or End-of-Study Visit) is provided in Table 4 and a schedule of events for the patients who do not receive the second course of treatment (from Week 24 to Week 48 or End-of-Study Visit) is provided in Table 5. For the Extension Study Period, a schedule of events for patients is provided in Table 6.

A patient will be considered as having completed the study if:

- A patient who does not continue on the Extension Study Period and completes all visits up to Week 48
- A patient who continue on the Extension Study Period and completes all visits up to Extension Week 24

Discontinuation is defined as early discontinuation for any reason. These patients, if possible, should have an End-of-Study Visit.

Study termination is defined as the date on which the last patient completes the last visit (if the study is not discontinued by CELLTRION, Inc.).

Patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value should be monitored every 8 weeks after the study completion until recovery is achieved for one of them (equal to or higher than the LLN OR at least 50% of the baseline value). Upon the study completion, additional follow-up of B-cell, IgM and IgG will be determined by the Data Safety Monitoring Board (DSMB).

4 Patient Selection and Withdrawal Criteria

4.1 Selection of Study Population

The first approximately 189 patients will be enrolled into Part 1 and approximately 172 subsequent patients will be enrolled into Part 2 at approximately 110 study centers in Europe, Asia Pacific, and Latin America. In total, approximately 361 patients will be available for analysis (a total of approximately 149 patients for the CT-P10 group and 212 patients for reference products group [Rituxan and MabThera groups], including up to 63 patients from each treatment group in Part 1). Patients will be assigned to study drug only if they meet all of the inclusion criteria and none of the exclusion criteria.

The specific inclusion and exclusion criteria for enrolling patients in this study are described in the following sections.

From a total of approximately 361 patients, more than 30% of the patients from European regions will be included in this study.

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 between 18 and 75 years old, inclusive.

2. Patient has a diagnosis of RA according to the revised 1987 ACR classification criteria (Arnett et al 1988) for at least 6 months prior to randomization.

3. Patient has active disease as defined by the presence of 6 or more swollen joints (of 66 assessed) and 6 or more tender joints (of 68 assessed), and serum CRP ≥1.5 mg/dL (≥15 mg/L) or an ESR ≥28 mm/hour.

4. Patient has experienced an inadequate response to previous or current treatment with the anti-TNF agents infliximab (≥3 mg/kg; at least 3 infusions for at least 3 months), golimumab (50 mg once a month for at least 12 to 14 weeks or 2 mg/kg IV infusion for at least 3 months), adalimumab (40 mg every other week for at least 3 months), or etanercept (25 mg twice weekly or 50 mg once weekly for at least 3 months), or was intolerant to at least 1 administration of these agents. Patients who discontinued etanercept for at least 4 weeks, infliximab or adalimumab for at least 8 weeks, or golimumab for at least 10 weeks prior to randomization are permitted to enter the study.

Patients who received any other anti-TNF agents not in this list can be enrolled if the patient discontinued the treatment at least 4 weeks or 5 half-lives prior to randomization, whichever is longer.

5. Patient has a proper discontinuation period after treatment with interleukin-1 receptor (IL-1R) antagonist, interleukin-6 receptor (IL-6R) antibody, or abatacept. Patients who discontinued IL-1R antagonist for at least 4 weeks, abatacept for at least 8 weeks, or IL-6R antibody for at least 17 weeks prior to randomization are permitted to enter the study.

   Patients who had any other biological drugs not in this list can be enrolled if the patient discontinued the treatment at least 4 weeks or 5 half-lives prior to randomization, whichever is longer.

6. Patient has received MTX treatment (7.5 to 25 mg/week orally or parenterally) for at least the past 12 weeks, with the last 4 weeks at a stable dose before Screening.

7. Patient has the following hematology laboratory test results at Screening:

   - Hemoglobin ≥8.0 g/dL
   - White blood cell count $\geq 3.5 \times 10^3$ cells/μL (SI [Système International d'Unités] units: $\geq 3.5 \times 10^9$ cells/L)
   - Neutrophil count $\geq 1.5 \times 10^3$ cells/μL (SI units: $\geq 1.5 \times 10^9$ cells/L)
   - Platelet count $\geq 75 \times 10^3$ cells/μL (SI units: $\geq 75 \times 10^9$ cells/L)

8. 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)
   - Serum alanine aminotransferase <2.5 × ULN
   - Serum aspartate aminotransferase <2.5 × ULN
   - Serum total bilirubin <2 × ULN

9. Patient has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.

10. Patient (or legal guardian, if applicable) has been informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information, and provide signed and dated written informed consent before inclusion in the study.

11. For both male and female patients, the patient and their partners of childbearing potential either agree to practice total abstinence or use 2 of the following medically acceptable methods of contraception during the course of the study and for 12 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilized):

    - Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
    - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
    - Intrauterine device

    Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use 2 medically acceptable methods of contraception or to practice total abstinence.

    Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing.

4.1.2 Exclusion Criteria

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

1. Patient has taken more than 2 biologic agents.

2. Patient has previously been administered rituximab or participated in a rituximab biosimilar study.

3. Patient has allergies or hypersensitivity to murine, chimeric, human, or humanized proteins.

4. Patient has current or past history of chronic infection with hepatitis B, hepatitis C, or infection with human immunodeficiency virus (HIV)-1 or -2 or who has a positive result to the screening test for these infections.

5. Patient has an infection requiring oral antibiotics 2 weeks before randomization, parenteral injection of antibiotics 4 weeks before randomization, other serious infection 6 months before randomization, a history of recurrent herpes zoster or other chronic or recurrent infection 6 weeks before randomization.

6. Patient has a past or current diagnosis of tuberculosis (TB), recent exposure to person with active TB, examination findings indicating the presence of TB, defined as a positive result for interferon-γ release assay, or other severe or chronic infection (such as sepsis, abscess or opportunistic infection, or invasive fungal infection such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of prophylaxis or complete resolution following treatment can be enrolled.

7. Patient is receiving any of the following medications or therapies:

   - Previous treatment within 6 months of IV gamma globulin or the Prosorba Column
   - Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to randomization or planned within 6 months after randomization
   - Intra-articular corticosteroids within 8 weeks prior to randomization. Patients are permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent), and nonsteroidal anti-inflammatory drug, if they have received a stable dose for at least 4 weeks prior to randomization. In addition, patients are permitted to receive low potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.
   - Disease-modifying antirheumatic drugs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine, within 4 weeks prior to randomization. Patients who discontinued leflunomide and have had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days must wait 4 weeks prior to randomization. Patients who discontinued leflunomide and did not have a cholestyramine discontinuation period must wait 12 weeks after last dose of leflunomide before randomization.
   - Live or live-attenuated vaccine within 8 weeks prior to randomization, and killed vaccines within 4 weeks prior to randomization
   - History of any biologic agent causing B-cell depletion or targeting B-cells

8. Patient has a medical condition including one or more of the following:

    - Uncontrolled diabetes mellitus, even after insulin treatment
    - Uncontrolled hypertension at the discretion of the investigator
    - Any other inflammatory or rheumatic disease, 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 study drug
    - History of any malignancy within the previous 5 years prior to date of informed consent except completely excised or cured squamous carcinoma of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
    - History of lymphoma, lymphoproliferative disease, or bone marrow hypoplasia
    - Patients with New York Heart Association class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the previous 6 months prior to date of consent
    - History of organ transplantation, including corneal graft/transplantation
    - Severe physical incapacitation (unable to perform routine self-care), has RA ACR functional status class 4, or no expected benefit from medication
    - Any uncontrolled clinically significant respiratory disease (in the opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion
    - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barré syndrome
    - Any condition significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage) if it may interfere with the investigator's assessment of disease assessment scores including joint counts
    - Any other serious acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results, in the opinion of the investigator

9. Patient has current or past history of drug or alcohol abuse within 6 months of randomization.

10. Patient has had treatment with any other investigational device or medicinal product within 4 weeks of randomization or 5 half-lives, whichever is longer.

11. Patient is a female who is currently pregnant or breastfeeding or is planning to become pregnant or breastfeed within 12 months of the last dose of study drug.

12. Patient, in the opinion of their general practitioner or investigator, should not participate in the study.

13. Patient has a history of rheumatic autoimmune disease other than RA (except secondary Sjögren's syndrome) or significant systemic involvement secondary to RA (vasculitis, pulmonary fibrosis, or Felty's syndrome).

4.2 Withdrawal of Patients from the Study

Completion of the study is defined in the Section 3.1.

Patients who are withdrawn from the study for any reason before completion will not be considered to have completed.

4.2.1 Reasons for Withdrawal

Reasons for withdrawal include the following:

- Patient develops signs of disease progression
- Patient experiences no efficacy from the study drug
- Patient withdraws consent or refuses to continue treatment or procedures/observations
- Patient develops any malignancy
- Patient has any AE that would compromise his or her safety if he or she continues to participate in the study
- Patient has a significant or major protocol violation
- Patient is lost to follow-up
- Patient dies
- Sponsor terminates the study

The investigator will also withdraw a patient upon the request of CELLTRION, Inc. Upon occurrence of a serious or intolerable AE, the principal investigator will confer with the sponsor. Any patient may withdraw his or her consent at any time. CELLTRION, Inc. or its designee may be contacted if clarification is required on a case-by-case basis.

4.2.2 Handling of Withdrawals

When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who withdraw from the study prematurely will undergo all end-of-study assessments. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before study completion. Patients who fail to return for final assessments will be contacted by the study center in an attempt to have them comply with the protocol.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

4.2.3 Replacements

Patients who receive study drug and discontinue prior to study completion will not be replaced. Patients who are screening failures, for any reason, may be rescreened only once.

4.3 Premature Discontinuation 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.

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 institutional review board (IRB)/independent ethics committee (IEC) of any premature termination or suspension of the study, where applicable.

5 Study Drugs

5.1 Method of Assigning Patients to Treatment Groups

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

Patients with positive status for either RF or anti-CCP at Screening will be classified as a positive.

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

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

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

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

All patients eligible for Extension Phase from Rituxan group will be randomized again at Extension Week 0. The randomization will be conducted and stratified by:

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

To keep the blind during the study, stratification factors will be entered for all patients at Extension Week 0. In the case there were no EULAR-CRP response status available at week 40, the last EULAR-CRP response status assessment done between Weeks 40 and 48 will be

used. Baseline values for assessment of EULAR-CRP will be the last value from screening to Day 0 (Week 0) of the study.

Sub-analysis may be performed using other stratification factors according to the statistical analysis plan (SAP).

5.2 Treatments Administered

Three courses of treatment may be administered to each patient. Each course consists of 2 infusions of study drug (1000 mg CT-P10, Rituxan or MabThera) with a 2-week interval between the first and second infusion. The first course will be an infusion of study drug at Week 0 and Week 2. If patients meet the predefined safety criteria, patients will be retreated with subsequent courses of study drug (2 infusions in each course with a 2-week interval) at the investigator's discretion.

In the Main Study Period, a visit window is not permitted from Day 0 to Day 21 (study drug may continue after discussion with the sponsor if a deviation occurs). A visit window of ±3 days is allowed from Week 4 to Week 24, and a visit window of ±5 days is allowed thereafter, including the EOS Visit. If patients receive the second course of infusion, the first infusion will be administered at Week 24 with a visit window of ±3 days and the second infusion should be administered after 2 weeks (14 days) from the first infusion. A visit window is not permitted on the day of second infusion in the second course of treatment (study drug may continue after discussion with the sponsor if a deviation occurs).

The third course of treatment will be initiated between Week 48 and Week 52 of the Entire Study Period if patients become eligible according to the predefined safety criteria for the course based on the results assessed within 8 weeks from the Extension Week 0. A visit window is not permitted on the day of second infusion for the third course of treatment (study drug may continue after discussion with the sponsor if a deviation occurs).

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

For both Main and Extension Study Periods, visit days during the each course of treatment will be calculated based on the date of the first infusion in the each course of treatment.

DO NOT ADMINISTER STUDY DRUG AS AN IV PUSH OR BOLUS.

The first and second infusions in each course of treatment in the Study will be administered at different infusion rates, as follows:

- First infusion: Initiate infusion at a rate of 50 mg/hour. In the absence of an infusion or hypersensitivity reaction, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.
- Second infusion: Initiate infusion at a rate of 100 mg/hour. In the absence of an infusion or hypersensitivity reaction, increase rate by 100 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

An infusion pump should be used to maintain the accurate infusion rates as stated above. Interrupt the infusion or slow the infusion rate for infusion reactions. Continue the infusion at one-half the previous rate upon improvement of symptoms.

5.2.1 Coadministration of Methotrexate and Folic Acid

Methotrexate with folic acid is coadministered to minimize or prevent AEs related to MTX side effects. Methotrexate will be administered at a dosage of between 7.5 and 25 mg orally or parenterally every week (dose and route must be maintained from beginning to study end). Folic acid will be administered at a dosage of at least 5 mg/week for as long as MTX treatment is continued.

5.2.2 Premedication

Each patient will receive a dose of 100 mg methylprednisolone administered IV 30 minutes before each infusion of study drug (CT-P10, Rituxan or MabThera).

Patients must also be premedicated with an antipyretic (acetaminophen or paracetamol usually 500 to 1000 mg) and an antihistamine (chlorpheniramine 2 to 4 mg or equivalent dose of equivalent antihistamine) 30 to 60 minutes before the start of the study drug infusion. Any locally appropriate medication other than antipyretics and antihistamines may also be used as premedication at the investigator's discretion.

5.3 Identity of Investigational Product

Dosing instructions described in the Rituxan and MabThera prescribing information are to be followed (MabThera 2015; Rituxan 2014).

CT-P10 is a drug product produced by CELLTRION, Inc. with a similar isoform profile to Rituxan and MabThera. The molecule has been engineered by development of DNA designed

to encode a protein that showed 100% sequence coverage to Rituxan and MabThera heavy and light chains by peptide mapping. Expression product purified from the vector clone pCT107, encoding heavy and light chain, was subjected to similarity analysis with Rituxan and MabThera.

The company code of the product is CT-P10. The International Nonproprietary Name of the commercially available products, Rituxan and MabThera, is rituximab. CT-P10 is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 145 kDa. Rituximab binds specifically with high affinity to the CD20 surface antigen that is expressed selectively on B lymphocytes. The affinity constant of rituximab for the CD20 antigen is from 5.2 to 11.0 nM.

Rituxan and MabThera will be prepared as detailed in the prescribing information (MabThera 2015; Rituxan 2014). CT-P10 should be prepared in the same way as Rituxan and MabThera.

CT-P10 is manufactured through a fed-batch culture process using a Chinese hamster ovary cell line. Like Rituxan and MabThera, CT-P10 will be supplied as a sterile, clear, colorless, preservative-free liquid at a concentration of 10 mg/mL in 500-mg (50 mL) vials for IV infusion. CT-P10 is formulated for IV infusion at 25 mM sodium citrate dihydrate, 154 mM sodium chloride, 0.07% polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

Stability testing is being conducted on CT-P10 to determine the stability profile and to assign a shelf-life.

CELLTRION, Inc. will provide adequate supplies of CT-P10 and Rituxan and MabThera for distribution to the study centers.

Once CT-P10, Rituxan or MabThera is reconstituted, these solutions should be used within 12 hours at room temperature or within 24 hours at 2.0 °C to 8.0°C and unused solutions should be discarded at the end of the day.

As a reference, according to the labeling for Rituxan and MabThera, the prepared infusion solution of Rituxan and MabThera is physically and chemically stable for 24 hours at 2.0 °C to 8.0°C and subsequently 12 hours at room temperature. From a microbiological point of view, the prepared infusion solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2.0 °C to 8.0°C, unless dilution has taken place in controlled and validated aseptic conditions.

5.4 Management of Clinical Supplies

5.4.1 Study Drug Packaging and Storage

The clinical supplies group will provide prepacked supplies (CT-P10 3.2 kits) for each patient. Kits will be assigned at randomization using the interactive Web response system (IWRS) or interactive voice response system (IVRS).

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/study center number
- Contents and quantity
- Lot number
- Randomization code/kit number
- Investigator's name
- Storage instructions
- Caution statement (for clinical study use only)
- CELLTRION, Inc.'s contact name and address
- Expiry date

All study drug supplies must be stored in a secure area (e.g., a locked cabinet), protected from moisture. CT-P10, Rituxan and MabThera must be kept at a controlled refrigerated temperature between 2.0°C and 8.0°C. The immediate containers must be kept in the outer carton until reconstitution takes place, in order to protect from light.

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 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 subinvestigators, 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 CELLTRION, Inc.

During the study, study drugs may need to be returned to the depot of origin. 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 CELLTRION, Inc.

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

5.4.3 Other Supplies

Infusion bags (500 mL) and ESR kit will be supplied.

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 by knowing the study drug status of the patient. In such cases, the investigator must contact the medical monitor. If the investigator is unable to contact the medical monitor, the investigator may, in an emergency, determine the identity of the study drug by using the applicable procedure in the IWRS or IVRS (see study manual).

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF. The medical monitor must be informed as soon as possible. Also, the unblinding process should be communicated with the medical monitor before unblinding.

Suspected unexpected SAEs, which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities if required.

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

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

5.6 Treatment Compliance

The investigator or designated study personnel will maintain a log of all CT-P10, Rituxan and MabThera dispensed and returned. Drug supplies for each patient will be inventoried and accounted for throughout the study.

Administration of coadministered treatments (MTX and folic acid) will be recorded throughout the study.

5.7 Prior, Concomitant, and Subsequent Therapy

The medical monitor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited medications are administered. Prohibited medications include:

- Acetaminophen/paracetamol and/or tramadol are allowed as rescue therapy but their dose should be stopped 24 hours before the joint evaluation; narcotic analgesics are not permitted.
- Live or live-attenuated vaccine.
- Any other medication for RA (including additional MTX), particularly anti-TNF or anti-IL-1 compounds or other biologics, and any investigational drug.
- Aspirin (salicylates) at a stable dosage is allowed for cardiovascular protection but the dose should not exceed 300 mg per day.
- Intra-articular injections are not allowed until Week 24. After Week 24, an intra-articular injection is allowed once to 1 joint during the study. However, the injection must not be given within 8 weeks of a final joint assessment. The injected joint must be considered a nonresponder joint during response evaluation.
- Herbal preparations are not permitted during participation in this study.

- Patients are permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and nonsteroidal anti-inflammatory drug during the study, if they have received a stable dose for at least 4 weeks prior to randomization and the same dose is maintained throughout the study. Any changes in terms of dose need to be reported to and discussed with the medical monitors of CELLTRION, Inc. or its designee in advance. In addition, patients are permitted to receive low potency topical, otic, and ophthalmic glucocorticoid preparations provided the preparations are administered per the instructions on the product label.

Contraindication of MTX is summarized as follows based on the current labeling of MTX:

- Significantly impaired hepatic function
- Significantly impaired renal function
- Preexisting blood dyscrasias, such as bone marrow hypoplasia, significant anemia, leukopenia, or thrombocytopenia
- Alcoholism
- Severe acute or chronic infections and immunodeficiency syndrome
- Ulcers of the oral cavity and known active gastrointestinal ulcer disease
- Pregnancy and breastfeeding
- Hypersensitivity to MTX or any of the excipients
- During MTX therapy, concurrent vaccination with live vaccines must not be carried out
- Nonsteroidal anti-inflammatory drugs should not be administered before or concurrently with high-dose MTX

The above information may not reflect any recent updates on contraindications of MTX.

Inhaled and topical corticosteroids are permitted (e.g., for asthma, chronic obstructive pulmonary disease).

Use of all concomitant medications, from within 30 days of randomization until the last assessment date or End-of-Study Visit, will be recorded in the patient's eCRF. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications also will be recorded in the patient's eCRF. The reasons (intolerance, inadequate response or other) for the discontinuation of biologic agents should also be recorded in the 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

principal investigator to ensure that details regarding the medication are recorded in full in the eCRF.

Information about previous RA treatment during whole life with biologic agents, anti-TNF agents, and disease-modifying antirheumatic drugs or surgical procedure history will also be collected separately. This will also include efficacy response results and any reason for discontinuation of anti-TNF agents.

6 Study Assessments and Procedures

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

6.1 Pharmacokinetic Assessments

Time points for collection of blood samples for analysis of study drug (CT-P10, Rituxan or MabThera) concentration are detailed in Section 6.6.1.

Details of blood sampling schemes are provided in Table 7 for patients who receive both courses of treatment in the Main Study Period and Table 8 for patients who receive only first course of treatment in the Main Study Period, respectively.

The total number of samples for analysis of study drug concentration in Part 1 will be 21 samples per patient if the patient receives both first and second courses of treatment and 15 samples per patient if the patient receives only first course of treatment.

The total number of samples for analysis of study drug concentration in Part 2 will be 13 samples per patient if the patient receives both first and second courses of treatment and 7 samples per patient if the patient receives only first course of treatment.

Samples can be obtained via an indwelling venous cannula and heparin lock or saline lock from the arm not receiving the study drug infusion, at the investigator's discretion.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. See Section 6.6.1 for further information on sample collection for PK analysis.

6.2 Efficacy Assessments

Details of the efficacy endpoint analysis are presented in Section 7.2.

For the Main Study Period, efficacy will be assessed by DAS28, ACR criteria (individual components, ACR20, ACR 50% improvement criteria [ACR50] and ACR 70% improvement criteria [ACR70], time to onset of ACR20, hybrid ACR response), European League Against Rheumatism (EULAR) response criteria, simplified disease activity index (SDAI) and clinical disease activity index (CDAI), joint damage progression, functional disability (Health

Assessment Questionnaire [HAQ]) and quality of life (Medical Outcomes Study Short-Form Health Survey [SF-36]) at Screening and during the Study Periods at the time points specified in Table 4 for patients, who receive both first and second courses of treatment and Table 5 for patients who do not receive second course of treatment.

For the Extension Study Period, efficacy will also be assessed between Extension Week 0 and Week 24 by ACR criteria, DAS28, EULAR response criteria, SDAI and CDAI, joint damage progression, functional disability (HAQ) and quality of life (SF-36) at the time points specified in Table 6.

6.2.1 Disease Activity Score Using 28 Joint Counts

Disease Activity Score using 28 joint counts (ESR) and DAS28 (C-reactive protein [CRP]) will be evaluated at Screening and during the Study Periods. The core set of variables for DAS28 for this study include:

- Number of tender and swollen joints with a total of 28 joints assessed for tenderness and 28 for swelling
- Patient's general health (GH) or global assessment of disease activity (VAS) (Appendices 12.8 for GH and 12.6 for VAS)
- ESR (Section 6.3)
- CRP (Section 6.3)

6.2.2 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:

- Number of tender and swollen joints with a total of 68 joints assessed for tenderness and 66 for swelling
- Patient's assessment of pain using visual analogue scale (VAS) (Appendix 12.5)
- Patient's and physician's global assessment of disease activity (VAS) (Appendix 12.6)
- HAQ estimate of physical ability (Appendix 12.7)
- ESR (Section 6.3)
- CRP (Section 6.3)

6.2.3 European League Against Rheumatism Response Criteria

European League Against Rheumatism response criteria will be evaluated at Screening and during the Study Periods (Appendix 12.9).

6.2.4 Simplified Disease Activity Index and Clinical Disease Activity Index

Simplified disease activity index (SDAI) and Clinical Disease Activity Index (CDAI) will be evaluated at Screening and during the Study Periods.

6.2.5 Joint Damage Progression

Joint damage progression based on radiographic evaluation (1 image of each hand and each foot, both the right and left hands and feet, a total of 4 images) will be assessed by the change in the van der Heijde modification of the Sharp scoring system (van der Heijde 2000). Joint damage progression will be evaluated at Screening and during the Study Periods.

6.2.6 Health Assessment Questionnaire Disability Index

The HAQ disability index will be assessed at Screening and during the Study Periods.

6.2.7 Quality of Life

Quality of life will be assessed using the SF-36 questionnaire at Screening and during the Study Periods.

6.3 Pharmacodynamic Assessments

Actual B-cell sampling times for each patient will be recorded in the patient's eCRF and individual source documents.

Time points for collection of blood samples for PD (B-cell kinetics, CRP, ESR, RF, anti-CCP) are detailed in Section 6.6.2.

For the Main Study Period, details of blood sampling schemes are provided in Table 7 for patients who receive both courses of treatment and Table 8 for patients who receive only first course of treatment, respectively.

For the Extension Study Period, the sampling schemes are provided in Table 9.

6.3.1 B-cells

Blood samples for B-cell kinetics (central laboratory) will be obtained from each patient during the Study Periods.

Patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value should be monitored every 8 weeks after the study completion until recovery is achieved for one of them (equal to or higher than the lower limit of normal OR at least 50% of the baseline value). Upon the study completion, additional follow-up of B-cell, IgM and IgG monitoring will be determined by the DSMB.

6.3.2 C-Reactive Protein and Erythrocyte Sedimentation Rate

Blood samples for CRP (central laboratory) and ESR (local laboratory) will be collected at Screening and during the Study Periods.

Where CRP or ESR is also required for efficacy and PD assessments, the same sample can be used.

A standard ESR kit using Westergren method of assessment will be supplied to study centers for use where the normal level will be considered to be no more than 20 mm/h for women and no more than 15 mm/h for men.

6.3.3 Rheumatoid Factor and Anti-cyclic Citrullinated Peptide

Blood samples for RF and anti-CCP will be collected at Screening and during the Study Periods.

6.4 Biomarker Assessments (Optional)

For patients who sign a separate ICF for the biomarker assessments, a blood sample (central laboratory) for evaluation of FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes) will be collected after randomization (before dosing on Day 0 of Week 0).

6.5 Safety Assessments

For the Main Study Period, safety will be assessed at the time points specified in Table 4 for patients who receive both courses of treatment and Table 5 for patients who do not receive second course of treatment.

For the Extension Study Period, safety will also be assessed at the time points specified in Table 6.

6.5.1 Hypersensitivity Monitoring

Hypersensitivity will be assessed by vital sign monitoring except for weight (Section 6.5.4) on each dosing day and recorded on each dosing day at the following time points:

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

In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including 12-lead ECG monitoring 1 hour (±15 minutes) after the end of the study drug infusion (Section 6.5.5).

Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator must be available.

For patients who experience or develop life-threatening infusion-related anaphylactic reactions, study treatment must be stopped immediately and the patient withdrawn from the study.

6.5.2 Immunogenicity Testing

Time points for collection of blood samples for assessment of antibodies to the drugs are detailed in Section 6.6.4.

Samples will be analyzed by the central laboratory.

6.5.3 Immunoglobulins (IgM, IgG and IgA)

Time points for collection of samples for assessment of immunoglobulin are detailed in Section 6.6.5.

Samples will be analyzed by the central laboratory.

6.5.4 Vital Signs and Weight

Vital signs and weight will be measured during the Study Periods.

Vital signs (including blood pressure, heart and respiratory rates, and temperature) and weight will be measured by the investigator or his or her designee after 5 minutes of rest (sitting).

All measurements will be documented at each visit. Vital sign measurements will also be monitored before and after study drug infusion as part of the hypersensitivity monitoring (Section 6.5.1). In addition, measurement of height will be documented at Screening. Details will be recorded in the both the source documents and the eCRF.

6.5.5 Electrocardiogram

A 12-lead ECG will be performed at Screening and during the Study Periods.

All scheduled 12-lead ECGs (performed locally) must be performed after the patient has rested quietly for at least 5 minutes in the supine position.

An ECG will also be used for monitoring during hypersensitivity monitoring (Section 6.5.1).

If, following ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient should be referred to a cardiologist and the findings recorded in both the source documents and the eCRF.

6.5.6 Tuberculosis Assessment

At Screening, a current or past diagnosis of TB, recent exposure to person with active TB, or examination findings indicating the presence of TB, defined as a positive result for interferon-γ release assay, will result in patient exclusion from the study. A patient with sufficient documentation of prophylaxis or complete resolution following treatment can be enrolled. Signs and symptoms of TB will be monitored throughout the study, and interferon-γ release assay can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.

6.5.7 Cardiac Disorder

At Screening, patients will be assessed for the presence of New York Heart Association class III or IV (Appendix 12.4) heart failure, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinically significant ECG abnormalities), or myocardial infarction within the previous 6 months prior to the date of consent. Patients with these cardiac disorders will be excluded from the study.

6.5.8 Hepatitis B

Hepatitis B surface antigen, HBsAb, and HBcIg will be assessed at Screening in all patients (mandatory). If the result is HBsAg (positive), the patient will be excluded from the study. For patients whose HBsAg is negative, HBsAb is negative or positive, and HBcIg is positive, a DNA test should be performed at Screening. If the DNA test result is positive, the patient will be excluded from the study and if the DNA test result is negative, the patient can be included. For those patients who are enrolled based on the DNA test, the DNA test will be done for monitoring purposes.

6.5.9 Physical Examination

Physical examinations with particular attention to infections and IRRs will be performed at Screening and during the Study Periods.

Investigators should carefully evaluate patients for any indication of infections and IRRs and pursue further investigation and treatment indicated in accordance with the investigator's medical judgment.

The investigator is required to monitor the patients at regular intervals throughout the trial for any new or worsening neurological symptoms or signs that may be suggestive of progressive multifocal leukoencephalopathy (PML)(typical symptoms are diverse and include cognitive or visual disorders, hemiparesis, confusion and behavioral disorders). If a patient develops new or worsening neurological signs or symptoms he/she will be evaluated for PML. Neurological warning signs include:

- major changes in vision, unusual eye movements;
- loss of balance or coordination;
- disorientation or confusion.

Any patient who is suspected of developing PML will be discontinued from the trial and the AE will be followed closely, at the discretion of the investigator. Consultation with a Neurologist should be considered as clinically indicated. If any doubt exists, further evaluation, including a magnetic resonance imaging scan (preferably with contrast), cerebrospinal fluid testing for JC viral DNA and repeat neurological assessments should be considered.

Information about the physical examination will be recorded by the investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source

documents. 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.

6.5.10 Adverse Events

6.5.10.1 Definitions

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

Adverse Event

An AE is defined as any untoward medical occurrence in a patient enrolled (i.e., when the ICF is signed) into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the principal investigator or subinvestigator at any time after the ICF is signed if any symptoms develop.

A treatment-emergent AE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug. If abnormal laboratory test results are reported after dosing with study drug, only the clinically significant cases should be considered as TEAEs. The clinically significant cases are defined as follows:

- 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

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.

Abnormal Laboratory Value

Any clinically significant laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded on the AE pages of the eCRF:

- Requires therapeutic intervention
- Leads to dose delay and dose modification
- Leads to discontinuation of study drug
- Is judged by the investigator as clinically significant

Adverse Events of Special Interest

The following AEs of special interest will be reported using the "infusion related reaction" form, which can be found in the eCRF as part of the AE page of the CRF.

- Infusion-related reaction/hypersensitivity/anaphylactic reactions

All AEs related to infusion include but are not limited to the following: urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, or anaphylactoid events

- Diagnosis of Anaphylactic Reactions

According to the Guideline for healthcare providers the following symptoms are indicative for anaphylactic reactions:

Anaphylaxis is highly likely when any one of the following 3 criteria is fulfilled:

- ❖ 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

  - Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF (peak expiratory flow), hypoxemia)
  - Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

- ❖ Two or more of the following that occur rapidly after exposure to a likely allergen for that subject (minutes to several hours):

- Involvement of the skin- mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
- Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
- Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
- Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

❖ Reduced blood pressure (BP) after exposure to known allergen for that subject (minutes to several hours):

- Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

- Infection

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

Serious Adverse Event

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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.

Unlisted (Unexpected) Adverse Event

An unlisted or unexpected AE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., investigator's brochure) for an unapproved investigational product or the label (e.g., package insert or Summary of Product Characteristics) for an approved product. If the investigator's brochure for CT-P10 is delayed, the prescribing information for Rituxan and MabThera will take precedence.

6.5.10.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the ICF is signed until the End-of-Study visit.

At every study visit, 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 will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings, ECG changes) or other documents that are relevant to patient safety.

6.5.10.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, date and/or time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, action taken, date and/or time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code medical history and all AEs. Previous and concomitant medications will be coded using the WHO Drug Dictionary. Versions of coding dictionaries will be stated in the clinical study report. Adverse events will be graded for severity and terminology of adverse events described according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Any medical condition that is present at the time that the patient is screened but does not deteriorate should not be reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

The investigator’s assessment of an AE's 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. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The intensity and the relationship or association of the study drug in causing or contributing to the AE should be characterized as defined in Sections 6.5.10.4 and 6.5.10.5.

Adverse events (and SAEs) should be reported until the last assessment date or the End-of-Study Visit regardless of the relationship to the study drug. If a patient is hospitalized purely for convenience (e.g., for easier performance of study assessments), the hospitalization does not qualify as an SAE. If a patient is hospitalized solely due to disease progression without any other adverse events, the hospitalization does not qualify as a SAE. After the last assessment date or the End-of-Study Visit, serious adverse drug reactions will be reported to CELLTRION, Inc. or its designee.

Serious Adverse Events

Any AE considered serious by the investigator or subinvestigator or which meets SAE criteria (Section 6.5.10.1) must be reported to [redacted] within 24 hours from the time study center personnel first learn about the event and during normal business hours. The following contact information is to be used for SAE reporting:

The SAE must be reported within 24 hours by completing the eCRF pages and sending a paper SAE notification fax to [redacted] PVG. If the patient is hospitalized during the course of an SAE, or because of an SAE, a copy of the hospital discharge summary should be faxed to [redacted] PVG as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the principal investigator or subinvestigator. All SAEs (regardless of relationship with the study drug) will be followed until satisfactory resolution or until the principal investigator or subinvestigator deems the event to be chronic or not clinically significant or the patient to be stable.

CELLTRION, Inc. 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), International Conference on Harmonisation (ICH) guidelines, and local regulatory requirements.

CELLTRION, Inc. or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug (expedited reports) to the

regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. CELLTRION, Inc. or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 15 calendar days of notification.

6.5.10.4 Assessment of Intensity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE v4.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only; radiographic findings only; marginal clinical relevance)
Grade 2: Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
Grade 3: Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
Grade 4: Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis; life-threatening physiological consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy, or operation)
Grade 5: Death related to AE

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

6.5.10.5 Assessment of Causality

The investigator's assessment of an AE's 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. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of CT-P10, Rituxan or MabThera in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

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

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study 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.

Definite: This relationship suggests that a definite causal relationship exists between study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

6.5.10.6 Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the principal investigator or subinvestigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

6.5.11 Pregnancy

In an event of unexpected pregnancy during study participation, patients will be counseled to inform the investigator of any pregnancy that occurs during the study drug and for 12 months after the last dose of study drug. 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 CELLTRION, Inc. and [redacted] PVG 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, for female patients study drug will be permanently discontinued and the patient withdrawn from the study. The study center must complete the supplied SAE form (female patient) or pregnancy form (partner of a male patient) and return it to [redacted] PVG with 24 hours.

Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (i.e., delivery, still birth, miscarriage), provided consent is obtained. The baby will be followed for 1 year after the birth, provided consent is obtained.

6.5.12 Laboratory Analyses

For the Main Study Period, blood and urine samples for clinical laboratory assessments will be collected at the time points specified in Table 4 who receives both courses of treatment and Table 5 for patients who do not receive second course of treatment. For the Extension Study Period, samples for clinical laboratory assessments will also be collected at the time points specified in Table 6.

Details of blood sampling schemes are provided in Table 7 for patients who receive both first and second courses of treatment in the Main Study Period and Table 8 for patients who receive only first course of treatment in the Main Study Period. For the Extension Study Period, the sampling schemes are provided in Table 9.

Blood samples do not need to be performed in a fasting state unless, in the opinion of the investigator, fasting blood samples are required.

A serum pregnancy test (central laboratory) should be conducted in patients, who receive both courses of treatment, at Screening and during Main the Study Periods at the time points specified in Table 4 and Table 5 for patients who do not receive second course of treatment, and then a urine pregnancy test (local laboratory) for women of childbearing potential who have not been surgically sterilized should be used to confirm that patients are not pregnant prior to study drug infusion at Week 0 and Week 2.

For the Extension Study Period, a serum pregnancy test (central laboratory) should be conducted at the time points specified in Table 6, then a urine pregnancy test (local laboratory) for women of childbearing potential who have not been surgically sterilized should be used to confirm that patients are not pregnant prior to study drug infusion.

If patients receive subsequent courses of treatment, additional urine pregnancy tests will be conducted prior to study drug infusion at Week 24, Week 26, Extension Week 0 and Extension Week 2, and additional serum pregnancy tests will be conducted at Week 48, Extension Week 24 and the End-of-Study Visit (if not obtained at Week 48 or Extension Week 24).

The following laboratory analyses will be performed at the central laboratory:

Hematology	Clinical Chemistry	Urinalysis
• Absolute neutrophil count • Hematocrit • Hemoglobin • Platelets • Red blood cell count • White blood cell count with differential	• Alanine aminotransferase • Albumin • Alkaline phosphatase • Aspartate aminotransferase • Blood urea nitrogen • Calcium • Chloride • Cholesterol • Creatine phosphokinase • Creatinine • Creatinine clearance (estimated by weight and Cockcroft-Gault formula) • Gamma-glutamyl transferase • Glucose • High-density lipoprotein cholesterol • Lactate dehydrogenase • Low-density lipoprotein cholesterol • Phosphorus • Potassium • Sodium • Total bilirubin • Total protein • Triglycerides	• Bilirubin • Color • Glucose • Ketones • Nitrite • Occult blood • pH • Protein • Specific gravity • Urobilinogen • Microscopic examination of sediment, *only if urinalysis dipstick results are abnormal*

6.6 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. For the Main Study Period, details of blood sampling schemes are provided in Table 7 for patients who receive both courses of treatment and Table 8 for patients who receive only first course of treatment.

For patients who receive the third course of treatment at Week 48, samplings should be performed according to the sampling schemes for the Extension Week 0 (Table 9). Otherwise, all scheduled samplings for Week 48 should be performed separately from the Extension

Week 0 according to the sampling schemes (Table 7 for patients who receive both courses of treatment and Table 8 for patients who receive only first course of treatment).

6.6.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be collected in accordance with laboratory manual at the time points specified in Table 4 (up to Week 48) and Table 5 (between Weeks 24 and 48) for patients who receive both first and second courses of treatment and receive only first course of treatment, respectively. All samples should be collected as close as possible to the scheduled time point and the actual sampling time must be recorded in both the source documents and the eCRF.

Samples will be stored and shipped to the central laboratory as detailed in Section 6.7.2.

6.6.2 Pharmacodynamic Blood Sampling

Blood samples for PD (B-cell kinetics, CRP, ESR, RF, anti-CCP) will be obtained in accordance with laboratory manual from each patient, who receives both courses of treatment, during the Study Periods at the time points specified in Table 4 for the Main Study Period and Table 5 for patients who do not receive second course of treatment in the Main Study Period. For the Extension Study Period, blood samples will also be obtained from each patient at the time points specified in Table 6. All samples should be collected as close as possible to the scheduled time point and the actual sampling time must be recorded in both the source documents and the eCRF.

Blood samples for CRP and ESR are the same samples as those for routine safety (clinical laboratory testing) assessments. Serum samples for the CRP assessment can be taken from the routine clinical chemistry sample and the frozen serum samples (anti-CCP) will be sent to the central laboratory for analysis. Where CRP assessment is required without routine clinical chemistry testing, an additional blood sample will be required.

Serum samples for RF and anti-CCP assessments will be sent to the central laboratory.

Samples for PD assessment (except ESR) will be stored and shipped to the central laboratory as detailed in Section 6.7.2. The ESR testing will be performed at the study center local laboratory.

6.6.3 Routine Safety Blood Sampling

Blood samples for clinical laboratory testing (hematology and serum chemistry) will be collected in accordance with laboratory manual from each patient, who receives both courses of treatment, for analysis at the central laboratory throughout the study at the time points specified in Table 4 for the Main Study Period and Table 5 for patients who do not receive second course of treatment in the Main Study Period. For the Extension Study Period, blood samples will also be obtained from each patient at the time points specified in Table 6.

An additional blood samples for hepatitis B and C, and HIV-1 and -2 testing will also be required at Screening. Serum pregnancy testing at Screening and the End-of-Study Visit will use serum from the clinical chemistry sample. If hepatic symptoms are suspected, additional blood samples will also be collected during the study.

Samples will be stored and shipped to the central laboratory as detailed in Section 6.7.2.

6.6.4 Immunogenicity Blood Sampling

Blood for immunogenicity assessments will be collected in accordance with laboratory manual from each patient, who receives both courses of treatment, at the time points specified in Table 4 for the Main Study Period and Table 5 for patients who do not receive second course of treatment in the Main Study Period. For the Extension Study Period, blood samples will also be obtained from each patient at the time points specified in Table 6. All samples should be collected as close as possible to the scheduled time point and the actual sampling time must be recorded in both the source documents and the eCRF.

Samples will be stored and shipped to the central laboratory as detailed in Section 6.7.2.

6.6.5 Immunoglobulin Blood Sampling

Blood for immunoglobulin assessments will be collected in accordance with laboratory manual from each patient, who receives both courses of treatment, at the time points specified in Table 4 for the Main Study Period and Table 5 for patients who do not receive second course of treatment in the Main Study Period.

For the Extension Study Period, blood samples will also be obtained from each patient at the time points specified in Table 6. All samples should be collected as close as possible to the scheduled time point and the actual sampling time must be recorded in both the source documents and the eCRF. Serum samples for immunoglobulin assessments will be sent to the central laboratory.

Samples will be stored and shipped to the central laboratory as detailed in Section 6.7.2.

6.6.6 Genotyping Blood Sampling

For patients who sign a separate ICF for the biomarker assessments, blood for FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes) testing will be collected in accordance with laboratory manual after randomization (before dosing on Day 0 of Week 0).

Samples will be stored and shipped to the central laboratory as detailed in Section 6.7.2.

6.7 Labeling, Storage, and Transport of Samples

6.7.1 Sample Labeling

Each sample tube should be clearly labeled with the following information: study number, study center number, patient number, tube identification, and the scheduled sampling time by day and hour.

6.7.2 Sample Storage and Shipment

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

Additionally, 1 sample for PK and immunogenicity analyses should be retained at the central laboratory as a back-up for additional required analyses up to 5 years after the end of the study unless a specific authorization is given by CELLTRION, Inc. to destroy the back-up sample. 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.

Biomarker samples will be stored at the central laboratory as a back-up for additional required analyses for up to 5 years after the end of the study unless a specific authorization is given by CELLTRION, Inc. to destroy the back-up sample.

Details in storage and shipment will be followed according to the lab manual.

6.8 Overdose Management

An overdose is defined as any dose that is 10% or more than the dose prescribed. Overdose may be symptomatic or asymptomatic. Symptoms associated with an overdose must be recorded as an AE and the details provided to [redacted] PVG according to the details in

Section 6.5.10, and an overdose without signs or symptoms must be documented in the study drug section of the eCRF.

Although not strictly due to an overdose, IRRs are possible and hypersensitivity must be monitored according to the details in Section 6.5.1.

7 Statistical and Analytical Plan

For the Part 2, reference products group will contain patients from both Rituxan and MabThera groups up to Week 48.

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

7.1 Pharmacokinetic Endpoints

7.1.1 Co-primary Pharmacokinetic Endpoints: Part 1

The following PK parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as co-primary PK endpoints in Part 1 (over the first 24 weeks):

- $AUC_{0\text{-last}}$: area under the serum concentration-time curve covering both infusions, time to the last measurable concentration
- $AUC_{0\text{-}\infty}$: area under the serum concentration-time curve covering both infusions, time zero to infinity
- C_{max}: maximum concentration after the second infusion

7.1.2 Secondary Pharmacokinetic Endpoints: Part 1

The following PK parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as secondary PK endpoints in Part 1 (over the first 24 weeks):

- $AUC_{0\text{-day14}}$: area under the serum concentration-time curve covering both infusion, time zero to day 14
- V_d: volume of distribution
- CL: total clearance
- $t_{1/2}$: terminal elimination half-life after the second infusion
- T_{max}: time to C_{max} after both the first and second infusions
- $C_{max,\ 1}$: maximum concentration after the first infusion
- C_{min}: concentration at Week 24
- C_{trough}: trough concentration prior to the second infusion

7.1.3 Secondary Pharmacokinetic Endpoints: Part 2

The following PK parameters for the study drug (CT-P10 and reference products) will be determined as secondary PK endpoints in Part 2 (up to Week 48 or over the first 24 weeks if second course of treatment is not administered):

- T_{max}: time to C_{max} after both the first and second infusions
- C_{max}: maximum concentration after both the first and second infusions
- C_{min}: concentration at Weeks 24 and 48
- C_{trough}: trough concentration prior to the second infusion

7.2 Efficacy Endpoints

7.2.1 Primary Efficacy Endpoint

The following efficacy parameter for the study drug (CT-P10 and reference products) will be determined as the primary efficacy endpoint:

- The change from Baseline in disease activity measured by DAS28 (CRP) at Week 24

7.2.2 Secondary Efficacy Endpoints

The following efficacy parameters for the study drug will be determined as secondary efficacy endpoints:

- ACR20, ACR50 and ACR 70 at Week 24, Week 48, and Extension Week 24
- Individual components of the ACR criteria compared with Baseline at Week 24, Week 48, and Extension Week 24
- Time to onset of ACR20 response over 24 weeks
- Mean change from Baseline in disease activity measured by DAS28 (CRP) at Weeks 12 and 48 and Extension Week 24 and DAS28 (ESR) at Weeks 12, 24 and 48 and Extension Week 24
- Proportion of patients with a good response, defined according to the European League Against Rheumatism (EULAR) response criteria at Week 24, Week 48, and Extension Week 24
- Hybrid ACR response at Week 24, Week 48, and Extension Week 24
- SDAI and CDAI at Week 24, Week 48, and Extension Week 24
- Joint damage progression based on radiographic evaluations, van der Heijde modification of the Sharp scoring system at Week 48, Extension Week 24 and the EOS visit

- Functional disability (HAQ disability index) at Week 24, Week 48, and Extension Week 24
- Health-related quality of life (SF-36 health survey score) compared with Baseline at Week 24, Week 48, and Extension Week 24

7.3 Secondary Pharmacodynamic Endpoints

The following PD parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as PD endpoints:

- B-cell kinetics over time including depletion and recovery
- CRP and ESR at Week 24, Week 48, and Extension Week 24
- Rheumatoid factor and anti-CCP at Week 24, Week 48, and Extension Week 24

7.4 Secondary Safety Endpoints

The following safety parameters for the study drug (CT-P10, Rituxan and MabThera) will be determined as secondary safety endpoints:

- Immunogenicity testing
- Immunoglobulin (IgM, IgG and IgA) testing
- Hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates, and temperature) and ECGs
- Vital sign measurements
- ECGs
- Signs and symptoms of TB monitoring
- Physical examination findings
- AEs
- Infections
- Infusion related reactions (IRRs)
- Clinical laboratory analyses
- Pregnancy testing
- Concomitant medications

7.5 Sample Size Calculations

Part 1 of this study is powered to demonstrate PK similarity of CT-P10, Rituxan and MabThera in $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max}. Similarity will be demonstrated if the 90%

confidence interval (CI) for the geometric mean ratio of CT-P10 to Rituxan and MabThera in $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max} is within the bounds of 80% and 125%.

In Part 1, based on overall 90% power, 2-sided alpha equal to 0.1, an interpatient coefficient of variation (CV) in $AUC_{0\text{-last}}$ of 30%, and a true of geometric mean equal to 1, fifty patients are needed in each treatment group being compared (50 patients in the CT-P10 treatment group, 50 patients in the MabThera treatment group, and 50 patients in the Rituxan treatment group: 150 patients total). The statistical power of each comparison, CT-P10 versus MabThera, CT-P10 versus Rituxan and MabThera versus Rituxan is 96.5% to achieve overall 90% power accounting for multiplicity with type II error correction. Allowing for a drop-out rate of 20%, 189 patients will be randomly assigned into the study in a 1:1:1 allocation.

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

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

7.6 Analysis Sets

Five patient populations are defined: PK, efficacy, PD, safety, and all-randomized populations.

The PK population is defined to be all patients who receive at least 2 doses (Week 0 and Week 2) of study drug (CT-P10, Rituxan or MabThera), who provide sufficient blood concentration data to compute the required PK variables, and who do not have any major protocol violation including a violation of the inclusion and exclusion of criteria. The PK population will be the primary population for the summary and analysis of PK data.

The efficacy population is defined to be all patients who receive at least 1 dose of study drug (CT-P10, Rituxan or MabThera), who have at least 1 post-treatment efficacy result, and who do not have any major protocol violation including a violation of the inclusion and exclusion of criteria. The efficacy population will be the primary population for the summary of efficacy data.

The PD population is defined to be all patients receiving at least 1 dose of study drug (CT-P10, Rituxan or MabThera) and providing at least 1 post-treatment PD result. The PD population will be the primary population for the summary of PD data.

The safety population is defined to be all patients who receive at least 1 dose (full or partial) of study drug (CT-P10, Rituxan or MabThera). The safety population will be the primary population for the summary of safety data.

The all-randomized population is defined to be all patients enrolled and randomly assigned to receive a dose of study drug, regardless of whether or not any study drug dosing was completed. All efficacy parameters will also be analyzed for the all-randomized population.

The number of patients, who discontinue from the study prematurely, together with the reasons for discontinuation, will be summarized. In addition, for each analysis population the number of patients will be presented.

7.7 Description of Subgroups to be Analyzed

Subgroup analysis could be implemented to reflect medical, regulatory, regional, or ethnic considerations.

7.8 Statistical Analysis

Statistical analyses will be carried out using [redacted]. The statistical methods for this study, summarized below, will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to locking of the database and unblinding of the treatment codes. 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 final study report.

Continuous variables will be summarized by reporting the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency tables showing the number and percentage of patients within a particular category.

Pharmacokinetic parameters will be computed by noncompartmental methods using appropriate validated software such as WinNonlin (Pharsight, St Louis, Missouri).

The following pair-wise treatment comparisons will be made for the Part 1 analyses:

- CT-P10 vs. Rituxan
- CT-P10 vs. MabThera
- Rituxan vs. MabThera

For the Part 2 analyses up to Week 48, patients from Rituxan and MabThera treatment groups will be combined as a reference products groups.

7.8.1 Pharmacokinetic Analyses

All PK analyses will be performed based on the results from Week 0 to Week 48.

7.8.1.1 Co-primary Pharmacokinetic Analysis

The primary PK analysis will assess the similarity of CT-P10, Rituxan and MabThera in terms of $AUC_{0\text{-last}}$ (over both infusions of the first course of treatment, from time zero to the last measurable concentration), $AUC_{0\text{-}\infty}$ (over both infusions of the first course of treatment, from time zero to infinity) and C_{max} (after the second infusion of the first course of treatment) as co-primary PK endpoints.

The following PK parameters as co-primary PK endpoints will be calculated using noncompartmental methods:

- $AUC_{0\text{-last}}$ will be calculated using trapezoidal rule. This will be calculated over both infusions in the first course of treatment.
- $AUC_{0\text{-}\infty}$ will be calculated using trapezoidal rule. This will be calculated over both infusions in the first course of treatment.
- C_{max} will be calculated after the second infusion in the first course of treatment.

In each part, for the calculation of PK parameters, all serum concentrations that are below the quantification limit (BQL) prior to the first measurable concentration will be set to zero. The BQL values after the first dose will be set equal to the lower limit of quantification. Actual sampling times, rather than scheduled sampling times, will be used in all computations of PK parameters.

- The primary PK parameter estimates will be analysed using an analysis of covariance (ANCOVA) with treatment as a fixed effect and country, gender, race, prior anti-TNF-alpha (anti-TNFα) blocker status (inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region defined in the SAP, for use as a covariate. Point estimates (geometric means and ratio of geometric means) will be calculated from back transforming the least squares means of the natural log-transformed values of $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$ and C_{max}, and 90% CIs for the ratio of the geometric means of the 2 treatments (CT-P10 versus Rituxan, CT-P10 versus MabThera, and Rituxan versus MabThera) will also be produced. $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max} will be summarized by treatment. Summary statistics will include the mean, SD, median, minimum, maximum, geometric mean, and CV.
- The similarity of pharmacokinetics between CT-P10, Rituxan and MabThera will be concluded if the 90% CIs for the ratios of geometric means based on all the combinations of the three treatments in a pairwise comparison are entirely contained within 80% to 125% for $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, and C_{max}. The equivalence margin of 80% - 125% is the universal standard PK similarity margin.

Serum concentrations of study drugs will be summarized by treatment at each scheduled collection time. In addition to the standard summary statistics, the geometric mean and CV will also be presented at each time point. Mean serum concentration time profiles of study drugs will be plotted by treatment on linear and semilogarithmic scales based on scheduled sample times. Individual concentrations and scheduled and actual sample times will be presented in data listings by treatment.

7.8.1.2 Secondary Pharmacokinetic Analysis

For patients in Part 1, the following secondary PK parameters will be considered: $AUC_{0\text{-day14}}$ (over both infusions of the first course of treatment, from time zero to Day 14), V_d, CL, $t_{1/2}$ (after the second infusion in the first course of treatment), T_{max} (after both the first and second infusions in the first course of treatment), $C_{max,\ 1}$ (after the first infusion in the first course of treatment), C_{min} (at Week 24), C_{trough} (prior to the second infusion in the first course of treatment).

For patients in Part 2, the following secondary PK parameters will be considered: T_{max} (after both the first and second infusions in the first and second courses of treatment), C_{max} (after

both the first and second infusions in the first and second courses of treatment), C_{min} (at Week 24), and C_{trough} (prior to the second infusion in the first and second courses of treatment).

These PK variables will be presented in listings and summarized in tables. For PK parameters, the summary tables will display the following descriptive statistics: n, mean, median, SD, minimum, maximum, geometric mean, and CV.

7.8.2 Efficacy Analyses

7.8.2.1 Primary Efficacy Analysis

The primary efficacy analysis includes patients from Part 1 and Part 2. The primary analysis for DAS28 is an analysis of covariance (ANCOVA) comparing the change from baseline of DAS28 after 24 weeks of treatment between two treatment groups, CT-P10 and reference products, considering the treatment as a fixed effect and country, gender, race, prior anti-TNF-α blocker status (inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region defined in the SAP, for use as a covariate.

Similarity for the change from baseline of DAS28 (CRP) at week 24 will be evaluated based on the two-sided 90% confidence interval obtained from the ANCOVA model for the difference of means of the change in DAS28 (CRP) between the two treatment groups. The equivalence margin for the 90% CI is defined as [-0.50, 0.50].

7.8.2.2 Secondary Efficacy Analyses

ACR20, ACR50, and ACR70

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

- A decrease of at least 20% in the number of tender joints
- A decrease of at least 20% in the number of swollen joints, and
- A 20% improvement in 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 0 to 10 cm, with higher scores indicating poorer status or more severe pain.

The following categories of patients are considered nonresponders at each week respectively:

- Patients with an improvement according to the ACR criteria of less than 20%
- Patients who discontinue the study prior to the week of interest, except for safety reasons
- Patients with missing data for the evaluation of ACR20 at the week of interest
- Patients with protocol prohibited changes in medication including initiation therapy with a new disease-modifying antirheumatic drugs, increase in dose of RA medication (MTX or corticosteroid), and administration of intra-articular corticosteroids
- Patients requiring a surgical joint procedure during the study

The ACR50 and ACR70 are calculated similarly to ACR20, however, an increase or decrease of 50% and 70%, respectively, must be achieved.

The proportion of patients demonstrating ACR20, ACR50, and ACR70 (based on 1995 ACR criteria) will be summarized by treatment at Week 24, Week 48, and Extension Week 24.

The mean change in the components of the ACR criteria from Baseline will be summarized for ACR20, ACR50, ACR70, and hybrid ACR.

Time to onset of the ACR20 response will also be summarized by treatment.

Hybrid ACR

The hybrid ACR is an outcome measure that combines the ACR20, the ACR50, and the ACR70 and a continuous score of the mean improvement in core set measures (American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007). The score is determined by calculating the mean percentage change in core set measures and reading the score from Table 2 using the patient's ACR status.

Table 2 Scoring Method for Hybrid ACR

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

Abbreviations: ACR, American College of Rheumatology; ACR20, ACR 20% improvement criteria; ACR50, ACR 50% improvement criteria; ACR70, ACR 70% improvement criteria.

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

Disease Activity Score Using 28 Joint Count Data

The DAS28 data will be listed and summarized by treatment (including ESR and CRP levels). In addition, change from Baseline will also be summarized, by treatment, for assessments after the first infusion.

European League Against Rheumatism Response Criteria

The DAS-based EULAR response criteria will be summarized by treatment.

Simplified Disease Activity Index and Clinical Disease Activity Index

Simplified and clinical disease activity will be measured using the SDAI and CDAI (Aletaha and Smolen 2009) calculated from the formulas presented in Table 3.

Table 3 Simplified Disease Activity Index and Clinical Disease Activity Index Formulas

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

Abbreviations: CDAI, clinical disease activity index; CRP, C-reactive protein; EGA, evaluator's global assessment of disease activity (physician's global assessment); PGA, patient's global assessment of disease activity; SDAI, simplified disease activity index; SJC, swollen joint count; TJC, tender joint count.
Source: Aletaha and Smolen 2009.

Joint Damage Progression

Joint damage progression based on radiographic evaluations (1 image of both the right and left hands and both the right and left feet for a total of 4 images) will be assessed by the change in the van der Heijde modification of the Sharp scoring system at Week 48, Extension Week 24 and the EOS visit (van der Heijde 1992). Hand and foot x-rays will be evaluated centrally by independent reviewers for reporting purposes and on a local level for treatment practice.

Health Assessment Questionnaire Disability Index and Short Form-36

The HAQ disability index and SF-36 data will be listed and summarized by treatment. Summaries will be included for the SF-36 physical component score and the mental component score.

7.8.3 Pharmacodynamic Analyses

All PD data will be listed and summarized by treatment, where appropriate. The comparison of the concentration of B-cell kinetics between CT-P10, Rituxan and MabThera will be performed using ANCOVA, with treatment as a fixed effect and baseline values, country, gender, race, prior anti-TNF-α blocker status(inadequate response versus intolerant case), and RF or anti-CCP status (both positive versus both negative versus either RF or anti-CCP negative) fitted as covariates. If country is found to be unsuitable as a covariate due to the number of levels, then this may be pooled into a new variable, region defined in SAP, for use as a covariate. Point estimates and 95% CIs will be provided. Pharmacodynamic data will also be summarized using quantitative descriptive statistics (including geometric mean and CV, where appropriate).

7.8.4 Safety Analyses

The safety analysis will be performed on the safety population by presenting data on hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates, and temperature), immunogenicity testing, immunoglobulin (IgM, IgG and IgA) testing, vital sign measurements, ECGs, signs and symptoms of TB monitored throughout the study, physical examination findings, AEs, infections, IRRs, clinical laboratory analyses, pregnancy testing, and concomitant medications.

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

7.8.4.1 Demographic, Baseline, and Background Characteristics

Demographics (age, gender, race, and etc.) and baseline and background characteristics 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.

7.8.4.2 Adverse Events

Adverse events will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA. Adverse events will be graded for severity according to the CTCAE v4.0.

The following AE summaries will be reported by SOC, PT, and treatment:

- Number and percentage of patients reporting at least 1 AE
- Number and percentage of patients reporting at least 1 SAE
- Number and percentage of patients discontinuing the study drug due to an AE
- Number and percentage of patients with AEs of special interest (infusion-related AEs and infections)

If more than 1 AE is recorded for a patient within any SOC or PT, the patient will be counted only once within the respective summary.

Adverse events will also be summarized by maximum intensity and relationship to study drug with the percentage of patients in each category. If more than 1 AE is recorded for a patient within any SOC or PT, the patient will only be counted once using the most severe assessment.

Adverse events of special interest will also be summarized by intensity.

7.8.4.3 Laboratory Test Analyses

Clinical laboratory tests (hematology, clinical chemistry, and urinalysis) will be summarized, by treatment, at each scheduled collection time. For continuous parameters, change from Baseline will also be summarized for all scheduled collection times after the first infusion. Baseline will be the latest available measurement prior to the first infusion.

All laboratory results will be listed. Additional listings will be provided showing laboratory results outside the normal range.

7.8.4.4 Immunogenicity

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

7.8.4.5 Immunoglobulin (IgM, IgG and IgA) Values

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

7.8.4.6 Vital Signs and Weight

Vitals signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) and weight will be summarized, by treatment, at each scheduled collection time. Change from Baseline will also be summarized for all scheduled collection times after the first infusion for vital signs. Baseline will be the latest available measurement prior to the first infusion.

All data will be listed.

7.8.4.7 Electrocardiograms

Overall assessment and ECG parameters will be summarized, by treatment, at each visit. In addition, change from Baseline in ECG parameters will also be summarized, by treatment. Baseline will be the result at Screening.

All data will be listed.

7.8.5 Missing Data Analysis

In order to evaluate the impact of missing data on the primary endpoint results, additional analyses with missing data imputation will be conducted for primary efficacy endpoint of DAS28 (CRP) in all randomized population. Multiple imputation (MI) with the missing at random (MAR) assumption and last observation carried forward (LOCF) with the missing completely at random (MCAR) assumption will be used for missing data imputation in all randomized population for both CT-P10 and reference (Rituxan and MabThera) groups.

Additionally, tipping point analysis will be conducted for a sensitivity analysis under the missing not at random (MNAR) assumption to identify assumptions (tipping point) under which confidence interval no longer rules out differences in the change from baseline of DAS28 (CRP) for the therapeutic equivalence margin of ±0.5.

7.8.6 Interim Analyses

Although no formal interim analyses are planned, the sponsor plans to prepare 2 clinical study reports. However, clinical study report(s) can be generated during the Study Period in addition to 2 clinical study reports as planned for regulatory or academic purpose.

1. To report data for each patient up to Week 24

2. To report data after completion of study (including safety laboratory [B-cell, IgM and IgG] follow-up closed)

7.9 Data Quality Assurance

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 personnel before the study, periodic monitoring visits by CELLTRION, Inc. 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 CELLTRION, Inc. 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 personnel from CELLTRION, Inc. 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 CELLTRION, Inc. or its designee if they have been contacted by a regulatory agency concerning an upcoming inspection.

8 Ethics

8.1 Independent Ethics Committee or Institution Review Board

Federal regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before 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 IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/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 obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

8.3 Patient Information and Consent

A written ICF in compliance with regulatory authority regulations or US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative 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 before IRB/IEC submission. Once reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before 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.

Before 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.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

9 Investigator's Obligations

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

9.1 Confidentiality and Data Protection

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 CELLTRION, Inc. its designee, the regulatory authorities, or the IRB/IEC.

The investigator and 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.

9.2 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 required under 21 CFR 54. 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 [redacted] 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 [redacted] is financially responsible for further treatment of the patient's disease.

9.3 Investigator Documentation

Prior to beginning the study, the principal investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval
- Original investigator-signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed For FDA 1572
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA1572
- IRB/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 guardians, and
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493

9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6 (R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

9.5 Data Collection

9.5.1 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 subinvestigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The principal investigator or subinvestigator agrees to maintain source documentation (e.g., laboratory reports, ECG strips), to enter patient data into the eCRF as accurately as possible, and to respond to any reported discrepancies rapidly.

The eCRFs are accessed through the Medidata Rave 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 person 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.

9.6 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6 (R1) and all applicable guidelines and regulations.

9.7 Adverse Events and Study Report Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study center IRB/IEC as appropriate.

9.8 Investigator's Final Report

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

9.9 Records Retention

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

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. 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.

9.10 Patient Identification Register

The investigator agrees to complete a patient identification register, which will be used for the purpose of long-term follow-up, if needed. This form will be treated as confidential and will be filed by the investigator in the Study Center Master File. Otherwise, all reports and communications relating to the study will identify patients by assigned number only.

9.11 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 will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, 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.

10 Study Management

10.1 Monitoring

10.1.1 Data Safety Monitoring Board

This study will be monitored by an independent DSMB consisting of a PK specialist, statistician, chairing physician, and an independent physician. Further details will be provided in a DSMB charter.

10.1.2 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 personnel.

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 GCP and current standard operating procedures.

10.1.3 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/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 other regulatory agency access to all study records.

The principal investigator or subinvestigator should promptly notify the sponsor and its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

The investigator should promptly notify the sponsor and [redacted] of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

10.2 Management of Protocol Amendments and Deviations

10.2.1 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 IRB/IEC for approval before patients can be enrolled into an amended protocol.

10.2.2 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 IRB/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 IRB/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 IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, enrollment of the patient without prior sponsor approval, or nonadherence to regulatory regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Deviations from the protocol, including deviations of inclusion/exclusion criteria, will be assessed as "minor" or "major" in agreement with the sponsor. Deviations will be defined prior to unblinding. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

10.3 Study Termination

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

Study termination is defined as the date on which the last patient completes the last visit (if the study is not discontinued by CELLTRION, Inc.).

10.4 Final Report

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

It is planned that 2 clinical study reports will be written (Section 7.8.6).

11 Reference List

Aletaha D, Smolen JS. The simplified disease activity index and clinical disease activity index to monitor patients in standard clinical care. Rheum Dis Clin North Am. 2009;35(4):759-72, viii.

American College of Rheumatology Committee to Reevaluate Improvement Criteria. A proposed revision to the ACR20: the hybrid measure of American College of Rheumatology response. Arthritis Rheum. 2007;57(2):193-202.

American Diabetes Association. Standards of medical care in diabetes – 2006. Diabetes Care. 2006;29(Suppl 1):S4-S42.

Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 1988;31(3):315-24.

Breedveld F, Agarwal S, Yin M, et al. Rituximab pharmacokinetics in patients with rheumatoid arthritis: B-cell levels do not correlate with clinical response. J Clin Pharmacol. 2007;47(9):1119-28.

Edwards JC, Cambridge G, Abrahams VM. Do self-perpetuating B lymphocytes drive autoimmune disease? Immunol. 1999;97(2):188-96.

Emergency treatment of anaphylactic reactions-guidelines for healthcare providers, Soar J, Pumphrey R, Cant A, et al. Resuscitation. 2008;77:157-169.

Emery P, Fleischmann R, Filipowicz-Sosnowska A, et al. DANCER Study Group. The efficacy and safety of rituximab in patients with active rheumatoid arthritis despite methotrexate treatment: results of a phase IIB randomized, double-blind, placebo-controlled, dose-ranging trial. Arthritis Rheum. 2006;54(5):1390-400.

Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology: preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38(6):727-35.

Fransen J, Bernelot Moens H, Speyer I, et al. Effectiveness of systematic monitoring of rheumatoid arthritis disease activity in daily practice: a multicenter, cluster randomized controlled trial. Ann Rheum Dis. 2005;64(9):1294-8.

Higashida J, Wun T, Schmidt S, et al. Safety and efficacy of rituximab in patients with rheumatoid arthritis refractory to disease modifying antirheumatic drugs and anti-tumor necrosis factor-alpha treatment. J Rheumatol. 2005;32(11):2109-15.

Lard LR, Visser H, Speyer I, et al. Early versus delayed treatment in patients with recent-onset rheumatoid arthritis: comparison of two cohorts who received different treatment strategies. Am J Med. 2001;111(6):446-51.

MabThera (rituximab) [Summary of Product Characteristics]. European Medicines Agency; March 2015 (revision date) [cited 2015 April 20]. Available from: https://www.medicines.org.uk/emc/medicine/2570.

McInnes IB. Rheumatoid arthritis. From bench to bedside. Rheum Dis Clin North Am. 2001 May;27(2):373-87.

Petersen J, Ingemann-Hansen T, Halkjaer-Kristensen JS. Spontaneous and induced immunoglobulin secretion by synovial fluid B lymphocytes in rheumatoid arthritis. Ann Rheum Dis. 1984;43(2):140-5.

Rituxan (rituximab) [Package Insert]. August 2014 (revision date) [cited 2015 Jan 30]. Available from: http://www.gene.com/download/pdf/rituxan_prescribing.pdf.

Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: Summary Report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006; 117(2):391-97

Scott DL, Symmons DP, Coulton BL, et al. Long-term outcome of treating rheumatoid arthritis: results after 20 years. Lancet. 1987;1(8542):1108-11.

Tan SM, Xu D, Roschke V, et al. Local production of B lymphocyte stimulator protein and APRIL in arthritic joints of patients with inflammatory arthritis. Arthritis Rheum. 2003;48(4):982-92.

Toubi E, Kessel A, Slobodin G, et al. Changes in macrophage function after rituximab treatment in patients with rheumatoid arthritis. Ann Rheum Dis. 2007;66(6):818-20.

Tran L, Baars JW, Aarden L, et al. Pharmacokinetics of rituximab in patients with CD20 positive B-cell malignancies. Hum Antibodies. 2010;19(1):7-13.

Vander Cruyssen B, Van Looy S, Wyns B, et al. DAS28 best reflects the physician's clinical judgment of response to infliximab therapy in rheumatoid arthritis patients: validation of the DAS28 score in patients under infliximab treatment. Arthritis Res Ther. 2005;7(5):R1063-71.

van der Heijde DM. Radiographic imaging: the 'gold standard' for assessment of disease progression in rheumatoid arthritis. Rheumatology. 2000;39(Suppl 1):9-16.

van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. Br J Rheumatol. 1995;34(Suppl2):74-8.

van der Heijde DM, van Leeuwen MA, van Riel PL, et al. Biannual radiographic assessments of hands and feet in a three-year prospective followup of patients with early rheumatoid arthritis. Arthritis Rheum 1992;35(1):26-34.

Wang H, Marsters SA, Baker T, et al. TACI-ligand interactions are required for T cell activation and collagen-induced arthritis in mice. Nat Immunol. 2001;2(7):632-7.

Youinou P, Jamin C, Saraux A. B-cell: a logical target for treatment of rheumatoid arthritis. Clin Exp Rheumatol. 2007;25(2):318-28.

12 Appendices

12.1 Appendix: Schedule of Events

Table 4 Schedule of Events for Screening and the Main Study Period (for patients who receive both first and second courses of treatment)

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

Week and Day[1] of Study Period	**Screen**	**Wk 0**		**Wk 1**	**Wk 2**		**Wk 3**	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 16**	**Wk20**	**Wk 24**	**Wk 26**	**Wk 32**	**Wk 40**	**Wk 48**	**EOS[2]**
Procedure	**Day -42 to -1**	**Day 0**	**Day 1**	**Day 7**	**Day 14**	**Day 15**	**Day 21**	**Day 28**	**Day 56**	**Day 84**	**Day 112**	**Day 140**	**Day 168**	**Day 182**	**Day 224**	**Day 280**	**Day 336**	
CRP	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
DAS28 examination[14]	X	X[5]						X	X	X	X	X	X[5]		X	X	X	X
QOL (SF-36) assessment	X	X[5]											X[5]				X	X
Rheumatoid factor	X												X[5]				X	X
Anticyclic citrullinated peptide	X												X[5]				X	X
Immunoglobulin testing[15,16]		X[5]							X		X		X[5]		X	X	X	X
Immunogenicity		X[5]											X[5]				X	X
Study drug infusion		X			X								X	X				
Hypersensitivity monitoring[17]		X			X								X	X				
PK blood sampling for Part 1		X[18]	X[18]	X	X[18]	X[18]	X	X	X	X	X		X[18]	X[18]			X	X[19]
PK blood sampling for Part 2		X[18]			X[18]								X[18]	X[18]			X	X[19]
B-cell kinetics blood sampling for both Part 1 and Part 2[16]		X[20]	X[20]	X	X		X	X	X	X	X		X[20]	X	X	X	X	X
Biomarker (FcγR genotypes)[21]		X																
Previous and concomitant medications monitoring[22]	X	X																
Adverse event monitoring[23]	X	X																

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

*** IMPORTANT! For patients who receive the third course of treatment at Week 48, the scheduled assessments and samplings should be performed according to the schedule of events and sampling schemes for the Extension Week 0 provided in the Table 6 and Table 9, respectively. Otherwise, all scheduled assessments for Week 48 should be performed separately from the Extension Week 0 according to this schedule of events.**

1. If the assessments or tests are done within 14 days from the randomization date, the omitting of that assessment or tests will be allowed. A visit window is not permitted from Day 0 to Day 21 (study drug may continue after discussion with the sponsor if a deviation occurs). A visit window of ±3 days is allowed from Week 4 to Week 24, a visit window of ±5 days is allowed thereafter, including the EOS Visit. If patients receive the second course of infusion, the first infusion will be administered at Week 24 with a visit window of ±3 days, and the second infusion should be administered after 2 weeks (14 days) from the first infusion. A visit window is not permitted on the day of second infusion in the second course of treatment (study drug may continue after discussion with the sponsor if a deviation occurs). Visit days during the second course of treatment will be calculated based on the date of the first infusion in the second course of treatment (Week 24 visit).
2. The EOS Visit only needs to be completed if the patient withdraws prior to study completion. End-of-study assessments should be completed at least 8 weeks after the last study drug infusion and before Week 48 of study period if a patient withdraws prior to the completion of Week 48 visit. If the patient has completed the Study Period, a separate EOS Visit is not required. In this case, the last visit will be considered the EOS Visit.
3. Hepatitis B surface antigen, HBsAb, and HBcIg should be assessed at Screening in all patients (mandatory). If the result is HBsAg (positive), the patient should be excluded from the study. For patients whose HBsAg is negative, HBsAb is negative or positive, and HBcIg is positive, a DNA test should be performed at Screening. If the DNA test result is positive, the patient should be excluded from the study and if the DNA test result is negative, the patient can be included. For those patients who have enrolled based on the DNA test, the DNA test will be done every 24 weeks for monitoring purposes. During the study, if hepatic symptoms are suspected, HBsAg, HBsAb, HBcIg, and DNA tests should be performed. Hepatitis C antibody and HIV-1 and -2 should be assessed at Screening in all patients (mandatory). Hepatitis and HIV testing will be performed at the central laboratory.
4. At Screening, patients will be assessed for the presence of New York Heart Association class III or IV (Appendix 12.4) heart failure, severe uncontrolled cardiac disease (unstable angina, arrhythmias, clinically significant ECG abnormalities), or myocardial infarction within the previous 6 months prior to the date of consent. Patients with these cardiac disorders will be excluded from the study.
5. Assessed prior to study drug infusion.
6. Tender joint count and swollen joint count need to be reconfirmed for inclusion criteria prior to randomization.
7. Vital signs (including blood pressure, heart and respiratory rates, and temperature) and weight will be measured by the investigator or his or her designee after 5 minutes of rest (sitting). In addition, measurement of height will be documented at Screening.
8. Hematology (hematocrit, hemoglobin, red blood cell count, white blood cell count with differential, absolute neutrophil count, platelets), clinical chemistry (albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, cholesterol, triglycerides, creatine phosphokinase, creatinine, creatinine clearance [estimated by weight and by Cockcroft-Gault formula], gamma-glutamyl transferase, glucose, high-density lipoprotein cholesterol, lactate dehydrogenase, low-density lipoprotein cholesterol, phosphorous, potassium, sodium, total bilirubin, total protein). Testing will be performed at the central laboratory.
9. Urinalysis (color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, occult blood, and microscopic examination of sediment, only if urinalysis dipstick results are abnormal). Testing will be performed at the central laboratory.

10. All scheduled 12-lead ECGs (performed locally) must be performed after the patient has rested quietly for at least 5 minutes in the supine position. On the day of infusion, 12-lead ECGs will be performed after 1 hour (15 minutes) after the end of the study drug infusion for the hypersensitivity monitoring.
11. At Screening, interferon-γ release assay will be performed. The results of the test should be entered in the electronic case report form. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.
12. One image of each hand and each foot (both the right and left hands and feet, a total of 4 images) for analysis of efficacy will be obtained at the scheduled times. Joint damage, as determined by radiography, will be assessed by change in the van der Heijde modification of the Sharp scoring system. The baseline radiographs must be assessed within 42 days prior to the randomization date. Hand and foot x-rays will be evaluated centrally by an independent reviewer for reporting purposes and on a local level for treatment practice.
13. ACR20, ACR50, ACR70, and hybrid ACR will be calculated from these assessments. It is recommended that the joint count assessments are performed by the same physician when possible.
14. The European League Against Rheumatism response criteria will be derived from the DAS28.
15. Immunoglobulin (IgM, IgG and IgA) testing will be performed at the central laboratory.
16. Patients with B-cell, IgM and IgG values below the LLN or less than 50% of their baseline value should be monitored every 8 weeks after the study completion until recovery is achieved for one of them (equal to or higher than the lower limit of normal OR at least 50% of the baseline value). Upon the study completion, additional follow-up of B-cell, IgM and IgG monitoring will be determined by the Data Safety Monitoring Board (DSMB).
17. Additional vital signs including blood pressure, heart and respiratory rates, and temperature (before administration [within 15 minutes prior to the beginning of the study drug infusion], within 15 minutes after the end of the study drug infusion, and at 1 hour (±15 minutes) after the end of the study drug infusion) will be assessed to monitor for possible hypersensitivity reactions. In addition, hypersensitivity should be monitored by routine continuous clinical monitoring including 12-lead ECG monitoring 1 hour (±15 minutes) after the end of the study drug infusion. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilator must be available.
18. Pharmacokinetic samples will be collected within 15 minutes prior to the beginning of the study drug infusion, within 15 minutes after the end of study drug infusion, and 1 hour (±15 minutes) after the end of study drug infusion on the day of each study drug infusion. For patients from Part 1, additional samples will be collected after 24 hours (±2 hours) from the start of each study drug infusion in the first treatment course and on Days 7, 21, 28, 56, 84 and 112. Testing will be performed at the central laboratory.
19. Pharmacokinetic sampling should be done at EOS Visit if the last visit occurs before Week 48.
20. B-cell kinetic samples will be collected in the each treatment course within 15 minutes prior to the beginning of the first study drug infusion, within 15 minutes after the end of first study drug infusion and 1 hour (±15 minutes) after the end of first study drug infusion. For patients from Part 1, additional sample will be collected after 24 hours from the start of the first study drug infusion in the first course of treatment.
21. Before dosing on Day 0 of Week 0 (after randomization only). Only for patients who sign a separate informed consent form for the biomarker study (genotypes). Blood samples will be evaluated for FcγR genotype (FcγRIIa, IIIa, and/or any necessary genotypes). Testing will be performed at the central laboratory.
22. Use of all concomitant medications, from within 30 days of randomization until the last assessment date or End of Study Visit, will be recorded in the patient's eCRF.

23. Adverse events will be assessed from the date the ICF is signed until the last assessment date or End of Study Visit.

Table 5 Schedule of Events for the Main Study Period between Weeks 24 and 48 (for patients who receive only first course of treatment)

Week and Day[1] of Study Period / Procedure	Week 24 / Day 168	Week 32 / Day 224	Week 40 / Day 280	Week 48 / Day 336	EOS[2]
Hepatitis B[3] & C, and HIV	(X)[3]			(X)[3]	(X)[3]
Serum pregnancy test				X	X
Vital signs[4]	X				
Physical examination	X				
Hematology and clinical chemistry[5]	X				
Urinalysis[6]	X				
12-lead ECG (local)[7]	X			X	X
TB monitoring[8]	X				
Hand and foot x-ray				X	X
ACR[9] including:					
Tender joint count	X				
Swollen joint count	X				
VAS pain score	X				
VAS global assessment of disease activity (patient and physician) score	X				
Health Assessment Questionnaire	X				
Erythrocyte sedimentation rate (local)	X				
C-reactive protein	X				
DAS28 examination[10]	X				
QOL (SF-36) assessment	X			X	X
Rheumatoid factor	X			X	X
Anti-cyclic citrullinated peptide	X			X	X
Immunoglobulin testing[11,12]	X				
Immunogenicity	X			X	X
Pharmacokinetic blood sampling for both Part 1 and 2	X				
B-cell kinetics blood sampling for both Part 1 and 2[12]	X				
Previous and concomitant medications monitoring[13]	X				
Adverse event monitoring[14]	X				

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

*** IMPORTANT! For patients who receive the third course of treatment at Week 48, the scheduled assessments and samplings should be performed according to the schedule of events and sampling schemes for the Extension Week 0 provided in the Table 6 and Table 9, respectively. Otherwise, all scheduled assessments for Week 48 should be performed separately from the Extension Week 0 according to this schedule of events.**

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

Table 6 Schedule of Events for the Extension Study Period

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

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

*** IMPORTANT! Assessments for hepatitis B, serum pregnancy test, hand and foot x-ray, PK blood sampling will be performed at Extension Week 0 according to this schedule of events ONLY IF patients receive the third course of treatment on the same day with Week 48.**
Samples for PK at Week 48 should be obtained ONLY for patients who receive the second course of treatment during the Main Study Period and who receive the third course of treatment on the same day with Week 48. The sampling scheme for the PK is provided in the Table 7.

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

days during the treatment course will be calculated based on the date of the first infusion in the Extension Study Period. Unscheduled visit(s) can be conducted for assessment of safety criteria until the initiation of the third course of treatment.

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

15. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring.
16. Adverse events will be assessed from the date the ICF is signed until the last assessment date or End of Study Visit.

Table 7 Sampling Times for Pharmacokinetic, Pharmacodynamic, and Safety Assessments for the Main Study Period (for patients who receive both first and second courses of treatment)

Study Period				PD			Safety		
Week	Day	PK for Part 1	PK for Part 2	B-Cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urinalysis
0	0	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Pretreatment[4]	NA	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]
	1	24 hours after start of infusion[5]	NA	24 hours after start of infusion[5] (only for patients from Part 1)	NA	NA	NA	NA	NA
1	7	Time not specified[6]	NA	Time not specified[6]	NA	NA	NA	NA	NA
2	14	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Time not specified[6]	NA	NA	NA	NA	Pretreatment[4]
	15	24 hours after start of infusion[5]	NA	NA	NA	NA	NA	NA	NA
3	21	Time not specified[6]	NA	Time not specified[6]	NA	NA	NA	NA	NA
4	28	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	NA	NA	NA

Study Period				PD			Safety		
Week	Day	PK for Part 1	PK for Part 2	B-Cell Kinetics	CRP, ESR	RF, anti-CCP	Immuno-globulin	Immuno-genicity	Hematology, Clinical Chemistry, Urinalysis
8	56	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
12	84	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	NA	NA	NA
16	112	Time not specified[6]	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
20	140	NA	NA	NA	Time not specified[6]	NA	NA	NA	NA
24	168	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]	Pretreatment[4]
26	182	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Predose[1]; end of infusion[2]; 1 hour after end of infusion[3]	Time not specified[6]	NA	NA	NA	NA	Pretreatment[4]
32	224	NA	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
40	280	NA	NA	Time not specified[6]	Time not specified[6]	NA	Time not specified[6]	NA	Time not specified[6]
48	336	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]
EOS[7]		Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]	Time not specified[6]

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

*** IMPORTANT! For patients who receive the third course of treatment at Week 48, the samples should be obtained according to the sampling schemes for the Extension Week 0 provided in the Table 9. Otherwise, all scheduled samplings for Week 48 should be performed separately from the Extension Week 0 according to this sampling scheme.**

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

Table 8 Sampling Times for Pharmacokinetic, Pharmacodynamic, and Safety Assessment for the Main Study Period between Weeks 24 and 48 (for patients who receive only first course of treatment)

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

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

*** IMPORTANT! For patients who receive the third course of treatment at Week 48, the samples should be obtained according to the sampling schemes for the Extension Week 0 provided in the Table 9. Otherwise, all scheduled samplings for Week 48 should be performed separately from the Extension Week 0 according to this sampling scheme.**

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

Table 9 Sampling Times for Pharmacodynamic, and Safety Assessments for the Extension Study Period

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

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

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

12.2 Appendix: Rheumatoid Arthritis Classification Criteria 1987

Adapted from Arnett et al 1988.

Criterion	Definition
1. Morning stiffness	Morning stiffness in and around joints, lasting at least 1 hour before maximal improvement
2. Arthritis of 3 or more joint areas	At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints
3. Arthritis of hand joints	At least 1 area of swollen (as defined above) in wrist, MCP, or PIP joint
4. Symmetric arthritis	Simultaneous involvement of the same joint areas (as defined in 2) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry)
5. Rheumatoid nodules	Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician
6. Serum rheumatoid factor	Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in <5% of normal control patients
7. Radiographic changes	Radiographic changes typical of rheumatoid arthritis on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify)

Abbreviations: MCP, metacarpophalangeal joints; MTP, metatarsophalangeal joints; PIP, proximal interphalangeal joints.
Note, For classification purposes, a patient shall be said to have rheumatoid arthritis is he or she has satisfied at least 4 of these 7 criteria. Criteria 1 through 4 must have been present for at least 6 weeks. Patients with 2 clinical diagnoses are not excluded. Designation as classic, definite, or probable rheumatoid arthritis is *not* to be made.

12.3 Appendix: Measurement of Disease Activity

Disease Activity Score Using 28 Joint Counts (DAS28)

The Disease Activity Score (DAS) is a clinical index of rheumatoid arthritis (RA) disease activity that combines information regarding the number of swollen and tender joints, acute phase response, and the patient's global assessment of disease activity. The DAS provides an absolute value which assesses rheumatoid inflammation (Fransen et al 2005). The DAS is a well-validated endpoint for clinical studies and has been modified as a DAS28 index consisting of 28 tender joint count, 28 swollen joint count, erythrocyte sedimentation rate (ESR) and general health assessment on a visual analogue scale (VAS). The DAS28 has a continuous scale ranging from 0 to 9.4 with disease activity considered low (DAS28≤3.2), moderate (3.2<DAS28≤5.1) or high (DAS28>5.1). The DAS28 can also be interpreted in terms of the European League Against Rheumatism (EULAR) response criteria which categorizes the DAS28 response (i.e., good, moderate, or none) based on changes in DAS28 from Baseline. One important advantage of using DAS28 is that it provides a continuous scale (as opposed to the categorical ACR20) which reflects the extent of underlying inflammation and disease activity. Also, since DAS28 provides an absolute value of disease activity, responses to treatment in clinical trials can be compared meaningfully and trial results can be expressed as clinically relevant outcomes (Fransen et al 2005). In addition DAS28 has been validated as a measure of disease activity in RA patients undergoing treatment with biologicals such as infliximab (Vander Cruyssen et al 2005; Fransen et al 2005).

Disease Activity Scores: ACR20, ACR50, ACR70

A standard measure of clinical activity in rheumatoid arthritis patients is the American College of Rheumatology (ACR) 20% improvement criteria (ACR20), 50% improvement criteria (ACR50), or 70% improvement criteria (ACR70) score. The American College of Rheumatology defines the ACR20 as the proportion of patients that exhibit a 20% improvement based on the number of tender and swollen joints, the patient assessment of pain and disease activity, the physician assessment of pain and physical function and acute-phase reactant levels. The ACR50 and ACR70 reflect the proportion of patients with a 50% and 70% improvement, respectively (Felson et al 1995; MabThera 2015).

DAS28

Mean decrease in disease activity, measured by DAS28 (Disease Activity Score in 28 joints).

a. Number of swollen joints (0-28): swollen joint count (SJC)

b. Number of tender joints (0-28): tender joint count (TJC)

c. Measurement of ESR (mm/hour) and CRP (mg/L)

d. Patient's general health (GH) or global disease activity measured on VAS

e. DAS28 can be calculated using the following formula:

DAS28 (ESR) = 0.56 × sqrt(TJC28) + 0.28 × sqrt(SJC28) + 0.70 × ln (ESR) + 0.014 × GH

DAS28 (CRP) = 0.56 × sqrt(TJC28) + 0.28 × sqrt(SJC28) + 0.36 × ln (CRP + 1) + 0.014 × GH + 0.96

Abbreviations: sqrt, square root, ln, natural logarithm.

The 28 joints to be assessed for tenderness (pain) and swelling consist of the following:

- Shoulders
- Elbows
- Wrists
- Interphalangeal on digit 1 (thumb)
- Proximal interphalangeal joints on digits 2–5
- Metacarpophalangeal joints on digits 1–5
- Knees

More information on DAS28 can be found at http: www.das-score.nl.

		Left		Right	
		Swollen	Tender	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: http://www.das-score.nl/DAS28frm.doc

ACR Responders

A patient is defined as a responder according to the ACR20/50/70 criteria if a, b, and c are fulfilled:

a. Decrease of at least 20/50/70 percent in the number of tender joints

b. Decrease of at least 20/50/70 percent in the number of swollen joints

c. 20/50/70 percent improvement in at least 3 of the following 5:

i. ESR or serum CRP concentration

ii. Patient's global assessment of disease activity on a VAS*

iii. Patient's assessment of pain on a VAS*

iv. Health Assessment Questionnaire (HAQ) estimate of physical ability

v. Physician's global assessment of disease activity on VAS*

* VAS: visual analogue scales (range, 0 to 10 cm, with higher scores indicating poorer status or more severe pain)

The ACR core set variables, including numbers of tender and swollen joints, will be assessed and documented at each visit; a total of 68 joints will be assessed for tenderness, and 66 for swelling.

Individual Components of the ACR Criteria:

Swollen joint count, tender joint count, patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), health assessment questionnaire estimating physical ability, CRP and ESR.

Health Assessment Questionnaire

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

General Health Status

General health status will be assessed using the Medical Outcomes Study Short-Form Health Survey (SF-36). The 36 items yield an 8-scale profile of functional and well-being, as well as 2 summary scores (Physical Component Score and Mental Component Score). The 8 scales of health status assessed are: general and mental health, physical function, social function, physical and emotional health, pain, and vitality. The scores and scales of the SF-36 survey ranges from 0 (worst) to 100 (best), a higher score indicating a better health-related quality of life.

12.4 Appendix: New York Heart Association Cardiac Assessment

The assessment of suitability of cardiac patients for participation in this study is assessed according to the New York Heart Association classes where classes III and IV are excluded from participating. The classes are:

Class I (Mild)

No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).

Class II (Mild)

Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.

Class III (Moderate)

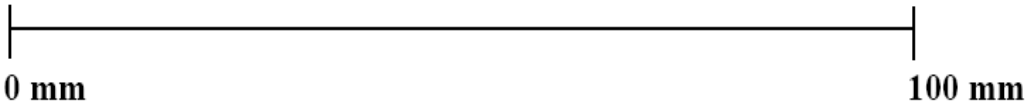
Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

Class IV (Severe)

Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

12.5 Appendix: Visual Analogue Scale Patient's Assessment of Pain

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

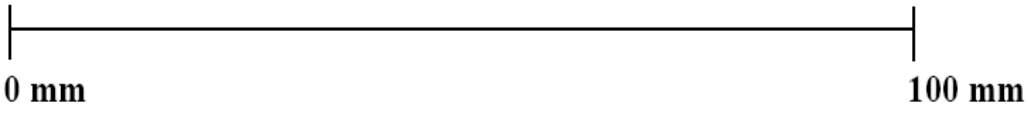


None Extreme

12.6 Appendix: Visual Analogue Scale Patient's and Physician's Global Assessment of Disease Activity

12.6.1 Visual Analogue Scale Physician's Global Assessment of Disease Activity

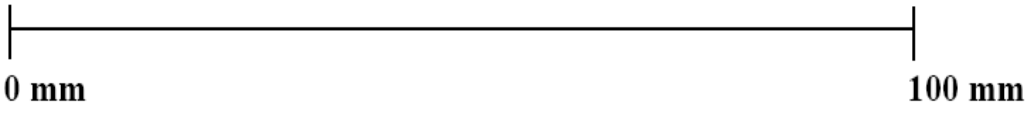
Physician's global assessment of disease activity is measured by the physician indicating the patient's current disease activity by marking an X through the 100-mm line (0 mm equals no activity and 100 mm equals extreme activity). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF.



None Extreme

12.6.2 Visual Analogue Scale 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 an X through the 100-mm line (0 mm equals no activity and 100 mm equals extreme activity). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's eCRF.



None Extreme

12.7 Appendix: Health Assessment Questionnaire and Scoring of the Health Assessment Questionnaire

HEALTH ASSESSMENT QUESTIONNAIRE

Name_____ **Date**_____

PATKEY#_____
QUESTDAT_____

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_____

RASTUDY_____

QUESTNUM_____

	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?	_____	_____	_____	_____	DRESSNEW_____
ARISING					
Are you able to:					
- Stand up from a straight chair?	_____	_____	_____	_____	
- Get in and out of bed?	_____	_____	_____	_____	RISENEW_____
EATING					
Are you able to:					
- Cut your meat?	_____	_____	_____	_____	
- Lift a full cup or glass to your mouth?	_____	_____	_____	_____	
- Open a new milk carton?	_____	_____	_____	_____	EATNEW_____
WALKING					
Are you able to:					
- Walk outdoors on flat ground?	_____	_____	_____	_____	
- Climb up five steps?	_____	_____	_____	_____	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_____

The HAQ is composed of 9 items investigating 2 domains.

Domains and Clusters

Domains	Number of Items	Cluster of Items	Item reversion	Direction of Domains
* Disability	8	Dressing (DRESSNEW), Arising (RISENEW), Eating (EATNEW), Walking (WALKNEW), Hygiene (HYGNEW), Reach (REACHNEW), Grip (GRIPNEW), Common activities (ACTIVNEW) & the type of assistance needed for each items (DRSGASST, RISEASST, EATASST, WALKASST, HYGASST, RCHASST, GRIPASST & ACTVASST)	No	Higher scores indicate greater dysfunction
* Discomfort and pain	1	VAS scale (PAINSCAL)	-	Higher score indicate more severe pain

**** The first two domains, which comprise the HAQ Disability Index and Pain Scale, can be used independently***

Scoring of Domains

Item scaling	4-point scale for the disability items: DRESSNEW, RISENEW, EATNEW, WALKNEW, HYGNEW, REACHNEW, GRIPNEW, ACTIVNEW 0= Without any difficulty 1= With some difficulty 2= With much difficulty 3= Unable to do 4-point scale for DRSGASST, RISEASST, EATASST, WALKASST, HYGASST, RCHASST, GRIPASST & ACTVASST: 0= No assistance is needed 1= A special device is used by the patient in his/her usual activities 2= The patient usually needs help from another person 3= The patient usually needs both a special device and help from another person Visual Analogue Scale for PAINSCAL from 0 (no pain) to 100 (Severe pain) **** Although the original scale was a 15-cm VAS scale, the usual length is a 10-cm VAS scale. Of note, depending on the printer used, the length of the VAS scale may vary, but this does not make any difference. Whatever the length, the scale should be divided into 100 equal parts***
Weighting of items	No
Range of scores	For Disability dimension: Range 0-3 The VAS Pain Scale ranges from 0 to 100. But it may be converted to a 0-3 scale
Scoring Procedure	<u>Disability Index:</u> 1. The highest score reported for any component question of the eight categories (DRESSNEW, RISENEW, EATNEW, WALKNEW, HYGNEW, REACHNEW, GRIPNEW, ACTIVNEW) determines the score for that category 2. If either devices and/or help from another person are checked for a category (DRSGASST, RISEASST, EATASST, WALKASST, HYGASST, RCHASST, GRIPASST & ACTVASST), then the score is set to “2” , but if the patient's highest score for that sub-category is a two it remains a two, and if a three, it remains a three. 3. A global score is calculated by summing the scores for each of the categories and dividing by the number of categories answered 4. If there are fewer than 6 categories with responses, an index score cannot be calculated <u>Alternative Disability Index:</u> Summing the scores of the eight categories (DRESSNEW, RISENEW, EATNEW, WALKNEW, HYGNEW, REACHNEW, GRIPNEW & ACTIVNEW) and dividing by the number of categories

<table>
<tr><td></td><td>answered. In that case, the aids and devices are not used

<u>Pain scale:</u>
Measure the distance (D in cm) from the left side of the line to the mark.

<u>For a 15-cm VAS scale:</u>
➢ For a 0-100 scale: Score = (100 * D) / 15
➢ For a 0-3 scale: Score = D * 0.2

<u>For a 10-cm VAS scale</u>:
➢ For a 0-100 scale: Score = (100 * D) / 10
➢ For a 0-3 scale: Score = D * 0.3

<u>For a X-cm VAS scale:</u>
➢ For a 0-100 scale: Score = (100 * D) / X
➢ For a 0-3 scale: Score = D * (3 / X)</td></tr>
<tr><td>Interpretation and Analysis of missing data</td><td><u>Disability Dimension:</u>
• If a component question is left blank or the response is too ambiguous to assign a score, then the score for that category is determined by the remaining completed question(s)
• If all component questions are blank or if more than one answer is given, then follow up with the respondent is required
• If the respondent's mark is between the response columns, then move it to the closest one. If it's directly between the two, move it to the higher one

<u>Pain:</u>
• If the patient writes in a number on the pain scale, or writes a number in addition to making a mark, you need only take the number, converting it to the corresponding score. In this case, do not measure the mark. For example, if the patient writes "50" on the line, this should be coded as 1.5.
• If an individual records a percentage, multiply the percentage by 3. Pain severity coding translations follow below: If a patient puts more than one mark, the midpoint is used

PAIN SEVERITY CODING TRANSLATIONS (0-3 scale)
Applicable only for a 15-cm VAS scale

Measurement (Cm) = Score
0 = 0
0.1 - 0 .7 = 0.1
0.8 - 1.2 = 0.2
1.3 - 1.7 = 0.3
1.8 - 2.2 = 0.4
2.3 - 2.7 = 0.5
2.8 - 3.2 = 0.6
3.3 - 3.7 = 0.7
3.8 - 4.2 = 0 .8
4.3 - 4.7 = 0 .9
4.8 - 5.2 = 1.0
5.3 - 5.7 = 1.1
5.8 - 6.2 = 1.2

Measurement (Cm) = Score
7.8 - 8.2 = 1.6
8.3 - 8.7 = 1.7
8.8 - 9.2 = 1.8
9.3 - 9.7 = 1.9
9.8 - 10.2 = 2.0
10.3 - 10.7 = 2.1
10.8 - 11.2 = 2.2
11.3 - 11.7 = 2.3
11.8 - 12.2 = 2.4
12.3 - 12.7 = 2.5
12.8 - 13.2 = 2.6
13.3 - 13.7 = 2.7
13.8 - 14.2 = 2.8</td></tr>
</table>

	6.3 - 6.7 = 1.3 14.3 - 14.7 = 2.9 6.8 - 7.2 = 1.4 14.8 - 15.0 = 3.0 • If a patient makes a horizontal line below the pain scale, instead of a vertical one, the midpoint of that line is taken. If the line starts at the beginning of the scale, measure to the end of the line not the middle Disability Index: • If an item does not apply to an individual, e.g., they don't shampoo their hair, take tub baths, or reach for a heavy object above their heads, then they should leave the item(s) blank since the purpose is to obtain data about what they can do • If a patient uses adapted or modified aids or devices (e.g., clothing, faucets, cars), then they should answer the questions based on their usual equipment. If they have no difficulty using the adapted equipment, then they would mark the "no difficulty" column. The adapted equipment (aids and devices) will be taken into account in the assistance variables (see below) • If an individual can open their own door but not for others, then they should respond in consideration of their own requirements • Relative to inquiries about distance in responding to the item about walking, patients should be advised to make their own decisions

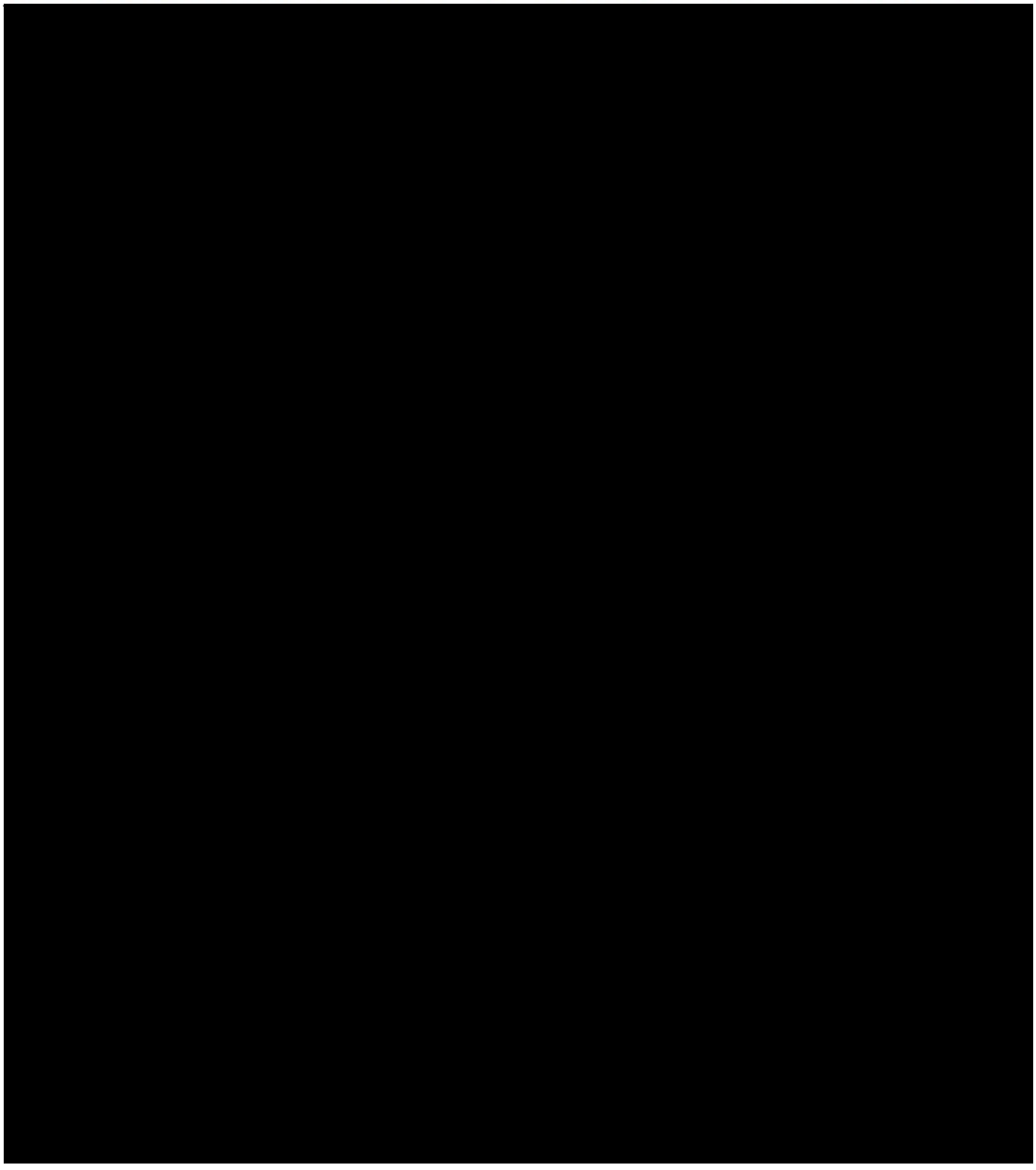
REFERENCE(S):

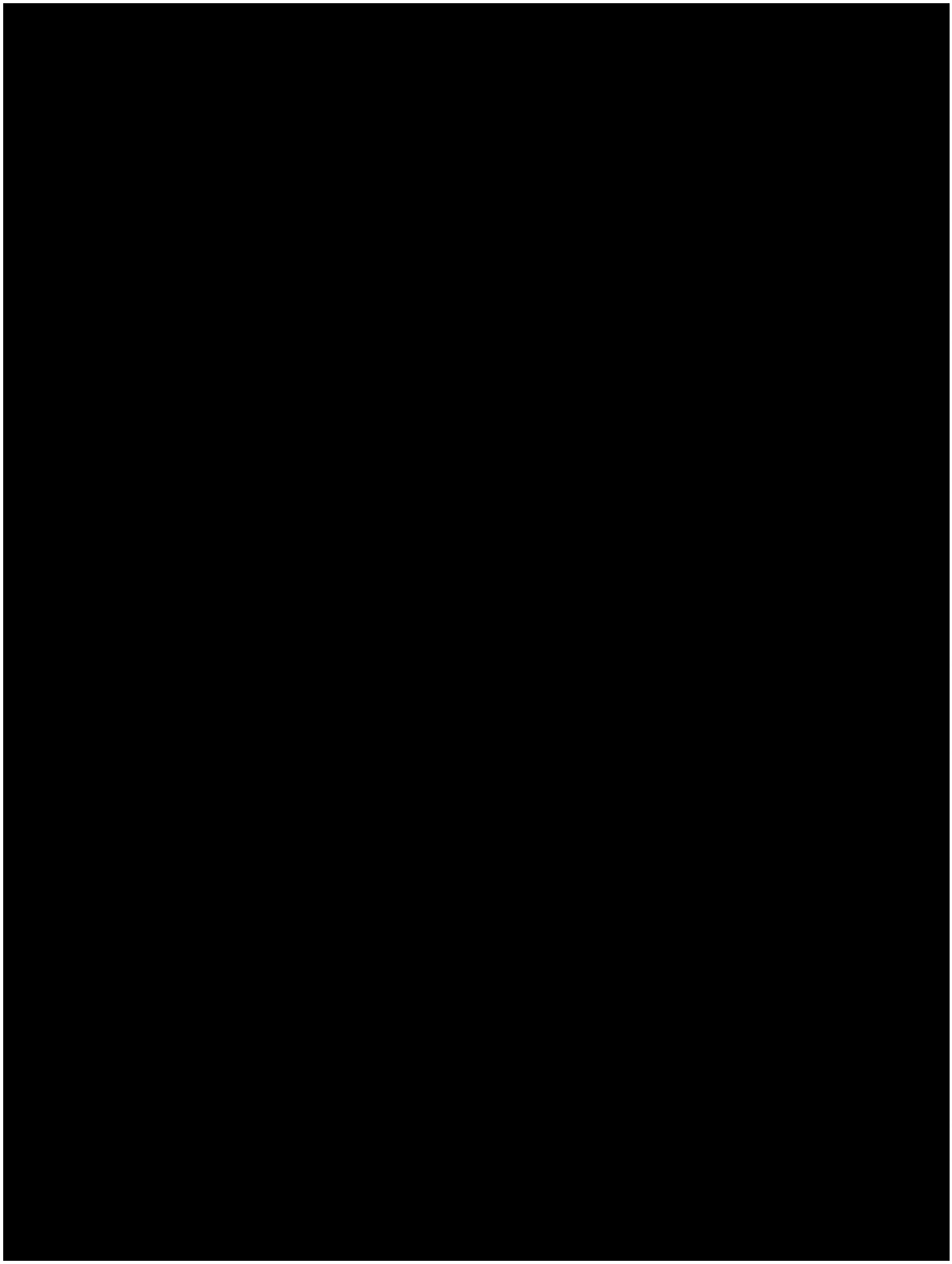
Ramey DR, Fries JF, Singh G. The Health Assessment Questionnaire 1995-status and review. In: Quality of Life and pharmacoeconomics in clinical trials. Second edition. Edited by B Spilker. Lippincott-Raven Publishers, Philadelphia, 1996

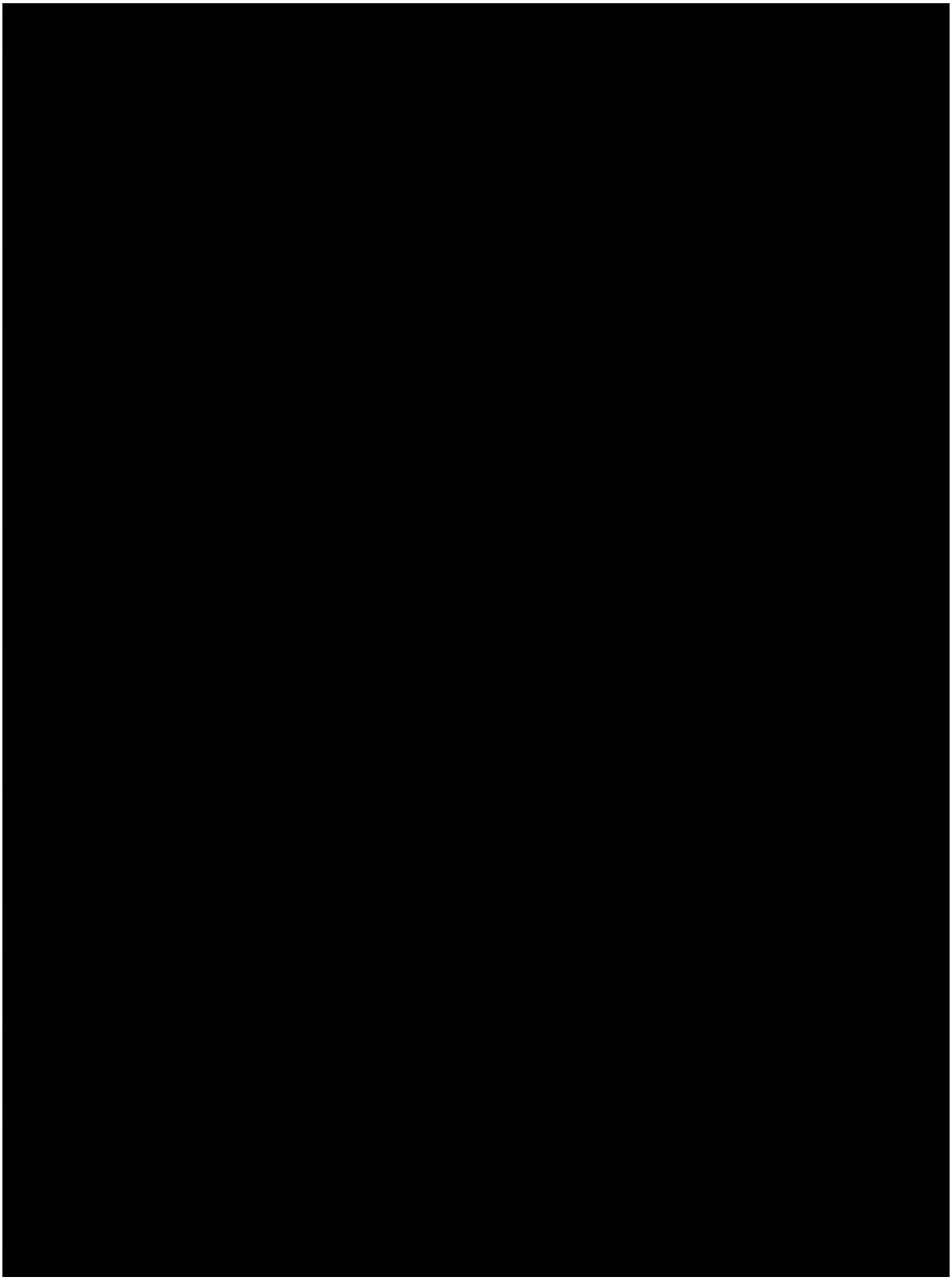
12.8 Appendix: General Health Status (Medical Outcomes Study Short-Form Health Survey)

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.

[redacted]







12.9 Appendix: European League Against Rheumatism Response Criteria

	DAS28 Improvement		
Present DAS28 or DAS28-CRP	**>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: CRP, C-reactive protein; DAS28, Disease Activity Score using 28 joint counts.