CLINICAL STUDY PROTOCOL

A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis

PROTOCOL NUMBER CT-P13 3.5

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Test Formulation: CT-P13 SC administered subcutaneously

Sponsor: [redacted]

Sponsor Contact: [redacted]

SAE Reporting [redacted]

Version and Date of Protocol: Protocol Version 4.0, including country specific C.2 – 10 September 2018

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Protocol Approval

Study Title	A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis
Protocol Number	CT-P13 3.5
Protocol Date	Protocol Version 4.0, including country specific C.2 – 10 September 2018

Protocol accepted and approved by:

[redacted]

Declaration of Investigator

I have read and understand all sections of the protocol entitled "A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis" 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 4.0, including country specific C.2, dated 10 September 2018, the International Conference on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and the Declaration of Helsinki (WMA2013), 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-P13 3.5

Title: A Randomized, Parallel-Group, Phase I/III Study to Evaluate Efficacy, Pharmacokinetics and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Rheumatoid Arthritis

Clinical Phase: Phase I/III

Planned number of centers/countries:

Part 1:

It is expected that up to approximately 40 study centers will enrol patients in approximately 10 countries.

Part 2:

It is expected that up to approximately 100 study centers will enrol patients in approximately 15 countries.

Test Product Formulation, Dose, and Regimen:

Two doses of CT-P13 (3 mg/kg) by intravenous (IV) infusion administered as a 2-hour infusion per dose will be given initially prior to receiving subcutaneous (SC) injection of CT-P13.

Part 1:

- CT-P13, 90 mg by SC injection via pre-filled syringe (PFS) every other week
- CT-P13, 120 mg by SC injection via PFS every other week
- CT-P13, 180 mg by SC injection via PFS every other week

CT-P13 will be co-administered with methotrexate (MTX) between 12.5 to 25 mg/week, oral or parenteral dose (dose must be maintained from beginning to end of study) and folic acid (≥5 mg/week, oral dose).

Part 2:

CT-P13 120 mg by SC injection via PFS every 2 weeks with placebo IV administered as a 2-hour infusion per dose, co-administered with MTX between 12.5 to 25 mg/week, oral or parenteral dose (dose must be maintained from beginning to end of study) and folic acid (≥5 mg/week, oral dose).

From Week 46 to Week 54, CT-P13 120 mg by SC injection via auto-injector (AI) every 2 weeks, and from Week 56 to Week 64, CT-P13 120 mg by SC injection via PFS every 2 weeks (will be implemented at selected sites), co-administered with MTX between 12.5 to 25 mg/week, oral or parenteral dose (dose must be maintained from beginning to end of study) and folic acid (≥5 mg/week, oral dose).

Reference Drug, Dose and Regimen:

Part 1:

CT-P13 (3 mg/kg) by IV infusion administered as a 2-hour infusion per dose co-administered with MTX between 12.5 to 25 mg/week, oral or parenteral dose (dose must be maintained from beginning to end of study) and folic acid (≥5 mg/week, oral dose).

Part 2:

CT-P13 (3 mg/kg) by IV infusion administered as a 2-hour infusion per dose with placebo SC, co-administered with MTX between 12.5 to 25 mg/week, oral or parenteral dose (dose must be maintained from beginning to end of study) and folic acid (≥5 mg/week, oral dose).

Objectives:

Part 1:

Primary objective:

- To find the optimal dose of CT-P13 SC over the first 30 weeks as determined by the area under the concentration-time curve (AUC_τ) at steady state between Week 22 and Week 30

Secondary objectives:

- To evaluate efficacy, pharmacokinetics (PK), pharmacodynamics (PD) and overall safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54

Part 2:

Primary objective:

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

Secondary objectives:

- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks)
- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54
- To evaluate usability of CT-P13 SC via AI from Week 46 to Week 54
- To evaluate usability of CT-P13 SC via PFS from Week 56 to Week 64

Tertiary objective:

- To evaluate biomarkers (optional)

Sample Size:

Part 1:

Approximately 40 (at least 24) male or female patients with active Rheumatoid arthritis (RA) will be randomly assigned at Week 6 in a 1:1:1:1 ratio into four study cohorts as follows:

Cohort Number	Dosage	Investigational Product	Method of Administration
Cohort 1	3 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Cohort 2	90 mg	CT-P13 SC 90 mg/PFS	Single SC injection
Cohort 3	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection
Cohort 4	180 mg	CT-P13 SC 90 mg/PFS	Double SC injection

IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

Part 2:

Minimum 218 male or female patients with active RA will be randomly assigned at Week 6 in a 1:1 ratio to the CT-P13 SC with Placebo IV and CT-P13 IV with Placebo SC (minimum 109 patients per treatment group) treatment groups as follows:

Arm Number	Dosage	Investigational Product	Method of Administration
Arm 1[1,2]	3 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Arm 2[2]	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection

IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

[1]CT-P13 IV will be switched to CT-P13 SC via PFS at Week 30.

[2]Patients will be administered CT-P13 SC via AI from Week 46 to Week 54 and switched back to CT-P13 SC via PFS at Week 56.

The final number of enrolled patients will be determined considering the dropout rate during patient enrolment.

Main selection criteria: Male or female patients with active RA who are not adequately responding to MTX administration over at least 3 months, will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

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

1. Patient is male or female aged 18 to 75 years old, inclusive.
2. Patient has a diagnosis of RA according to the 2010 ACR/EULAR classification criteria [Aletaha et al. 2010] for at least 6 months prior to the first administration of the study drug (Day 0).
3. Patient has active disease as defined by the presence of 6 or more swollen joints (of 28 assessed), 6 or more tender joints (of 28 assessed), and a serum CRP concentration > 0.6 mg/dL at Screening. Unexplained or unexpected Screening CRP value that does not match the clinical activity of RA according to the investigator's assessment or recent test can be retested once within the Screening period.
4. Patient who has completed at least 3 months of treatment of oral or parenteral dosing with methotrexate

between 12.5 to 25 mg/week and on stable dosing with methotrexate between 12.5 to 25 mg/week for at least 4 weeks prior to the first administration of the study drug (Day 0).

5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
   - Serum creatinine <1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula)
   - Serum alanine aminotransferase <2.5 × ULN
   - Serum aspartate aminotransferase <2.5 × ULN
   - Serum total bilirubin <2 × ULN
6. Patient has the following hematology laboratory test results at Screening:
   - Hemoglobin ≥8.5 g/dL (SI [Système International d'Unités] units: ≥85 g/L or 5.28 mmol/L)
   - White blood cell count ≥3.5 × 10^3 cells/μL (SI 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 ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L)
7. 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.
8. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read or understand this information, signed and dated the written informed consent before inclusion in the study.
9. For both male and female patients, the patient and their partners of childbearing potential agree to use one of the following medically acceptable methods of contraception during the course of the study and for 6 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 any medically acceptable methods of contraception.

   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:

The exclusion criteria are divided into 2 categories: tuberculosis exclusion criteria and general exclusion criteria. Patients meeting any of the following criteria will be excluded from the study:

Tuberculosis Exclusion Criteria

1. Patient who has a history of tuberculosis (TB) or a current diagnosis of TB. A patient who has a past diagnosis of active TB with sufficient documentation of complete resolution can be enrolled.
2. Patient who has had exposure to person with active TB such as first degree family members or co-workers.
3. Patient who has an indeterminate result for interferon-γ release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at Screening. A patient who has a past diagnosis of latent TB with sufficient documentation of prophylaxis can be enrolled.

   For **Part 2**, if the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the screening period. If the repeated IGRA result is again indeterminate, the patient must be excluded from the study. If the repeated IGRA result is negative, the patient can be included in the study. A patient with a confirmed latent TB during Screening who has received at least the first 30 days of country-specific TB therapy and intends to complete the entire course of that therapy can be enrolled.

General Exclusion Criteria

1. Patient who has previously received a biological agent for the treatment of RA and/or a TNFα inhibitor for the treatment of other disease.
2. Patient who has allergies to any of the excipients of infliximab or any other murine and/or human proteins or patient with a hypersensitivity to immunoglobulin product.
3. Patient who has a current or past history of following infection:
    - Current or past history of chronic infection with hepatitis C or human immunodeficiency virus-1 or -2 or current infection with hepatitis B
    - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 0)
    - Other serious infection within 6 months prior to the first administration of the study drug (Day 0)
    - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 0)
    - Past or current granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of complete resolution can be enrolled
4. Patient who has a medical condition including one or more of the following:
    - Classified as obese (body mass index ≥35 kg/m^2)
    - Uncontrolled diabetes mellitus, even after insulin treatment
    - Uncontrolled hypertension (as defined by systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg)
    - Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, fibromyalgia, that may confound the evaluation of the effect of study drug
    - History of any malignancy within the 5 years prior to the first administration of the study drug (Day 0) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
    - History of lymphoma or lymphoproliferative disease or bone marrow hyperplasia
    - New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the 6 months prior to the first administration of the study drug (Day 0)
    - History of organ transplantation, including corneal graft/transplantation
    - 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
    - Severe physical incapacitation (unable to perform routine self-care, has RA ACR functional status class 4 [Arnett et al 1988], or who cannot benefit from medication)
    - Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage) if it may interfere with the investigator's assessment on disease activity 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.
5. Patient who has received or has plan to receive any of following prohibited medications or treatment:
    - Any biological agents for the treatment of RA
    - Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 0). Patient is 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 the first administration of the study drug (Day 0). 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 (DMARDs), other than methotrexate, including hydroxychloroquine, chloroquine, or sulfasalazine, within 4 weeks prior to the first administration of the study drug (Day 0). 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 the first administration of the study drug (Day 0). Patients who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after last dose of leflunomide the first administration of the study drug (Day 0).
- Alkylating agents within 12 months prior to the first administration of the study drug (Day 0)
- Live or live-attenuated vaccine within 4 weeks the first administration of the study drug (Day 0)
- Any planned live or live-attenuated vaccination at the time of the first administration of the study drug (Day 0)
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 0) or planned within 6 months after the first administration of the study drug (Day 0)

6. Patient who has a current or past history of drug or alcohol abuse.
7. Patient who has had treatment with any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 0) or 5 half-lives, whichever is longer.
8. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.
9. Patient who, in the opinion of his or her general practitioner or investigator, should not participate in the study.

Study Design:

This study is a randomized, multicenter, parallel group, Phase I/III study designed to evaluate efficacy, PK and safety between CT-P13 SC and CT-P13 IV when co-administered with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose and folic acid (≥5 mg/week, oral dose) in patients with active RA who are not adequately responding to methotrexate administration over at least 3 months.

This study consists of two parts:

- **Part 1**, designed to find the optimal dose of CT-P13 SC, includes:
  - Screening (Days -21 to -1)
  - Treatment Period (Week 0 dosing through Week 54)
  - End of Study (8 weeks after the last dose is received)

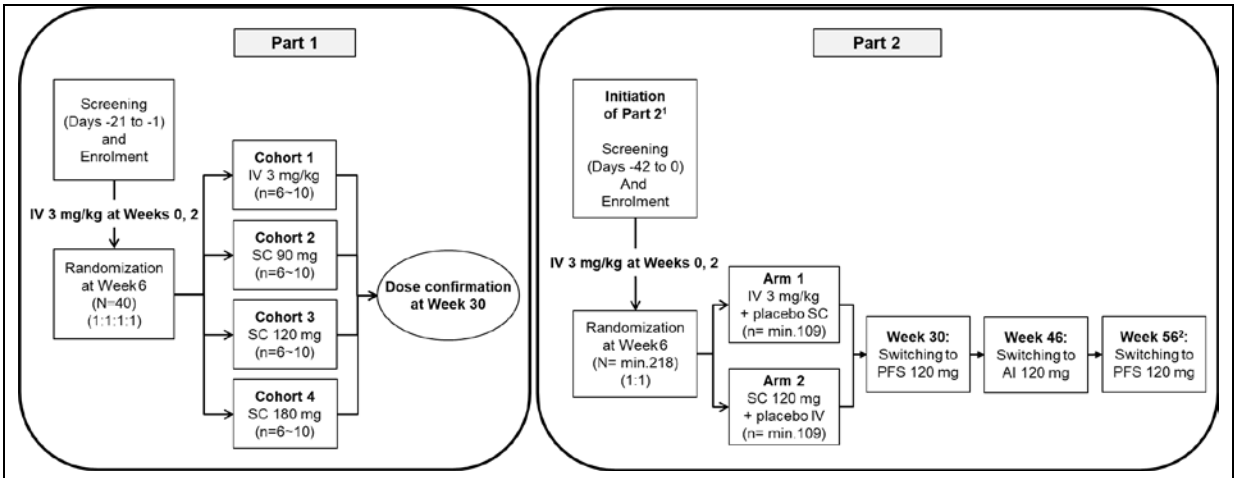
The duration of the study will be up to 65 weeks for Part 1, which includes Screening (up to 3 weeks) and the last dose at 54 weeks plus the following 8 weeks off-dose period, prior to the End-of-Study Visit.

- **Part 2**, designed to demonstrate noninferiority in efficacy between CT-P13 SC and CT-P13 IV, includes:
  - Screening (Days -42 to 0)
  - Treatment Period (Week 0 dosing through Week 64)
  - End of Study (2 weeks after the last dose is received)

The duration of the study will be up to 72 weeks for Part 2, which includes Screening (up to 6 weeks) and the last dose at 64 weeks plus the following 2 weeks off-dose period, prior to the End-of-Study Visit.

The overview of study design is illustrated in Figure S1.

Figure S1 Overview of Study Design



AI, auto-injector; IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

1. Part 2 will be initiated based upon the independent data safety monitoring board (DSMB)'s review of the PK data as well as efficacy, PD and safety found over the first 30 weeks from Part 1.
2. Switching back to CT-P13 SC via PFS at Week 56 will be implemented at selected sites.

Study Schedule:

Part 1:

The study will comprise 3 study periods including Screening, Treatment Period (Dose-Loading Phase and Maintenance Phase) and the End-of-Study.

Screening: Screening will take place between Days –21 and –1, prior to the first administration of the study drug.

Treatment Period: On Day 0, Week 0, patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study. All enrolled patients will initially receive CT-P13 IV at Weeks 0 and 2 and patients who received two full doses and have no safety concern based on the investigator's discretion will be randomly assigned to receive either CT-P13 SC or CT-P13 IV before treatment on Day 42, Week 6.

The randomization to treatment assignment will be stratified by:

- Country
- Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL)
- Week 6 body weight (≤70 kg vs. >70 kg)

An oral or parenteral dose of methotrexate between 12.5 to 25 mg/week and an oral dose folic acid (≥5 mg/week) will be administered throughout the duration of the study. Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

The Dose-Loading Phase will consist of 2 doses of CT-P13 IV infusion. All patients will receive a 2 hour CT-P13 IV infusion at Week 0 and Week 2.

The Maintenance Phase of the study will consist of further doses of study treatment with the last dose administered no later than Week 54.

- **Cohort 1:** further 7 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter (Weeks 14, 22, 30, 38, 46 and 54)
- **Cohort 2, 3 and 4:** first CT-P13 SC will be administered by pre-filled syringe (PFS) at Week 6. Further SC injections will be given every 2 weeks up to Week 54

The initially assigned dose will be adjusted to the optimal dose in all patients from Cohort 2, 3 and 4 if the optimal dose is confirmed after dose finding. Further SC injections with the optimal dose will be given up to Week 54.

Patients will return to the site at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be

monitored for the clinical signs and symptoms of TB.

The patient assessment overview for Part 1 is illustrated in Figure S2.

Figure S2 Patient Assessment Overview for Part 1

	Dose-loading		Maintenance[1]															
Week	**0**	**2**	**6**	**8**	**10**	**14**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**38**	**46**	**54**
Visit[2]	X	X	X	X[3]	X[3]	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X	X	X
Evaluation																		
Primary Pharmacokinetic[4]							←	—	—	—	—	—	—	—	→			
Efficacy	X	X	X			X	X								X			X
Pharmacokinetic	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→
Pharmacodynamic	X	X	X			X	X								X	X	X	X
Safety Evaluation	←	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	→

1. Additional visits will only be made by patients who will need extra training for CT-P13 SC injection.
2. A visit window of ±3 days is allowed up to and including Week 30; a visit window of ±5 days is allowed thereafter, including the End-of-Study Visit.
3. Only patients from Cohorts 2, 3, and 4 will make visits for additional pharmacokinetic assessment.
4. Visit window for primary PK assessment is allowed according to Section 5.2

End-of-Study Visit: An End-of-Study Visit will occur 8 weeks after the last dose is received, either at the end of the Maintenance Phase or earlier if the patient withdraws from the study.

Part 2:

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

The study will comprise 3 study periods including Screening, Treatment Period (Dose-Loading Phase and Maintenance Phase) with a double-blinded period during the Maintenance Phase up to Week 30 followed by an open-label period of 34 weeks and the End-of-Study.

Screening: Screening will take place between Days –42 and 0, prior to the first administration of the study drug.

Treatment Period: On Day 0, Week 0, patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study. All enrolled patients will initially receive CT-P13 IV at Weeks 0 and 2 and patients who received two full doses and have no safety concern based on investigator's discretion will be randomly assigned to receive either CT-P13 SC with placebo IV or CT-P13 IV with placebo SC before treatment on Day 42, Week 6.

The randomization to treatment assignment will be stratified by:

- Country
- Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL)
- Week 6 body weight (≤100 kg vs. >100 kg)

An oral or parenteral dose of methotrexate between 12.5 to 25 mg/week and an oral dose folic acid (≥5 mg/week) will be administered throughout the duration of the study. Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

The Dose-Loading Phase will consist of 2 doses of CT-P13 IV infusion. All patients (Arm 1 and 2) will receive a 2 hour CT-P13 IV infusion at Week 0 and Week 2.

The Maintenance Phase of the study will consist of further doses of study treatment with the last dose administered no later than Week 64. A double-dummy design will be used to maintain blinding during the

Maintenance Phase up to Week 30. The study will be unblinded at Week 30 for reporting purposes. The unblinded team will be predefined prior to performing the analyses. The study will remain blinded to the investigators, patients and predefined blinded team from the Sponsor and [redacted] until all patients have completed the study and the database has been finalized for study termination.

- **Arm 1:** further 3 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22) with placebo SC at Week 6 and every 2 weeks thereafter up to Week 28. CT-P13 IV will be switched to CT-P13 SC via PFS at Week 30. Further doses of study treatment with CT-P13 SC via PFS will be given up to Week 44
- **Arm 2:** first CT-P13 SC will be administered by PFS at Week 6 and every 2 weeks thereafter up to Week 44 with placebo IV at Weeks 6, 14 and 22

Patients will be administered CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54 and will be switched back to CT-P13 SC via PFS at Week 56. Further doses of study treatment with CT-P13 SC via PFS every 2 weeks will be given up to Week 64.

Patients will return to the site at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about AEs and concomitant medications and will be monitored for the clinical signs and symptoms of TB.

The patient assessment overview for Part 2 is illustrated in Figure S3.

Figure S3 Patient Assessment Overview for Part 2

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

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

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

Efficacy Assessments:

Primary Endpoint for Part 2

- Change from baseline in disease activity measured by DAS28 (CRP) at Week 22

Secondary Endpoints for both Part 1 and Part 2

The following secondary efficacy endpoints will be assessed:

- Individual components of the DAS28
- DAS28 (CRP) and DAS28 (ESR)
- Individual components of the ACR
- ACR 20, 50 and 70
- Hybrid ACR response
- Proportion of patients with a good response, defined according to the EULAR response criteria

- SDAI and CDAI
- Health assessment questionnaire (HAQ)
- 36-item short form health survey (SF-36) (Part 2 only)

Pharmacokinetic Assessments:

Primary Endpoint for Part 1

The following primary PK endpoint will be assessed at steady state between Week 22 and 30:

- AUC_{τ} Area under the concentration-time curve at steady state between Week 22 and Week 30

Secondary Endpoints for Part 1

The following secondary PK endpoints will be assessed between Week 22 and Week 30:

- AUC_{ss8W} Total exposure over the 8 weeks interval from Week 22 to Week 30
- C_{max} Observed maximum serum concentration after study drug administration
- T_{max} Time of observed maximum serum concentration
- $T_{1/2}$ Terminal half life
- C_{trough} Trough concentration (concentration before the next study drug administration)
- MRT Mean residence time
- CL Clearance after IV dosing
- CL/F Apparent clearance after SC dosing
- BA Bioavailability (absolute and/or relative)
- AUC_{τ}/DN Dose normalized total exposure over dosing interval (=AUC_{τ}/total dose administered)
- C_{max}/DN Dose normalized peak exposure (=C_{max}/total dose administered)

The following secondary PK endpoint will be assessed up to Week 54:

- C_{trough} Trough concentration (concentration before the next study drug administration)

Secondary Endpoints for Part 2

The following secondary PK endpoints will be assessed between Week 22 and Week 30:

- AUC_{τ} Area under the concentration-time curve at steady state between Week 22 and Week 30
- C_{max} Observed maximum serum concentration after study drug administration

The following secondary PK endpoint will be assessed up to Week 54:

- C_{trough} Trough concentration (concentration before the next study drug administration)

Pharmacodynamic Assessments:

Secondary Endpoints for both Part 1 and Part 2

The following PD parameters for CT-P13 SC and CT-P13 IV will be determined as secondary PD endpoints (up to Week 54):

- Rheumatoid Factor (RF)
- Anti-cyclic citrullinated peptide (anti-CCP)
- CRP
- ESR

Biomarker Assessment (Optional for Part 2): For patients who sign a separate informed consent form for the biomarker assessment, a blood sample for evaluation of any necessary genotypes will be collected before dosing on Day 0 of Week 0. These genes will include, but are not limited to FcγRIIIa.

Safety Assessments:

Secondary Endpoints for both Part 1 and Part 2

Safety assessments will be performed on immunogenicity, hypersensitivity monitoring (including delayed hypersensitivity monitoring), vital sign measurements (including blood pressure, heart and respiratory rates and body temperature), weight, interferon-γ release assay, chest x-ray, hepatitis B and C and HIV-1 and -2 status,

physical examination findings, ECGs, AEs (including serious AEs), adverse events of special interest (infusion-related reactions/hypersensitivity/anaphylactic reactions [administration-related reactions], delayed hypersensitivity, injection site reactions, infection and malignancies), clinical laboratory analyses, pregnancy testing, local site pain using 100 mm Visual Analogue Scale (VAS), signs and symptoms of TB and previous and concomitant medications.

In case of delayed hypersensitivity occurred after 24 hours of study drug administration, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption or edema), following assessments will be additionally performed to determine Serum Sickness during the study period;

- Immunogenicity
- Clinical Laboratory Analyses
- Complement (C3, C4) and Total Haemolytic Complement

Usability Assessments:

Secondary endpoint for Part 2:

The following assessments will be performed for usability of CT-P13 SC via AI (between Week 46 and 54) and via PFS (between Week 56 and Week 64):

- PRE- and POST-Self Injection Assessment Questionnaire (SIAQ) by the patients at every CT-P13 SC injection
- Self-Injection Assessment Checklist by observer (healthcare professional) rating of successful self-injection
- Potential Hazards Checklist by the observer (healthcare professional) rating of hazard-free self-injection

Data Analysis:

Statistical Analysis: Statistical analysis will be performed using [redacted]). The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to locking of the database. 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. For Part 1, the randomization will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL) and Week 6 body weight (≤70 kg vs. >70 kg). For Part 2, the randomization will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL) and Week 6 body weight (≤100 kg vs. >100 kg).

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

Pharmacokinetic parameters will be computed by noncompartmental methods using [redacted]).

Pharmacokinetic Analysis:

Part 1 Primary:

No formal sample size estimation was performed because no confirmatory analyses are planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) are considered to be sufficient to investigate the primary objective of this study. The primary PK endpoint of the observed AUC_{τ} between patients treated with CT-P13 IV or CT-P13 SC at steady state between Week 22 and Week 30 will be presented in listing and summarized in table. Summary statistics will include the n, mean, SD, median, minimum, maximum, geometric mean, and coefficient of variation (CV).

Part 1 & 2 Secondary:

The secondary 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 the CV.

Efficacy Analysis:

Part 2 Primary:

The primary endpoint is the mean change from baseline in DAS28 (CRP) at Week 22. A sample size of 174 subjects (87 patients each in the CT-P13 SC and CT-P13 IV treatment groups) provide 80% power to

demonstrate noninferiority of CT-P13 SC to CT-P13 IV based on the 97.5% one-sided confidence interval for the difference in the mean change from baseline of DAS28 (CRP) at Week 22. In the sample size calculation, noninferiority margin of -0.6, one-sided alpha level 2.5% and standard deviation of 1.4 were assumed. Considering 20% drop-out rate, total 218 patients (109 patients each in the CT-P13 SC and CT-P13 IV treatment groups) will be randomized. The primary analysis for DAS28 (CRP) is analysis of covariance (ANCOVA) comparing the change from baseline of DAS28 at Week 22 of treatment between two treatment groups, CT-P13 SC and CT-P13 IV. A point estimate and 95% CI for the treatment difference will also be provided.

Part 1 & 2 Secondary:

The following secondary efficacy parameters will be summarized using descriptive statistics: individual components of the DAS28, DAS28 (ESR/CRP), individual components of the ACR, ACR 20/50/70, Hybrid ACR response, EULAR response criteria, SDAI, CDAI, HAQ and SF-36 (Part 2 only).

Pharmacodynamic Analysis:

Part 1 & 2 Secondary:

The following pharmacodynamic parameters will be summarized using descriptive statistics: RF, anti-CCP, CRP and ESR.

Biomarker Analysis:

Part 2 Tertiary:

Descriptive analyses will be performed on genotypes (including but not limited to FcγRIIIa) by treatment groups.

Usability Analysis:

Part 2 Secondary: The following parameters will be summarized using descriptive statistics: usability assessed by patient using PRE- and POST-SIAQ and assessed by observer rating of successful self-injection using Self-Injection Assessment Checklist and hazard-free self-injection using Potential Hazards Checklist.

Safety Analysis:

Part 1 & 2 Secondary:

Analysis will be performed on the observed cases. Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. All safety data will be listed and summarized by treatment group as appropriate.

List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
ACR20	20% response, as defined by the American College of Rheumatology
ACR50	50% response, as defined by the American College of Rheumatology
ACR70	70% response, as defined by the American College of Rheumatology
AE	adverse event
AI	auto-injector
ANCOVA	analysis of covariance
anti-CCP	Anti-cyclic citrullinated peptide
AS	ankylosing spondylitis
AUC_{τ}	area under the concentration-time curve
AUCss8W	Total exposure over the 8 weeks interval from Week 22 to Week 30
AUCτ/DN	Dose normalized total exposure over dosing interval (=AUCτ/total dose administered)
BA	bioavailability
CDAI	clinical disease activity index
CI	confidence interval
CL	total clearance
CL/F	Apparent clearance after SC dosing
C_{max}	Observed maximum serum concentration after study drug administration
C_{max}/DN	Dose normalized peak exposure (=C_{max}/total dose administered)
CRP	C-reactive protein
C_{trough}	minimum concentration immediately before the next application
CTCAE	Common Terminology Criteria for Adverse Events
CT-P13	infliximab (CELLTRION, Inc.)
CT-P13 IV	intravenous infliximab (CELLTRION, Inc.)
CT-P13 SC	subcutaneous infliximab (CELLTRION, Inc.)
CV	coefficient of variation
DMARD	disease-modifying antirheumatic drug
DAS28	disease activity score in 28 joints
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form
EGA	evaluator global assessment of disease activity

Abbreviation	Definition
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HAQ	health assessment questionnaire
HIV	human immunodeficiency virus
IB	Investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IGRA	interferon-γ release assay
INN	International Nonproprietary Name
IRB	Institutional review board
ITT	Intended- to-Treated
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
PD	pharmacodynamics
PFS	pre-filled syringe
PGA	patient global assessment of disease activity
PK	pharmacokinetic
PT	preferred term
PVG	pharmacovigilance
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SDAI	simplified disease activity index

Abbreviation	Definition
SF-36	Medical Outcomes Study Short Form Health Survey
SI	Système International d'Unités
SIAQ	self-injection assessment questionnaire
SJC	swollen joint count
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
$T_{1/2}$	Terminal half life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
T_{max}	time to maximum serum concentration
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VAS	visual analogue scale

1 Introduction

1.1. Background

Tumor necrosis factor-alpha (TNFα), a proinflammatory cytokine, is a key mediator of inflammation shown to be a central factor in inflammatory immune response [Harriman et al 1999; Hsia et al 2006]. In general, TNFα is produced mainly by macrophages, but also by a broad variety of other cell types. It has a wide spectrum of activities including coordinating host immune and inflammatory response to infectious, malignant, and autoimmune conditions. There are 2 types of TNF receptors, p55 and p75, part of a large family of structurally related cell-surface receptors [Bazzoni and Beutler 1996]. There is evidence that the p75 receptor stimulates T cells proliferation and suppresses TNFα-mediated inflammatory responses, whereas the p55 receptor appears to be critical in triggering host defense and inflammatory responses [Tartaglia et al 1993; Peschon et al 1998].

Large amounts of TNFα are released in response to lipopolysaccharide, other bacterial products, and interleukin-1. Tumor necrosis factor-alpha induces proinflammatory cytokines such as interleukin-1 and interleukin-6, enhances leukocyte migration, activates neutrophil and eosinophil functional activity, and induces acute phase reactants, other liver proteins, and tissue-degrading enzymes. Although there is a benefit to TNFα expression in response to infection or injury, there are increased concentrations associated with rheumatoid arthritis (RA), Crohn's disease, ulcerative colitis, ankylosing spondylitis (AS), psoriatic arthritis, and plaque psoriasis.

Greater understanding of the role of inflammatory mediators has produced safer and more effective treatments for inflammatory conditions, such as infliximab, a chimeric monoclonal antibody against TNFα.

Rheumatoid arthritis is one of the most common autoimmune diseases, affecting 1% of the world's population [Hsia et al 2006]. Infliximab reduces infiltration of inflammatory cells into inflamed joints and expression of molecules mediating cellular adhesion, chemoattraction, and tissue degradation. Infliximab treatment decreases serum interleukin-6 and C-reactive protein (CRP) concentrations compared with Baseline [Black and Green 1998]. Its effect on the upregulation of inflammatory events in joints makes it an appropriate pharmacological target in RA.

1.2. CT-P13

CT-P13 IV is an approved biosimilar to EU-approved Remicade and US-licensed Remicade. Remicade was constructed by combining the antigen-binding variable regions of the A2 mouse monoclonal antibody with the constant regions of human IgG kappa light chain [Cohen and Dittrich 2001]. CT-P13 IV is produced by a recombinant cell line cultured by fed batch and is purified by a series of steps that includes measures to inactivate and remove

viruses. CT-P13 IV has an identical primary sequence to that of US-licensed Remicade and EU-approved Remicade.

The nonclinical program for CT-P13 IV has been designed to support clinical trials in patients and to demonstrate similarity in binding profiles and functional activity of CT-P13 IV, US-licensed Remicade and EU-approved Remicade. Clinical trials with CT-P13 IV have been completed in patients with RA and AS and additional clinical trials are currently ongoing.

A new formulation of CT-P13 SC for subcutaneous administration is under development as a liquid type filled aseptically into a 1 mL pre-filled syringe (PFS) or auto-injector (AI). Each PFS contains 120 mg or 90 mg of active substance (1 mL or 0.75 mL fill volume, respectively) and AI contains 120 mg of active substance (1 mL fill volume). The excipient lists, except for active substance, are 10 mM Sodium Acetate, 4.5 % (w/v) Sorbitol, and 0.05 % (w/v) Polysorbate 80 (pH 5.0). No preservatives are present.

Unless otherwise specified, the name ‘CT-P13 IV’ will implicate what has initially been developed for intravenous infusion throughout the document. The subcutaneous formulation of CT-P13 will use the name ‘CT-P13 SC’.

1.3. Synergistic Effects of Infliximab with Methotrexate

In the early RA trials, it was noted that patients who received lower doses of infliximab and patients receiving infliximab alone were more likely to develop antibodies to infliximab [Hsia et al 2006]. It was observed that the number of patients developing antibodies to infliximab decreased in the presence of methotrexate [Maini et al 1998]. For this reason, infliximab is indicated for administration with methotrexate in RA, except in patients with intolerance to or contraindication for methotrexate. Methotrexate is an established folate antagonist that inhibits DNA and protein synthesis resulting in lymphocyte apoptosis [Genestier et al 1998]. The presence of a synergistic mechanism between these 2 products is, however, still under debate [Maini et al 1998; Rezaian 1999].

1.4. Preclinical Studies

Detailed information regarding the nonclinical pharmacology and toxicology of CT-P13 SC is found in the Investigator’s Brochure (IB).

1.5. Clinical Study

The safety, clinical response and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in RA was assessed in an open-label, randomized, Phase I study [Westhovens et al. 2006]. The study was conducted in 3 stages. In Stage I, 15 subjects were randomly assigned to receive a single SC injection of infliximab 0.5 mg/kg, 1.5 mg/kg or 3.0 mg/kg. In Stage II, 21 subjects received one of the following 3

infliximab treatment regimens, with 7 subjects randomized to each treatment group: 100 mg SC injections at Weeks 0, 2 and 4 (Group 1); 3 mg/kg IV infusions of infliximab at Weeks 0 and 2 followed by 100 mg SC injections of the SC formulation at Weeks 4, 6 and 8 (Group 2); or 100 mg intramuscular injections at Weeks 0, 2 and 6 (Group 3). In Stage III, 7 additional subjects received 100 mg SC infliximab injections at Weeks 0, 4 and 8. All patients were on stable methotrexate treatment for at least 4 weeks prior to enrolment. Regardless of the route of administration or dosage of infliximab, clinical response as assessed by ACR20 was achieved by over 80% of subjects treated in this study.

Because of the small overall sample size, AE data for the various treatment regimens were pooled. Of the 43 subjects, 34 (79.1%) experienced one or more AE during the study through Week 16, which were generally transient and mild to moderate in intensity. The events most commonly observed were respiratory infection, pain after vaccination, and headache, each occurring in 14.0% of subjects. The only 2 serious adverse events (SAEs) were experienced by a single subject but these events were not considered by the investigator to be related to infliximab. One or more infections were experienced by a total of 10 subjects (23.3%) during the study. The infections were generally transient and mild to moderate in intensity, and no serious or opportunistic infections were observed. Overall, both the single and multiple-dose SC infliximab regimens and the multiple-dose intramuscular infliximab regimen were generally well tolerated in this relatively small sample.

1.6. Study Rationale

Infliximab has initially been developed for intravenous infusion. A new subcutaneous infliximab formulation is being developed by Celltrion, Inc. as an alternative to the intravenous regimen where subcutaneous infliximab injection typically takes less than 2 minutes. Potential benefits of such administration include improved patient convenience, better compliance, reduced pharmacy preparation times, and optimisation of medical resources. The availability of a subcutaneous formulation of infliximab would increase the treatment options available to patients, particularly those wishing to self-administer their therapy [Jackisch et al. 2014]. This Phase I/III randomized, multicenter, parallel-group study is designed to evaluate efficacy, pharmacokinetics, pharmacodynamics, safety and biomarkers between CT-P13 SC and CT-P13 IV and usability of CT-P13 SC via AI and PFS in patients with active RA. Auto-injectors offer several advantages over PFS including simplifying self-administration, reducing patient anxiety, improved safety by reducing risk of injury and improper administration, as well as improved compliance through controlled and standardized administration.

2. Study Objectives

2.1. Primary Objective for Part 1

- To find the optimal dose of CT-P13 SC over the first 30 weeks as determined by the area under the concentration-time curve (AUC_{τ}) at steady state between Week 22 and Week 30

2.2. Secondary Objectives for Part 1

- To evaluate efficacy, pharmacokinetics (PK), pharmacodynamics (PD) and overall safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54

2.3. Primary Objective for Part 2

- To demonstrate that CT-P13 SC is noninferior to CT-P13 IV at Week 22, in terms of efficacy, as determined by clinical response according to change from baseline in disease activity measured by Disease Activity Score using 28 joint counts (DAS28) (CRP)

2.4. Secondary Objectives for Part 2

- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks)
- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54
- To evaluate usability of CT-P13 SC via AI from Week 46 to Week 54
- To evaluate usability of CT-P13 SC via PFS from Week 56 to Week 64

2.5. Tertiary Objective for Part 2

- To evaluate biomarkers (optional)

3. Investigational Plan

3.1. Study Design

This study is a randomized, multicenter, parallel group, Phase I/III study designed to evaluate efficacy, pharmacokinetics and safety between CT-P13 SC and CT-P13 IV when co-administered with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose and folic acid (≥5 mg/week, oral dose) in patients with active RA who are not adequately responding to methotrexate administration over at least 3 months.

This study consists of two parts:

- **Part 1**, designed to find the optimal dose of CT-P13 SC, includes (described in Section 3.2.1):
  - Screening (Days -21 to -1)
  - Treatment Period (Week 0 dosing through Week 54)
  - End of Study (8 weeks after the last dose is received)

- **Part 2**, designed to demonstrate noninferiority in efficacy between CT-P13 SC and CT-P13 IV, includes (described in Section 3.2.2):
  - Screening (Days -42 to 0)
  - Treatment Period (Week 0 dosing through Week 64)
  - End of Study (2 weeks after the last dose is received)

In Part 1, approximately 40 (at least 24) male or female patients with active RA will be randomly assigned at Week 6 in a 1:1:1:1 ratio into four study cohorts as presented in Table 3-1.

Table 3-1 Study Drug Randomization for Part 1

Cohort Number	Dosage	Investigational Product	Method of Administration
Cohort 1	3 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Cohort 2	90 mg	CT-P13 SC 90 mg/PFS	Single SC injection
Cohort 3	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection
Cohort 4	180 mg	CT-P13 SC 90 mg/PFS	Double SC injection

IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

The duration of the study will be up to 65 weeks for Part 1, which includes Screening (up to 3 weeks) and the last dose at 54 weeks plus the following 8 weeks off-dose period, prior to the End-of-Study Visit.

In Part 2, minimum 218 male or female patients with active RA will be randomly assigned at Week 6 in a 1:1 ratio to 1 of 2 treatment groups, CT-P13 SC with Placebo IV and CT-P13 IV with Placebo SC (minimum 109 patients per treatment group) as presented in Table 3-2.

Table 3-2 Study Drug Randomization for Part 2

Arm Number	Dosage	Investigational Product	Method of Administration
Arm 1[1, 2]	3 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Arm 2[2]	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection

IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

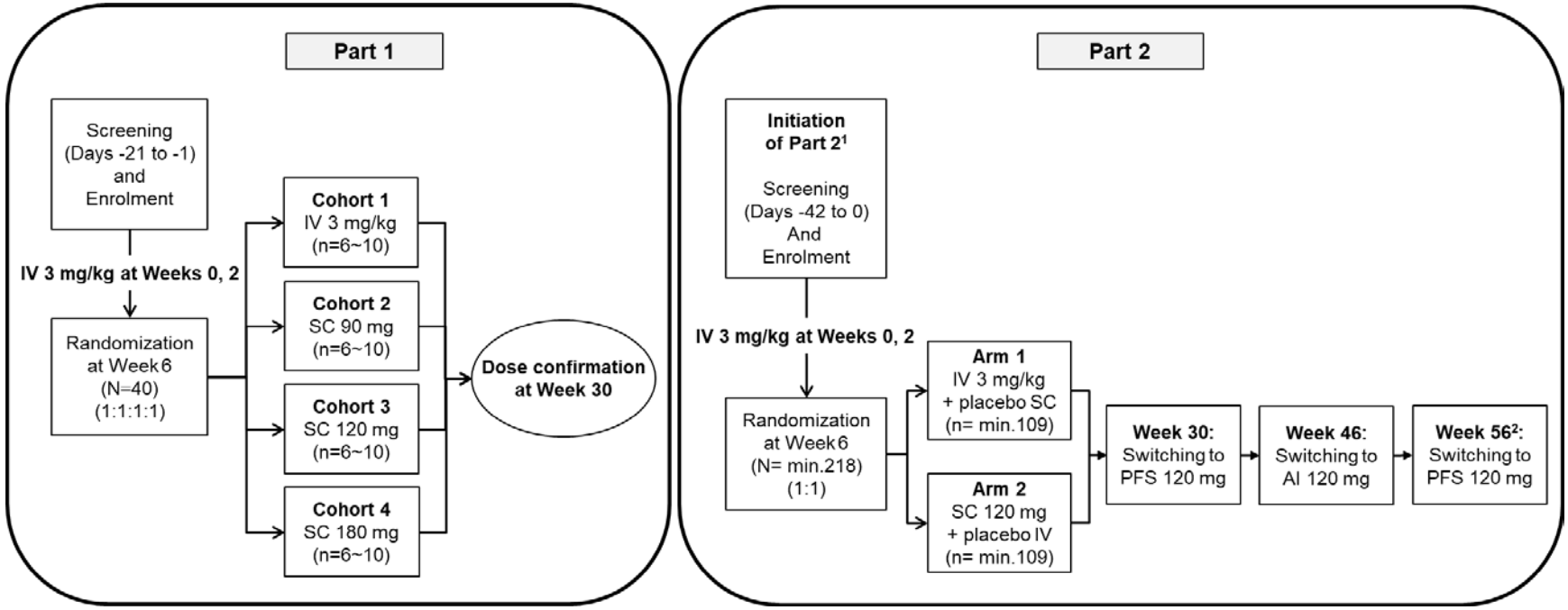
[1]CT-P13 IV will be switched to CT-P13 SC via PFS at Week 30.

[2]Patients will be administered CT-P13 SC via AI from Week 46 to Week 54 and switched back to CT-P13 SC via PFS at Week 56.

The duration of the study will be up to 72 weeks for Part 2, which includes Screening (up to 6 weeks) and the last dose at 64 weeks plus the following 2 weeks off-dose period, prior to the End-of-Study Visit.

The overview of study design is illustrated in Figure 3–1.

Figure 3–1 Overview of Study Design



AI, auto-injector; IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

1. Part 2 will be initiated based upon the independent data safety monitoring board (DSMB)'s review of the PK data as well as efficacy, PD and safety found over first 30 weeks from Part 1.
2. Switching back to CT-P13 SC via PFS at Week 56 will be implemented at selected sites.

3.2. Study Overview

3.2.1. Part 1

The study will comprise 3 study periods including Screening, Treatment Period (Dose-Loading Phase and Maintenance Phase) and the End-of-Study.

Screening: Screening will take place between Days –21 and –1, prior to the first administration of the study drug.

Treatment Period: On Day 0, Week 0, patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study. All enrolled patients will initially receive CT-P13 IV at Weeks 0 and 2 and patients who received two full doses and have no safety concern based on the investigator's discretion will be randomly assigned to receive either CT-P13 SC or CT-P13 IV before treatment on Day 42, Week 6.

The randomization to treatment assignment will be stratified by:

- Country
- Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL)
- Week 6 body weight (≤70 kg vs. >70 kg)

An oral or parenteral dose of methotrexate between 12.5 to 25 mg/week and an oral dose folic acid (≥5 mg/week) will be administered throughout the duration of the study. Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

The Dose-Loading Phase will consist of 2 doses of CT-P13 IV infusion. All patients will receive a 2 hour CT-P13 IV infusion at Week 0 and Week 2.

The Maintenance Phase of the study will consist of further doses of study treatment with the last dose administered no later than Week 54.

- **Cohort 1:** further 7 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter (Weeks 14, 22, 30, 38, 46 and 54)
- **Cohorts 2, 3 and 4:** first CT-P13 SC will be administered by PFS at Week 6. Further SC injections will be given every 2 weeks up to Week 54.

The initially assigned dose will be adjusted to the optimal dose in all patients from Cohorts 2, 3 and 4 if the optimal dose is confirmed after dose finding. Further SC injections with the optimal dose will be given up to Week 54.

Patients will return to the site at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of TB.

The primary pharmacokinetic endpoint evaluation will be conducted during the Maintenance Phase between Week 22 to Week 30, and secondary pharmacokinetic endpoint evaluations will be conducted during the Dose-Loading Phase and Maintenance Phase up to Week 54, with blood samples for analysis obtained at the time points specified in the schedule of events (Table 10-1).

Efficacy, PD and safety assessments will be performed at the time points specified in the schedule of events (Table 10-1).

The patient assessment overview for Part 1 is illustrated in Figure 3–2.

Figure 3–2 Patient Assessment Overview for Part 1

	Dose-loading			Maintenance[1]														
Week	**0**	**2**	**6**	**8**	**10**	**14**	**22**	**23**	**24**	**25**	**26**	**27**	**28**	**29**	**30**	**38**	**46**	**54**
Visit[2]	X	X	X	X[3]	X[3]	X	X	X	X	X[3]	X	X[3]	X	X[3]	X	X	X	X
Evaluation																		
Primary Pharmacokinetic[4]							←								→			
Efficacy	X	X	X			X	X								X			X
Pharmacokinetic	←																	→
Pharmacodynamic	X	X	X			X	X								X	X	X	X
Safety Evaluation	←																	→

1. Additional visits will only be made by patients who will need extra training for CT-P13 SC injection.
2. A visit window of ±3 days is allowed up to and including Week 30; a visit window of ±5 days is allowed thereafter, including the End-of-Study Visit.
3. Only patients from Cohorts 2, 3 and 4 will make visits for additional pharmacokinetic assessment.
4. Visit window for primary PK assessment is allowed according to Section 5.2.

CT-P13 SC will be injected by a healthcare professional at each site visit (Weeks 6, 8, 10, 14, 22, 24, 26, 28, 30, 38, 46 and 54). After proper training in injection technique, patients may self-inject with CT-P13 SC if their investigator determines that it is appropriate at any other weeks (Weeks 12, 16, 18, 20, 32, 34, 36, 40, 42, 44, 48, 50 and 52).

End-of-Study Visit: An End-of-Study Visit will occur 8 weeks after the last dose is received, either at the end of the Maintenance Phase or earlier if the patient withdraws from the study.

3.2.2. Part 2

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

The study will comprise 3 study periods including Screening, Treatment Period (Dose-Loading Phase and Maintenance Phase) with a double-blinded period during Maintenance Phase up to Week 30 followed by an open-label period of 34 weeks and the End-of-Study.

Screening: Screening will take place between Days –42 and 0, prior to the first administration of the study drug.

Treatment Period: On Day 0, Week 0, patients who meet all inclusion criteria and none of the exclusion criteria will be enrolled in the study. All enrolled patients will initially receive CT-P13 IV at Weeks 0 and 2 and patients who received two full doses and have no safety concern based on investigator's discretion will be randomly assigned to receive either CT-P13 SC with placebo IV or CT-P13 IV with placebo SC before treatment on Day 42, Week 6.

The randomization to treatment assignment will be stratified by:

- Country
- Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL)
- Week 6 body weight (≤100 kg vs. >100 kg)

An oral or parenteral dose of methotrexate between 12.5 to 25 mg/week and an oral dose folic acid (≥5 mg/week) will be administered throughout the duration of the study. Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

The Dose-Loading Phase will consist of 2 doses of CT-P13 IV infusion. All patients will receive a 2 hour CT-P13 IV infusion at Week 0 and Week 2.

The Maintenance Phase of the study will consist of further doses of study treatment with the last dose administered no later than Week 64. A double-dummy design will be used to maintain blinding during the Maintenance Phase up to Week 30. The study will be unblinded at Week 30 for reporting purposes. The unblinded team will be predefined prior to performing the analyses. The study will remain blinded to the investigators, patients and predefined blinded team from the Sponsor and [redacted] until all patients have completed the study and the database has been finalized for study termination.

- **Arm 1:** further 3 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22) with placebo SC at Week 6 and every 2 weeks thereafter up to Week 28. CT-P13 IV will be then switched to CT-P13 SC via PFS at Week 30. Further doses of study treatment with CT-P13 SC via PFS will be given up to Week 44.
- **Arm 2:** first CT-P13 SC will be administered by PFS at Week 6 and every 2 weeks thereafter up to Week 44 with placebo IV at Weeks 6, 14 and 22.

Patients will be administered CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54 and will be switched back to CT-P13 SC via PFS at Week 56. Further doses of study treatment with CT-P13 SC via PFS every 2 weeks will be given up to Week 64.

Patients will return to the site at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about AEs and concomitant medications and will be monitored for the clinical signs and symptoms of TB.

Primary efficacy will be assessed by change from baseline in disease activity measured by DAS28 (CRP) at Week 22. Secondary efficacy will be assessed at the time points specified in the schedule of events (Table 10-2).

The secondary PK endpoint evaluations will be conducted during the Treatment Period up to Week 54, with blood samples for analysis obtained at the time points specified in the schedule of events (Table 10-2).

Efficacy, pharmacodynamics, safety, biomarkers and usability assessments will be performed at the time points specified in the schedule of events (Table 10-2).

The patient assessment overview for Part 2 is illustrated in Figure 3–3.

Figure 3–3 Patient Assessment Overview for Part 2

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

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

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

CT-P13 SC via AI will be self-injected under observation of healthcare professional at each site visits (Week 46 and 54). Self-injection training will be provided at Week 46 prior to the

first AI injection. After proper training in AI injection technique, patient may self-inject with CT-P13 SC via AI at home at any other weeks (Weeks 48, 50 and 52). If healthcare professional determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via AI.

At Week 56, patients will be switched back to CT-P13 SC via PFS and self-injection retraining will be provided prior to the Week 56 PFS injection. CT-P13 SC via PFS will be self-injected under observation of healthcare professional at Week 56 and 64. After proper training in PFS injection technique, patient may self-inject with CT-P13 SC via PFS at home at Weeks 58, 60 and 62. If healthcare professional determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via PFS.

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

4. Study Population

4.1. Selection of Study Population

In Part 1, it is expected that approximately 40 study centers will enrol patients in approximately 10 countries. It is planned to enrol appropriate 50 male or female patients with active RA to randomize approximately 40 (at least 24) patients. Patients will be randomized at Week 6 in a 1:1:1:1 ratio into four study cohorts as presented in Table 3-1.

In Part 2, it is expected that approximately 100 study centers will enrol patients in approximately 15 countries. Approximately 20% of the target patients will additionally be enrolled to randomize minimum 218 male and female patients with active RA. The final number of enrolled patients will be determined considering the dropout rate during patient enrolment. Patients will be randomized at Week 6 in a 1:1 ratio (minimum 109 patients per treatment group) into the CT-P13 IV or CT-P13 SC treatment groups as presented in Table 3-2.

Male and female patients with RA diagnosed according to the 2010 ACR/EULAR classification criteria [Aletaha et al. 2010], despite previous treatment with methotrexate over at least 3 months, will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Patients with active disease are defined by the presence of 6 or more swollen joints (of 28 assessed), 6 or more tender joints (of 28 assessed), and a serum CRP concentration greater than 0.6 mg/dL.

4.2. Inclusion Criteria

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

1. Patient is male or female aged 18 to 75 years old, inclusive.
2. Patient has a diagnosis of RA according to the 2010 ACR/EULAR classification criteria [Aletaha et al. 2010] for at least 6 months prior to the first administration of the study drug (Day 0).
3. Patient has active disease as defined by the presence of 6 or more swollen joints (of 28 assessed), 6 or more tender joints (of 28 assessed), and a serum CRP concentration >0.6 mg/dL at Screening. Unexplained or unexpected Screening CRP value that does not match the clinical activity of RA according to the investigator's assessment or recent test can be retested once within the Screening period.
4. Patient who has completed at least 3 months of treatment of oral or parenteral dosing with methotrexate between 12.5 to 25 mg/week and on stable dosing with methotrexate between 12.5 to 25 mg/week for at least 4 weeks prior to the first administration of the study drug (Day 0).
5. Patient has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
    - Serum creatinine <1.5 × upper limit of normal (ULN) or an estimated creatinine clearance level >50 mL/min (by Cockcroft-Gault formula)
    - Serum alanine aminotransferase <2.5 × ULN
    - Serum aspartate aminotransferase <2.5 × ULN
    - Serum total bilirubin <2 × ULN
6. Patient has the following hematology laboratory test results at Screening:
    - Hemoglobin ≥8.5 g/dL (SI [Système International d'Unités] units: ≥85 g/L or 5.28 mmol/L)
    - White blood cell count ≥3.5 × 10^3 cells/μL (SI 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 ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L)
7. 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.
8. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read or understand this information, signed and dated the written informed consent before inclusion in the study.

9. For both male and female patients, the patient and their partners of childbearing potential agree to use one of the following medically acceptable methods of contraception during the course of the study and for 6 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 any medically acceptable methods of contraception.

    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.

4.3. Exclusion Criteria

The exclusion criteria are divided into 2 categories: tuberculosis (TB) exclusion criteria and general exclusion criteria. Patients meeting any of the following criteria will be excluded from the study:

4.3.1. Tuberculosis Exclusion Criteria

1. Patient who has a history of TB or a current diagnosis of TB. A patient who has a past diagnosis of active TB with sufficient documentation of complete resolution can be enrolled.
2. Patient who has had exposure to person with active TB such as first degree family members or co-workers.
3. Patient who has an indeterminate result for interferon-γ release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at Screening. A patient who has a past diagnosis of latent TB with sufficient documentation of prophylaxis can be enrolled.

   For **Part 2**, if the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the screening period. If the repeated IGRA result is again indeterminate, the patient must be excluded from the study. If the repeated IGRA result is negative, the patient can be included in the study. A patient with a confirmed latent TB during Screening who has received at least the first 30 days of country-specific TB therapy and intends to complete the entire course of that therapy can be enrolled.

4.3.2. General Exclusion Criteria

1. Patient who has previously received a biological agent for the treatment of RA and/or a TNFα inhibitor for the treatment of other disease.
2. Patient who has allergies to any of the excipients of infliximab or any other murine and/or human proteins or patient with a hypersensitivity to immunoglobulin product.
3. Patient who has a current or past history of following infection:
   - Current or past history of chronic infection with hepatitis C or human immunodeficiency virus -1 or-2 or current infection with hepatitis B
   - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 0)
   - Other serious infection within 6 months prior to the first administration of the study drug (Day 0)
   - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 0)
   - Past or current granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as

histoplasmosis). A patient who has a past diagnosis with sufficient documentation of complete resolution can be enrolled

4. Patient who has a medical condition including one or more of the following:
    - Classified as obese (body mass index ≥35 kg/m^2)
    - Uncontrolled diabetes mellitus, even after insulin treatment
    - Uncontrolled hypertension (as defined by systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥100 mmHg)
    - Any other inflammatory or rheumatic diseases, including but not limited to psoriatic arthritis, ankylosing spondylitis, spondyloarthritis, systemic lupus erythematosus, Lyme disease, or fibromyalgia, that may confound the evaluation of the effect of study drug
    - History of any malignancy within the 5 years prior to the first administration of the study drug (Day 0) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
    - History of lymphoma or lymphoproliferative disease or bone marrow hyperplasia
    - New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within the 6 months prior to the first administration of the study drug (Day 0)
    - History of organ transplantation, including corneal graft/transplantation
    - 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
    - Severe physical incapacitation (unable to perform routine self-care, has RA ACR functional status class 4 [Arnett et al 1988], or who cannot benefit from medication)
    - Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage) if it may interfere with the investigator's assessment on disease activity 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.
5. Patient who has received or has plan to receive any of following prohibited medications or treatment:
    - Any biological agents for the treatment of RA

- Intra-articular corticosteroids within 4 weeks prior to the first administration of the study drug (Day 0). Patient is 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 the first administration of the study drug (Day 0). 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 (DMARDs), other than methotrexate, including hydroxychloroquine, chloroquine, or sulfasalazine, within 4 weeks prior to the first administration of the study drug (Day 0). 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 the first administration of the study drug (Day 0). Patients who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after last dose of leflunomide prior to the first administration of the study drug (Day 0).
- Alkylating agents within 12 months prior to the first administration of the study drug (Day 0)
- Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 0)
- Any planned live or live-attenuated vaccination at the time of the first administration of the study drug (Day 0)
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 0) or planned within 6 months after the first administration of the study drug (Day 0)

6. Patient who has a current or past history of drug or alcohol abuse.
7. Patient who has had treatment with any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 0) or 5 half-lives, whichever is longer.
8. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.
9. Patient who, in the opinion of his or her general practitioner or investigator, should not participate in the study.

4.4. Withdrawal of Patients from the Study

Patients are free to withdraw from the study at any time for any reason. The investigator may also withdraw the patient at any time in the interest of patient safety. The primary reason for withdrawal must be recorded in the patient's medical record and on the withdrawal form in the electronic case report form (eCRF).

When possible, the sponsor should be notified of the withdrawal of a patient from the study. For patients who drop out for any reason, all study procedures should be performed on the day of withdrawal (or the day after withdrawal) and all attempts should be made to complete all End-of-Study assessments at planned time points of End-of-Study Visit (see Section 3.2). Any comments (spontaneous or elicited) or complaints made by the patient, together with the reason for termination and the date of cessation of study drug must be recorded in the eCRF and source documents. It is vital to obtain follow-up data on any patient withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified safety and follow-up procedures. All withdrawn patients will retain their study number.

Reasons for withdrawal include the following:

- Patient develops signs of disease progression in the judgement of the investigator
- Patient withdraws consent or refuses to continue treatment and/or procedures/observations
- 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 protocol violation(s)
- Patient is lost to follow-up
- Death
- Study terminated by the sponsor
- Pregnancy
- Investigator's decision

The investigator will also withdraw a patient upon the request of CELLTRION, Inc. The sponsor may be contacted if clarification is required on a case-by-case basis.

4.4.1. Recruitment of Additional Patients

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.

4.5. 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) or independent ethics committee (IEC) of any premature termination or suspension of the study, where applicable.

5. Study Procedures

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

Patients will undergo the procedures at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

5.1. Efficacy Assessments

Efficacy will be assessed by the evaluation of the mean decrease in DAS28 (individual components, DAS28 [CRP], DAS28 [ESR]), ACR criteria (individual components, ACR20, ACR50, and ACR70 and hybrid ACR response), EULAR response criteria, CDAI, SDAI, health assessment questionnaire (HAQ) and SF-36 (Part 2 only) at the following time points specified in the schedule of events (Table 10-1 and Table 10-2).

5.1.1. Joint Count Assessment for Part 2

An independent joint count assessor will be assigned to each site. It is recommended that the joint count assessments are performed independently by the same person, when possible, at each site throughout the entire study period. Joint taken any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will not be included in the joint count. For the assessment, independent joint assessor will be informed about history of patient's joint surgery with the name of the surgery, date and location. Standardizing training will be provided to all joint count assessors and evidence of such training will be recorded in the joint assessor's training records.

5.1.2. Disease Activity Score Using 28 Joint Counts

Disease Activity Score using 28 joint counts (CRP) and DAS28 (ESR) 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 global disease activity measured on visual analogue scale (VAS) (Appendix 10.5)
- ESR (Section 5.3.2)
- CRP (Section 5.3.2)

5.1.3. ACR Criteria and Individual Components

The ACR criteria are a series of individual assessments used for 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 measured on VAS (Appendix 10.4)
- Patient's and physician's global disease activity measured on VAS (Appendix 10.5)
- HAQ estimate of physical ability (Appendix 10.6)
- ESR (Section 5.3.2)
- CRP (Section 5.3.2)

5.2. Pharmacokinetic Assessments

For all patients in Part 1 and Part 2, blood samples for the determination of serum concentrations of infliximab will be collected at pre-dose (prior to the beginning of the study treatment administration on dosing day) at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

For **Part 1**, all patients in SC cohorts (Cohorts 2, 3 and 4) will be randomly assigned at Week 14 in a 1:1 ratio to either of Group A or B to collect blood samples at specific PK sampling time points (Table 5-1):

- **Group A (Cohorts 2A, 3A and 4A):** frequent PK sampling at Weeks 22 and 26
- **Group B (Cohorts 2B, 3B and 4B):** frequent PK sampling at Weeks 24 and 28

Table 5-1 Steady state PK Sampling Time points – Part 1

Visit (Day)	Cohort 1	Cohorts 2, 3 and 4	
		Group A	Group B
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 3, 8 and 24 hr (±15 min) after SOI • 48 hr (±2 hr) after SOI • 96 hr (±4 hr) after SOI • 168 ±6 hr after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection

Week 26 (Day 182)	• 28 days (±1 day) after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 28 (Day 196)	• 42 days (±1 day) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 30 (Day 210)	• Pre-dose* (or 56 days after SOI at Week 22**)	• Pre-dose* (or 14 days after the Week 28 injection**)	

EOI, End of the infusion; hr, hours; min, minutes; SOI, Start of the infusion
* prior to the beginning of study treatment administration on dosing day
** only if patient has not received study treatment at Week 30

For **Part 2**, all patients will be randomly assigned at Week 14 in a 1:1:1:1 ratio to one of the 4 groups, Group A, B, C or D, to collect blood samples at specific PK sampling time points (Table 5-2):

Table 5-2 Steady state PK Sampling Time points – Part 2

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

EOI, End of the infusion; hr, hours; min, minutes; SOI, Start of the infusion
* prior to the beginning of study treatment administration on dosing day
** only if patient has not received study treatment at Week 30

If the investigator deems hospitalization necessary for the PK blood sample collection, patients should remain in the hospital until blood samples for PK analysis have been collected. If the investigator deems hospitalization unnecessary and sampling can be adequately obtained without hospitalization, the patient does not have to remain hospitalized.

For **Part 1**, the following pharmacokinetic endpoints will be assessed between Week 22 and Week 30:

- AUC_{τ} Area under the concentration-time curve at steady state between Week 22 and Week 30
- AUC_{ss8W} Total exposure over the 8 weeks interval from Week 22 to Week 30
- C_{max} Observed maximum serum concentration after study drug administration
- T_{max} Time of observed maximum serum concentration
- $T_{1/2}$ Terminal half life
- C_{trough} Trough concentration (concentration before the next study drug administration)

- MRT Mean residence time
- CL Clearance after IV dosing
- CL/F Apparent clearance after SC dosing
- BA Bioavailability (absolute and/or relative)
- AUC_{τ}/DN Dose normalized total exposure over dosing interval (=AUC_{τ}/total dose administered)
- C_{max}/DN Dose normalized peak exposure (=C_{max}/total dose administered)

The following pharmacokinetic endpoint will be assessed up to Week 54:

- C_{trough} Trough concentration (concentration before the next study drug administration)

For **Part 2**, the following secondary pharmacokinetic endpoints will be assessed using population PK between Week 22 and 30:

- AUC_{τ} Area under the concentration-time curve at steady state between Week 22 and Week 30
- C_{max} Observed maximum serum concentration after study drug administration

The following secondary pharmacokinetic endpoint will be assessed up to Week 54:

- C_{trough} Trough concentration (concentration before the next study drug administration)

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. See Section 5.7.1 for further information on sample collection for pharmacokinetic analysis.

5.3. Pharmacodynamic Assessments

Blood samples for pharmacodynamic assessments (Rheumatoid factor [RF], anti-cyclic citrullinated peptide [anti-CCP], CRP and ESR) will be collected prior to beginning of study treatment administration at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

Actual sampling dates for each patient will be recorded in the patient's eCRF and individual source documents. See Section 5.7.2 for further information on sample collection for pharmacodynamic analysis.

5.3.1. Rheumatoid Factor and Anti-cyclic Citrullinated Peptide

Blood samples for RF and anti-CCP will be collected at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

5.3.2. C-Reactive Protein and Erythrocyte Sedimentation Rate

Blood samples for CRP (central laboratory) and ESR (local laboratory) will be collected at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

Where CRP and ESR are also required for efficacy, PD assessments, and safety (clinical laboratory testing) assessments, the same sample can be used.

A standard ESR kit using Westergren method of assessment will be supplied to sites 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.

5.4. Biomarker Assessments (Optional)

For patients in Part 2 who sign a separate ICF for the biomarker assessments, a blood sample for evaluation of any necessary genotypes will be collected before dosing on Day 0 of Week 0. These genes will include, but are not limited to FcγRIIIa. These samples will be used for research purposes to identify dynamic biomarkers that maybe predictive of response to CT-P13 treatment (in terms of dose, efficacy, safety and tolerability).

5.5. Safety Assessments

5.5.1. Patient's Self-reporting of Adverse Events

Patient diary will be distributed to all patients and patients will be instructed on how to appropriately complete the diary according to patient diary instruction. If there are any signs and symptoms after study treatment administration, patient will record them in patient diary and site personnel will review diary at each visit throughout the study up to and including EOS visit. However, patient will contact the principal investigator or subinvestigator at any time after the first administration of the study drug (Day 0) if any severe symptoms develop and investigator will determine whether patient to be referred to investigator or to continue the next dose administration. Details will be recorded in both the source documents and the eCRF.

5.5.2. Immunogenicity Testing

Serum samples for immunogenicity testing will be collected at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

Anti-CT-P13 antibodies will be assessed by validated Immunoassay. The assay will involve both a screening and confirmatory assay to confirm positive results. Samples that are positive in the screening assay will be spiked with excess drug to determine if they are a true positive. According to Section 5.5.3.1, additional immunogenicity testing will be performed when patient has delayed hypersensitivity reaction.

5.5.3. Hypersensitivity Monitoring

Hypersensitivity will be assessed by vital sign monitoring on each visit day at the time points specified in the schedule of events (Table 10-1 and Table 10-2) and recorded at the following time points:

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

During the double-blinded period of Part 2, hypersensitivity will be assessed at the time points specified in the schedule of events (Table 10-2) and recorded at the following time points:

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

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms (Section 5.5.1). In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed.

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

5.5.3.1. Delayed Hypersensitivity Monitoring

Delayed hypersensitivity will be defined as onset of hypersensitivity 24 hours after the study drug administration, including patient-reported signs and symptoms (Section 5.5.1).

In case of delayed hypersensitivity, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption or edema), patient will be asked to visit study center and following assessments will be additionally performed to determine Serum Sickness during the study period;

- Immunogenicity
- Clinical Laboratory Analyses
- Complement (C3, C4) and Total Haemolytic Complement

5.5.4. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, and body temperature) and weight will be measured at all visits by the investigator or his/her designee after 5 minutes of rest (sitting). Vital signs and weight will be measured before the

beginning of the study drug administration (on the same visit day as the study drug administration) at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

All measurements will be documented at each visit. Vital sign measurements will also be monitored as part of the hypersensitivity monitoring (Section 5.5.3). In addition, height will be documented once at Screening. Details will be recorded in both the source documents and the eCRF.

5.5.5. Electrocardiogram

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. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). If, following the ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality, then after investigator will report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion. In case of hypersensitivity, any types of ECG can be performed (Section 5.5.3).

5.5.6. Tuberculosis Assessment

At Screening, a current diagnosis of TB or a past diagnosis will result in patient exclusion from the study. A patient who has a past diagnosis of active TB with sufficient documentation of complete resolution can be enrolled.

Patients with latent TB or who have had exposure to person with active TB such as first degree family members or co-workers will not be included in the Study.

Patient who has an indeterminate result for IGRA or latent TB at Screening will not be included in the Study. Latent TB is defined as the presence of a positive IGRA (Section 5.5.8) with a negative examination of chest x-ray (Section 5.5.7). A patient who has a past diagnosis of latent TB with sufficient documentation of prophylaxis can be enrolled.

For **Part 2**, if the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the repeated IGRA result is again indeterminate or positive, the patient should be excluded from the study. If the repeated IGRA result is negative, the patients may be included in the study. A patient with a confirmed latent TB during Screening who has received at least the first 30 days of country-specific TB therapy and intends to complete the entire course of that therapy can be enrolled.

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. Patients with active TB based on the chest x-ray result and/or the clinical signs and symptoms must be withdrawn from the study.

If the result of the IGRA is indeterminate during the study, 1 retest will be possible. If the repeated IGRA test result is again indeterminate, investigator will discuss and agree with Sponsor or its designee for next action taken.

If the result of the IGRA is positive during the study, patients should be referred to the clinicians immediately to be investigated the presence of active TB based on medical history and any clinical signs and symptoms including chest x-ray result. In the absence of clinical suspicion for active TB, study drug administration should be temporarily stopped. Study drug is recommended to be reintroduced to patient who have received at least the 3 weeks of country-specific TB therapy and intends to complete the entire course of TB therapy. Study drug can be reintroduced simultaneously with the start of country-specific TB therapy after discussion with the medical monitors of CELLTRION, Inc. or its designee in advance.

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

No further IGRA test is required during Treatment Period and at EOS visit for the following patient:

- Patient who has a history of active TB with sufficient documentation of complete resolution
- Patient who has a history of latent TB with sufficient documentation of complete prophylaxis
- Patient with a confirmed latent TB and enrolled after 30 days of latent TB prophylaxis during Screening for **Part 2**. This patient should have sufficient documentation of complete prophylaxis.
- Patient with positive IGRA result during the study for **Part 2**
- If the patient early discontinued the study at Week 30 and was assessed IGRA, no IGRA test is required at EOS visit for **Part 2**.

5.5.7. Chest X-Ray

A chest x-ray (both posterior–anterior and lateral views) should be taken during Screening and read by a qualified radiologist or pulmonary physician to specifically look for evidence of current active TB or prior inactive TB. If a chest x-ray from within 42 days prior to the first administration of the study drug (Day 0) is available, a chest x-ray is not required at Screening, and the results of this will be recorded in both the source documents and the eCRF.

Radiographic findings suggestive of healed TB or active TB may include but are not limited to pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations,

and pleural effusions. Any abnormal x-ray changes should be discussed with the medical monitor before the first administration of the study drug (Day 0). The chest x-ray should be available to the investigator for review before the first administration of the study drug (Day 0) of the patient.

5.5.8. Interferon-γ Release Assay

Given the seriousness of TB in this patient population, an IGRA will be used to identify positive conversion of negative results for patients.

As described in the literature [Park et al 2009], IGRAs can be used as a method of identifying patients with a false negative response to latent TB infections or new TB infections in patients with RA. Specifically, these assays detect cell-mediated immune responses to TB infections by quantifying interferon-γ in the presence of specific antimicrobial agents. Samples for this analysis will be obtained at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

5.5.9. Diabetes Mellitus Assessment

At Screening, patients will be assessed for the presence of diabetes mellitus according to American Diabetes Association criteria (Appendix 10.2). Patients with diabetes mellitus will be excluded from the study if they have uncontrolled diabetes mellitus even after insulin treatment at Screening.

5.5.10. Congestive Heart Failure Assessment

At Screening, patients will be assessed for the presence of congestive heart failure according to NYHA functional classification. Patients with congestive heart failure of class III or IV, severe uncontrolled cardiac disease (unstable angina or clinically significant ECG abnormalities), or myocardial infarction within the 6 months prior to the first administration of the study drug (Day 0) will be excluded from the study (Appendix 10.3).

5.5.11. Hepatitis B and C and Human Immunodeficiency Virus-1 and -2

At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), this patient can be enrolled by the investigator's discretion based on clinical laboratory results and the infection history of hepatitis.

Hepatitis C antibody and HIV-1 and -2 must be assessed at Screening in all patients (mandatory). If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.

5.5.12. Physical Examinations

Physical examinations with particular attention to infections and administration-related reactions/injection site reactions will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Investigators should carefully evaluate patients for any indication of infections and administration-related reactions/injection site reactions and pursue further investigation and treatment indicated in accordance with the investigator's medical judgment.

Physical examinations will be performed before the beginning of the study drug administration (on the same visit day as the study drug administration).

Information about the physical examinations 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.

5.5.13. Adverse Events

5.5.13.1. 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 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 (see Section 5.5.1). Adverse Events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or worsening of the underlying disease or of other pre-existing conditions will be reported. In addition, changes in vital signs, physical examinations and laboratory tests will be recorded as (S)AE(s) in the eCRF if they are judged clinically relevant by the investigator.

If Rheumatoid arthritis worsens temporarily, disease aggravation will be used as (S)AE(s) term. However, if disease has worsened continuously in the judgment of the investigator (e.g., worsened for more than 8 weeks), this is disease progression, not disease aggravation, and disease progression will not be used as (S)AE(s) term. If disease progression is decided by investigator, patient will be discontinued from the study by investigator's judgement and then disease aggravation reported in the previous visit will be deleted in eCRF.

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

severity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they:

- 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
- Are abnormal laboratory findings

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

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 or diagnostic tests
- Leads to discontinuation of study drug
- Accompanies or induces symptoms or signs
- Is judged by the investigator as clinically significant; laboratory abnormalities due to underlying disease (RA) are not be recorded based on the investigator's judgement

Adverse Events of Special Interest

The following AEs of special interest will be reported using the same process as for AEs:

- Infusion-related reactions/hypersensitivity/anaphylactic reactions (administration-related reaction)

All AEs related to infusion-related reactions/hypersensitivity/anaphylactic reactions (administration-related reaction), occurred within 24 hours after the administration include but are not limited to the following: dyspnea, wheezing, bronchospasm, stridor, reduced peak expiratory flow, hypoxemia, laryngeal irritation, throat irritation, hypotonia (collapse), syncope, incontinence, dizziness, vascular headache, generalized urticaria, rash, itch, flushing, swollen lips, swollen tongue, swollen uvula, angioedema, crampy abdominal pain, nausea, vomiting, hypotension, hypertension, tachycardia, bradycardia, palpitation, arthralgia, myalgia, pyrexia (fever).

- Delayed hypersensitivity

All AEs related to delayed hypersensitivity (including serum sickness-like reactions), occurred 24 hours after the study drug administration, include but are not limited to the following: arthralgia, myalgia with fever or rash, lymphadenopathy, skin eruption, edema.

- Injection site reactions

Injection site reactions will be observed after the study treatment administration and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) v4.03. All AEs related to injection site reactions include but are not limited to the following: erythema, pain, pruritus, hematoma, hemorrhage, swelling, urticaria, induration, bruising, irritation, paraesthesia, rash, tenderness with or without symptoms (e.g., warmth, erythema, itching), lipodystrophy, edema, ulceration, necrosis, severe tissue damage.

- Infection

All AEs related to infection include but are not limited to the following: bacterial (including tuberculosis), viral, mycobacterial, invasive fungal, candidiasis, aspergillosis, blastomycosis, coccidiodomycosis, histoplasmosis, legionellosis, listeriosis, pneumocytosis, upper respiratory tract infections, sinusitis, pharyngitis, bronchitis, urinary tract infection, pneumonia, cellulitis, abscess, skin ulceration, sepsis, nocardiosis, cytomegalovirus, reactivation of hepatitis B virus, and other serious infections leading to hospitalization or death.

- Malignancy

All AEs related to malignancy include but are not limited to the following: lymphoma, non-Hodgkin’s lymphoma, Hodgkin’s disease, leukaemia, melanoma, Merkel cell carcinoma, hepatosplenic T-cell lymphoma.

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 SAEs 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) Serious Adverse Event

An unlisted or unexpected SAE 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/US product insert) for an approved product. Assessment of expectedness will be made with the use of the Investigator's Brochure and the summary of product characteristics.

5.5.13.2. Eliciting and Documenting Adverse Events

For **Part 1** and **2**, AEs will be assessed from the date the ICF is signed until the last assessment date or End-of-Study Visit. Where AEs are ongoing at the End-of-Study Visit, the patient should be followed up for a further 30 days regardless of the relationship to study drug.

For **Part 2**, serious adverse drug reactions (SADRs) occurring up to 8 weeks after last dose of study drug will be reported and followed up until 8 weeks after last dose of study drug. In addition, if it is ongoing until 8 weeks after last dose of study drug, it will be followed up for a further 30 days (Section 5.5.13.6).

Adverse events of special interest (i.e. administration-related reaction, injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

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) or other documents relevant to patient safety.

5.5.13.3. 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, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as action taken with study treatment, any required treatment or evaluations, and outcome. All AEs will be followed to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA Version 19.0 or the most recent version) will be used to code all AEs. Adverse events will be graded for severity according to the CTCAE v4.03.

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 will be reported.

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 5.5.13.4 and 5.5.13.5.

For **Part 1 and 2**, AEs (and SAEs) should be reported until the End-of-Study Visit regardless of the relationship to the study drug. For **Part 2**, any SADRs which occur up to 8 weeks after last dose of study drug received will be reported.

For Part 1 and 2, after the End-of-Study, SADRs 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 5.5.13.1) must be reported to [redacted] pharmacovigilance (PVG) 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:

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax to [redacted] PVG within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. If the patient is hospitalized during the course of an SAE or because of an SAE, a copy of the hospital discharge summary will 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/or local regulatory requirements.

CELLTRION, Inc. or its designee is responsible for reporting unexpected fatal or life-threatening Suspected Unexpected Serious Adverse Reactions (SUSARs) (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 should report other relevant SAEs associated with the use of the study drug 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.

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

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

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

5.5.13.4. Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be graded based on the CTCAE v4.03, 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, or 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. If an AE upgrades in intensity or, changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in intensity, it should not be reported as a new AE. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

5.5.13.5. Assessment of Causality

The investigator's assessment of an AE's relationship to the 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-P13 IV or CT-P13 SC 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.

5.5.13.6. Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF. The related AEs will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure (See also Section 5.5.13.2).

5.5.14. Pregnancy

In an event of unexpected pregnancy during study participation, patients will be counselled to inform the investigator of any pregnancy that occurs during the study and for 6 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 pregnancy form (female patient or partner of a male patient) and return it to [redacted] PVG within 24 hours.

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

5.5.15. Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Blood samples do not need to be collected in a fasting state unless in the opinion of the investigator fasting blood samples are required.

A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the End-of-Study Visit. Patients with only negative results from serum

pregnancy test can be enrolled. A urine pregnancy test for women of childbearing potential should be used to confirm patients are not pregnant prior to study drug administration on each visit day or more frequently if required by country-specific legislation.

The following laboratory analyses will be performed:

Clinical Chemistry	total protein, serum bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, creatine kinase, lactate dehydrogenase, and C-reactive protein (CRP)
Hematology	red blood cells, erythrocyte sedimentation rate (ESR), total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	urine microscopy

Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analyzed at the central laboratory. Urine pregnancy test samples will be analyzed at the local laboratory. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.

5.5.16. Patient's Assessments of Local Site Pain

All patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug at the time points specified in the schedule of events (Table 10-1 and Table 10-2). During the double-blinded period of Part 2, local site pain will be assessed at the following time points:

- Immediately (within 15 minutes) after the end of SC injection (either CT-P13 SC or placebo SC) prior to receiving IV infusion (either CT-P13 IV or placebo IV)
- Immediately (not exceeding 1 hour) after the end of IV infusion (either CT-P13 IV or placebo IV)

Patient assessment of pain is measured by the patient indicating the extent of their pain by marking one line (|) through the 100 mm line (Appendix 10.9).

5.6. Usability Assessments for Part 2

5.6.1. PRE- and POST- Self Injection Assessment Questionnaire (SIAQ)

Usability will be assessed using the Self Injection Assessment Questionnaire (SIAQ) prior and after self-injection of CT-P13 SC via AI or PFS at the time points specified in the schedule of events (Table 10-2). PRE-SIAQ module and POST-SIAQ module (Appendix 10.10) should be done by the patients.

The PRE-SIAQ module is a 7-item questionnaire that investigates feelings about injections, self-confidence (regarding self-administration), and satisfaction with self-injection. At Week 46 and Week 56, patients will complete PRE-SIAQ after self-injection training and immediately (not exceeding 1 hour) before the administration of study drug. For other weeks, patients will complete PRE-SIAQ immediately (not exceeding 1 hour) before the administration of study drug.

The POST-SIAQ module is a 27-item questionnaire that assesses feelings about injection, self-image, self-confidence (regarding self-administration), pain and skin reactions during or after the injection (injection-site reactions), ease of use of the self-injection device (either AI or PFS), and satisfaction with self-injection. Patients will complete POST-SIAQ immediately (not exceeding 1 hour) after the administration of study drug.

5.6.2. Self-Injection Assessment Checklist

Patients' ability to successfully follow the steps in the Instruction for Use to self-administer CT-P13 SC via AI or PFS will be assessed using self-injection assessment checklist (Appendix 10.11 and 10.12) at the time points specified in the schedule of events (Table 10-2). The healthcare professional will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection.

5.6.3. Potential Hazard Checklist

The occurrence of observed or reported difficulties ('potential hazards') will be assessed using potential hazards checklist (Appendix 10.13) at the time points specified in the schedule of events (Table 10-2). The healthcare professional will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection.

5.7. 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.

5.7.1. Pharmacokinetic Blood Sampling

Blood samples for PK assessments collected into serum sample tubes will be obtained at the time points specified in the schedule of events (Table 10-1 and Table 10-2). All samples should be collected as close as possible to the scheduled time point and the actual sampling date will be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 5.8.2.

5.7.2. Pharmacodynamic Blood Sampling

Blood samples for PD (RF, anti-CCP, CRP and ESR) will be obtained in accordance with laboratory manual from each patient at the time points specified in the schedule of events

(Table 10-1 and Table 10-2). All samples should be collected as close as possible to the scheduled time point and the actual sampling date 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 RF, anti-CCP and CRP assessment will be stored and shipped to the central laboratory as detailed in Section 5.8.2. The ESR testing will be performed at the study site local laboratory using kits supplied centrally.

Samples should be stored and shipped as detailed in Section 5.8.2.

5.7.3. Biomarker Blood Sampling

For patients in Part 2 who sign a separate ICF for the biomarker assessments, blood samples for evaluation of any necessary genotypes testing will be collected in accordance with laboratory manual before dosing on Day 0 of Week 0. These genes will include, but are not limited to FcγRIIIa. These samples will be used for research purposes to identify dynamic biomarkers that maybe predictive of response to CT-P13 treatment (in terms of dose, efficacy, safety and tolerability).

Samples should be stored and shipped as detailed in Section 5.8.2.

5.7.4. Routine Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing) will be collected for analysis throughout the study at the time points specified in the schedule of events (Table 10-1 and Table 10-2). An additional blood for hepatitis B and C and HIV-1 and -2 testing will also be required at Screening.

Samples should be stored and shipped as detailed in Section 5.8.2.

5.7.5. Immunogenicity Blood Sampling

Blood samples for immunogenicity assessments will be obtained at the time points specified in the schedule of events (Table 10-1 and Table 10-2). All samples should be collected as close as possible to the scheduled time point and the actual sampling date should be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 5.8.2.

5.7.6. Interferon-γ Release Assay Blood Sampling

Blood samples for IGRA will be obtained at the time points specified in the schedule of events (Table 10-1 and Table 10-2). All samples should be collected as close as possible to the scheduled time point and the actual sampling date should be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 5.8.2.

5.8. Labelling, Storage, and Transportation of Samples

5.8.1. Sample Labelling

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

5.8.2. Sample Storage and Shipment

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

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

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

5.9. 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 detail provided according to the details in Section 5.5.13.3 and an overdose without signs or symptoms must be documented in the study medication section of the eCRF.

Although not strictly due to an overdose, administration-related reactions or injection site reactions are possible and hypersensitivity must be monitored according to the details in Section 5.5.3.

6. Study Treatments

6.1. Method of Assigning Patients to Treatment Groups

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

For **Part 1**, the randomization will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL) and Week 6 body weight (≤70 kg vs. >70 kg). For **Part 2**, the randomization will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL vs. >0.6 mg/dL) and Week 6 body weight (≤100 kg vs. >100 kg). The randomization numbers will be blocked, and within each block the same number of patients will be allocated to each treatment group. The block size will not be revealed.

6.2. Treatments Administered

CT-P13 IV will be administered as a 2-hour (+15 minutes) IV infusion. Patients will be dosed at specific time points as detailed in the schedule of events (Table 10-1 and Table 10-2).

The CT-P13 SC via PFS will be injected by the investigator or by his/her designee at each site visit at the time points specified in the schedule of events (Table 10-1 and Table 10-2). CT-P13 SC via PFS will be injected at a slow, steady rate at any of following site;

- the front of the middle thighs, or
- the abdomen, except for the 5 cm area right around the navel, or
- the outer area of the upper arms (except for self-injection)

For each new injection, a different injection site will be used (i.e. injection site should be rotated). The same injection sites can be used only if the other sites are unavailable due to safety reasons and in that case, it is recommended that new injection should be given at least 3 cm away from the most recent area injected.

During the double-blinded period of **Part 2**, SC formulation (either CT-P13 SC or placebo SC) will be injected initially prior to receiving IV infusion (either CT-P13 IV or placebo IV). IV infusion will be initiated immediately within 15 minutes after the completion of SC injection (either CT-P13 SC or placebo SC).

CT-P13 SC PFS and AI should sit at room temperature for 15 to 30 minutes prior to injection. The PFS and AI must not be warmed in any other way.

After proper training in injection technique, patients may self-inject with CT-P13 SC via PFS if their investigator determines that it is appropriate. CT-P13 SC via PFS can be administered by another person, such as a family member or friend who is instructed properly by investigator or designee. Patients will be dosed at specific time points as detailed in the schedule of events (Table 10-1 and Table 10-2).

CT-P13 SC via AI will be self-injected under observation of healthcare professional at each site visits (Week 46 and 54). Self-injection training will be provided at Week 46 prior to the first AI injection. After proper training in AI injection technique, patient may self-inject with CT-P13 SC via AI at home at any other weeks (Weeks 48, 50 and 52). If healthcare professional determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via AI.

CT-P13 SC via AI will be self-injected (not by the investigator, his/her designee nor caregiver) at a slow, steady rate at any of following site;

- the front of the middle thighs, or
- the abdomen, except for the 5 cm area right around the navel

The outer area of the upper arms is not allowed for CT-P13 via AI self-injection during the study.

At Week 56, patients will be switched back to CT-P13 SC via PFS and self-injection retraining will be provided prior to the Week 56 PFS injection. CT-P13 SC via PFS will be self-injected under observation of healthcare professional at Weeks 56 and 64. After proper training in PFS injection technique, patient may self-inject with CT-P13 SC via PFS at home at Weeks 58, 60 and 62. If healthcare professional determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via PFS.

CT-P13 SC via PFS will be self-injected (not by the investigator, his/her designee nor caregiver) at a slow, steady rate at any of following site;

- the front of the middle thighs, or
- the abdomen, except for the 5 cm area right around the navel

The outer area of the upper arms is not allowed for CT-P13 via PFS self-injection during the study.

6.2.1. Co-administration of Methotrexate and Folic Acid

Methotrexate with folate is co-administered to minimize or prevent AEs related to methotrexate side effects. Therefore, all patients should have completed at least 3 months of treatment with methotrexate between 12.5 to 25 mg/week oral or parenteral (intra-muscular or subcutaneous) prior to study enrolment and should be on a stable dose of methotrexate for at least 4 weeks prior to the first administration of the study drug (Day 0). The dose (between 12.5 to 25 mg/week) must be maintained from beginning to end of study.

Patients are also required to take folic acid (≥5 mg/week, oral dose) throughout the duration of the study [Whittle and Hughes 2004].

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

6.2.2. Premedication

Patient may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating

antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion.

6.3. Identity of Investigational Product

CT-P13 IV is a monoclonal antibody currently being developed by CELLTRION, Inc. which is an approved biosimilar to US-licensed Remicade and EU-approved Remicade. Like other IgG molecules, infliximab possesses 1 N-linked glycosylation site in the CH_2 domain of each heavy chain.

The company code of the product is CT-P13. The International Nonproprietary Name (INN) of the commercially available reference material (Remicade) is infliximab and the Chemical Abstract Service number of infliximab is 170277-31-3. The company code of the subcutaneous formulation for CT-P13 is 'CT-P13 SC'.

The International Union of Pure and Applied Chemistry name of infliximab is chimeric mouse/human anti-TNFα antibody (cA2). The molecular formulas for the light and heavy chains of CT-P13 are $C_{1028}H_{1587}N_{279}O_{337}S_6$ and $C_{2203}H_{3411}N_{585}O_{682}S_{16}$, respectively. The molecular weight of CT-P13 is 145878 g/mol.

CT-P13 IV will be prepared as detailed in the Remsima summary of product characteristics.

CT-P13 IV is formulated as a sterile, lyophilized powder (white solid) and each vial is designed to deliver 100 mg of CT-P13 active substance. The reconstituted drug product is a colourless to light yellow, slightly opalescent to opalescent solution. The solution may develop a few translucent particles, as CT-P13 active substance is a protein. The solution must not be used if opaque particles, discoloration, or other foreign particles are present. The CT-P13 lyophilized powder should be reconstituted with 10 mL of sterile water for injections to yield a reconstituted formulation containing 10 mg/mL of CT-P13 active substance, at a pH of approximately 7.2.

During reconstitution prolonged or vigorous agitation should be avoided. The solution should not be shaken. Foaming of the solution on reconstitution is not unusual. The reconstituted solution should be allowed to stand for 5 minutes before checking that the solution is colourless to light yellow and opalescent.

The total volume of the reconstituted solution dose is further diluted to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. This can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250 mL glass bottle or infusion bag equal to the volume of reconstituted drug product, slowly adding the total volume of reconstituted drug product solution to the 250 mL infusion bottle or bag, and mixing gently.

As CT-P13 (infliximab) vials do not contain preservatives, the solution for infusion should be used as soon as possible and within 3 hours of reconstitution and dilution. (a maximum of

1-hour interruption is permitted during administration [see Section 6.7]). Including the maximum interruption allowed, the solution for infusion must be used within 4 hours of reconstitution and dilution. Any unused portion should be discarded. An infusion pump or gravity method will be used to administer the investigational product.

CT-P13 SC is formulated at 120 mg/mL of CT-P13 active substance at a pH of approximately 5.0 and presented as a liquid formulation in PFS or AI. It is a colourless to brown, clear to opalescent solution and free of foreign particles. A 1.0 mL (120 mg of CT-P13 per syringe and AI) or 0.75 mL (90 mg of CT-P13 per syringe) of formulation including active substance is filled into a 1 mL PFS or AI for SC administration.

The CT-P13 SC finished product includes 10 mM Sodium Acetate, 4.5 % (w/v) Sorbitol, and 0.05 % (w/v) Polysorbate 80 (pH 5.0).

CELLTRION, Inc. will provide adequate supplies of CT-P13 for distribution to the sites.

The following drug supplies will be used in the study:

Investigational Product	**Supplied as:**
CT-P13 IV	Vials containing 100 mg of CT-P13
CT-P13 SC	Pre-filled syringe containing either 90 or 120 mg of CT-P13
	Auto-injector containing 120 mg of CT-P13

No preservatives are present and all excipients are compendial grade in both CT-P13 IV and CT-P13 SC finished products.

6.4. Identity of CT-P13 Placebo Product

CT-P13 IV placebo is formulated as a sterile, lyophilized powder (white solid) and the reconstituted placebo product include 5mM Sodium Phosphate, 5% Sucrose, 0.005% (w/v) Polysorbate 80 at a pH of approximately 7.2. The reconstituted CT-P13 IV Placebo is a colourless to light yellow, clear to opalescent solution. The solution must not be used if opaque particles, discoloration, or other foreign particles are present. The CT-P13 IV Placebo lyophilized powder should be reconstituted with 10 mL of sterile water for injections to yield a reconstituted formulation at a pH of approximately 7.2.

During reconstitution prolonged or vigorous agitation should be avoided. The solution should not be shaken. Foaming of the solution on reconstitution is not unusual. The reconstituted solution should be allowed to stand for 5 minutes before checking that the solution is colourless to light yellow and opalescent.

The total volume of the reconstituted solution dose is further diluted to 250 mL with sodium chloride 9 mg/mL (0.9%) solution for infusion. This can be accomplished by withdrawing a volume of the sodium chloride 9 mg/mL (0.9%) solution for infusion from the 250 mL glass

bottle or infusion bag equal to the volume of reconstituted drug product, slowly adding the total volume of reconstituted drug product solution to the 250 mL infusion bottle or bag, and mixing gently.

As CT-P13 IV Placebo vials do not contain preservatives, the solution for infusion should be used as soon as possible and within 3 hours of reconstitution and dilution. (a maximum of 1 hour interruption is permitted during administration [see Section 6.7]). Including the maximum interruption allowed, the infusion must be within 4 hours of reconstitution and dilution. Any unused portion should be discarded. An infusion pump or gravity method will be used to administer the investigational product.

CT-P13 SC Placebo is formulated at 10mM Sodium Acetate, 4.5% Sorbitol, 0.05% (w/v) Polysorbate 80 at a pH of approximately 5.0 as a sterile and liquid formulation in a PFS. It is a colourless, clear to opalescent solution and free of foreign particles. A 1.0 mL of CT-P13 SC Placebo presented as a liquid formulation is filled into a 1 mL PFS for subcutaneous administration.

CELLTRION, Inc. will provide adequate supplies of CT-P13 Placebo Product for distribution to the sites.

The following CT-P13 Placebo product supplies will be used in the study:

Product	Supplied as:
CT-P13 IV Placebo	Vials containing CT-P13 IV formulation buffer without CT-P13
CT-P13 SC Placebo	Pre-filled syringes containing CT-P13 SC formulation buffer without CT-P13

No preservatives are present and all excipients are compendial grade in both CT-P13 IV and CT-P13 SC Placebo products.

6.5. Management of Clinical Supplies

6.5.1. Study Drug Packaging and Storage

The clinical supplies group will provide prepacked supplies for each patient. Kits will be assigned at randomization using the IWRS or 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 study use only)
- CELLTRION, Inc.'s contact name and address
- Expiry date

All study treatment supplies must be stored in a secure area kept out of reach of children (e.g., a locked cabinet), protected from moisture and light. Both CT-P13 IV and CT-P13 SC PFS and AI must be kept at a controlled refrigerated temperature between 2°C and 8°C. In case CT-P13 SC PFS and AI for self-injection has been kept at temperature over 8°C (maximum 25°C) by patients, the PFS and AI should not be refrigerated again and should be used within 14 days or before the expiry date, whichever is earlier. The recommended storage conditions, and expiry date where required, are stated on the product label approved by each regulatory authority.

6.5.2. 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.

The investigator will retain and store all original containers until these containers are inventoried by CELLTRION, Inc. unless otherwise instructed by CELLTRION, Inc., the investigator agrees at the end of the study to return all original containers, whether empty or containing study drug, to CELLTRION, Inc.

Patients will return all the unused and empty syringes and containers. The used vials and PFSs can only be destroyed if it is written in local standard operating procedures and a specific authorization is given by CELLTRION, Inc. Permission will be granted by CELLTRION, Inc. on a study-center-by-study-center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used vials immediately after administering to patients. Authorization from CELLTRION, Inc. is required before a patient is randomly assigned to a treatment group. 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.

6.6. Blinding

Part 1 is an open-label study.

6.6.1. Breaking the Blind for Part 2

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. 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.

Suspected unexpected serious adverse reactions (SUSAR), 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. This will occur once all final clinical data up to Week 30 have been entered into the database and the database up to Week 30 is finalized for analysis. The unblinded team will be predefined prior to performing the analyses. Final determination of the analysis sets will occur prior to the finalizing the database. While the study data are analysed at Week 30, both the patient and physician and predefined blinded team from the Sponsor and [redacted] will be blinded until all patients have completed the study and the database has been finalised for study termination.

6.7. Treatment Compliance

The CT-P13 IV will be administered by the investigator or by his/her designee while the patient is at the investigational site. CT-P13 IV should be administered as a 2-hour infusion (+15 minutes). Interruption of the infusion is permitted but should be no longer than 1 hour. If an interruption is required, the infusion should be resumed as soon as possible. The start and end time of the infusion as well as any deviations from the planned infusion time will be recorded in both the source documents and the eCRF.

CT-P13 SC will be injected at a slow, steady rate (Section 6.2). The date and time of injection visit as well as any deviations from the planned injection visit will be recorded in both the source documents and the eCRF.

After proper training in injection technique, patients may self-inject with CT-P13 SC if their investigator determines that it is appropriate at any other weeks.

At each time of CT-P13 SC self-injection, patients should record details of injection in patient’s diary including the date and time of injection, kit number of each syringe/AI, the number of syringes/AIs administered and administration sites. At each visit date, the investigator or designee will review the patient diary and check the number of returned

syringes/AIs (unused), to judge patient's dosing compliance and the source data will be recorded in eCRF.

For **Part 1**, every effort will be made to encourage patients' compliance with the study day visits and self-injection schedule with following window allowed:

- a dosing and visit window of ±3 days up to and including Week 30
- a dosing and visit window of ±5 days after Week 30, including EOS

For **Part 2**, every effort will be made to encourage patients' compliance with the study day visits and self-injection schedule with following window allowed:

- a dosing and visit window of ±3 days throughout the study period, including EOS

Patient will contact the principal investigator or subinvestigator at any time if he/she missed a dose or a dosing was out of window. Administration of co-administered treatments (methotrexate and folic acid) will be recorded throughout the study.

6.8. Prior, Concomitant, and Subsequent Medications

All patients should have completed at least 3 months of treatment with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose prior to study enrolment and should be on a stable dose of methotrexate between 12.5 to 25 mg/week, oral or parenteral dose for at least 4 weeks prior to the first administration of the study drug (Day 0). Patients should continue to take methotrexate between 12.5 to 25 mg/week, oral or parenteral dose throughout the duration of the study.

Patients are required to take folic acid (≥5 mg/week, oral dose) throughout the duration of the study.

Use of all prior and concomitant medications for the treatment of Rheumatoid arthritis, from the diagnosis of disease until the last assessment date or End-of-Study Visit, will be recorded in the patient's eCRF.

Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) until the last assessment date or End-of-Study Visit, will be recorded in the patient's eCRF. All concomitant medications will also be recorded when any SADRs occur after the End-of-Study Visit. 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.

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.

6.8.1. Prior, Concomitant, and Subsequent Medications for Part 1

Killed vaccinations are acceptable during the study.

Oral glucocorticoids of maximum equivalent daily dose of 10 mg of prednisolone or NSAIDs are permitted during the study, if the patient has been administered a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 0). If patients are treated prior to enrolment by these drugs, then the same dose will be maintained throughout the study.

Acetaminophen (<3000 mg/day) and/or tramadol (<300 mg/day) are allowed as rescue therapy.

6.8.2. Prior, Concomitant, and Subsequent Medications for Part 2

Patient is 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 the first administration of the study drug (Day 0) 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.

Killed vaccinations are acceptable during the study.

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.

6.9. Prohibited Therapy

The following medications and treatments during the study period are prohibited:

- Any biological agents for the treatment of RA or any investigational drug
- DMARDs, other than methotrexate, including hydroxychloroquine, chloroquine, or sulfasalazine
- Alkylating agents
- Live or live-attenuated vaccine
- For **Part 2**, intra-articular injections are not allowed until Week 22. After Week 22, an intra-articular injection is allowed once to 1 joint during the study. The injected joint must be considered a nonresponder joint during response evaluation.

7. Statistical Analysis Plans

Statistical analysis will be performed using [redacted] The statistical methods for this study will be described

in a detailed statistical analysis plan (SAP), which will be finalized prior to locking of the database. 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. For **Part 1**, the randomization will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL, >0.6 mg/dL) and Week 6 body weight (≤70 kg, >70 kg). For **Part 2**, the randomization at Week 6 will be stratified by country, Week 2 serum CRP concentration (≤0.6 mg/dL, >0.6 mg/dL) and Week 6 body weight (≤100 kg, >100 kg).

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

7.1. Pharmacokinetic Analyses

Serum concentrations of study drug will be summarized by treatment at each scheduled collection time. In additional to the standard summary statistics, the geometric mean and coefficient of variation (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.

Pharmacokinetic parameters will be computed by noncompartmental methods using [redacted] PK population will be used for PK analysis.

7.1.1. Primary Pharmacokinetic Analysis for Part 1

The primary PK endpoint of the observed AUC_{τ} between patients treated with CT-P13 IV or CT-P13 SC at steady state between Week 22 and Week 30 will be presented in listing and summarized in table. Summary statistics will include the n, mean, SD, median, minimum, maximum, geometric mean, and CV.

7.1.2. Secondary Pharmacokinetic Analysis for Part 1

The following secondary PK parameters for the study drug will be considered in Part 1 (between Week 22 and Week 30):

- AUC_{ss8W} Total exposure over the 8 weeks interval from Week 22 to Week 30
- C_{max} Observed maximum serum concentration after study drug administration
- T_{max} Time of observed maximum serum concentration
- $T_{1/2}$ Terminal half life

- C_{trough} Trough concentration (concentration before the next study drug administration)
- MRT Mean residence time
- CL Clearance after IV dosing
- CL/F Apparent clearance after SC dosing
- BA Bioavailability (absolute and/or relative)
- AUC_{τ}/DN Dose normalized total exposure over dosing interval (=AUC_{τ}/total dose administered)
- C_{max}/DN Dose normalized peak exposure (=C_{max}/total dose administered)

For head-to-head comparison of the CT-P13 IV and CT-P13 SC, dosing interval-normalization will be used for analyzing total exposure over 8 weeks (AUC_{ss8W}) at steady state between Week 22 and Week 30 and will be calculated over actual dosing interval (observed tau [τ_{obs}]), according to the following formula: AUC_{τ} [ng·h/mL]/τ_{obs} [h]×1344 [h].

The following secondary PK endpoints will be considered up to Week 54:

- C_{trough} Trough concentration (concentration before the next study drug administration)

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.

7.1.3. Secondary Pharmacokinetic Analysis for Part 2

The following secondary PK parameters for the study drug will be considered in Part 2 (between Week 22 and Week 30):

- AUC_{τ} Area under the concentration-time curve at steady state between Week 22 and Week 30
- C_{max} Observed maximum serum concentration after study drug administration

The following secondary PK endpoint will be considered up to Week 54:

- C_{trough} Trough concentration (concentration before the next study drug administration)

Population PK modelling will be performed for AUC_{τ}, C_{max} and C_{trough} and 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.

7.2. Efficacy Analyses

7.2.1. Primary Efficacy Analysis for Part 2

The primary analysis for DAS28 (CRP) is an analysis of covariance (ANCOVA) comparing the change from baseline of DAS28 at Week 22 of treatment between two treatment groups, CT-P13 SC and CT-P13 IV. The least squares mean and corresponding standard error of the change from baseline in DAS28 (CRP) at Week 22 will be presented for each treatment group. A point estimate and 95% CI for the treatment difference will also be provided.

All-randomized population and efficacy population will be used for primary efficacy analysis, respectively. The additional ANCOVA with missing data imputation will be conducted on all-randomized population. The details of missing data imputation will be described in SAP.

7.2.2. Secondary Efficacy Endpoints for both Part 1 and 2

All secondary efficacy endpoints will be summarized using descriptive statistics. Efficacy population will be used for secondary efficacy analysis.

7.2.2.1. DAS28

Disease activity score in 28 joints (Appendix 10.7) will be assessed using the following equation:

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

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

Where:

- TJC = number of tender joints (0-28): tender joint count (TJC)
- SJC = number of swollen joints (0-28): swollen joint count (SJC)
- ESR = ESR measurement (mm/h)
- CRP = CRP measurement (mg/L)
- GH = patient's global disease activity measured on VAS (Appendix 10.5)

Mean change from baseline in the disease activity measured by DAS28 (ESR and CRP) and components of the DAS28 (ESR and CRP) from baseline will be summarized.

7.2.2.2. 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 from 0 to 100 mm, with higher scores indicating poorer status or more severe pain.

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 will be summarized by treatment and the mean change from baseline in the components of the ACR criteria will be summarized.

7.2.2.3. Hybrid ACR Response

The hybrid ACR is an outcome measure that combines the ACR20, the ACR50, and the ACR70 and a continuous score of the mean improvement in core set measures, [ACR Committee 2007]. The score is determined by calculating the mean percentage change in core set measures and reading the score from Table 7-1 using the patient's ACR status.

Table 7-1 Scoring Method for the 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.
Reference: American College of Rheumatology Committee to Reevaluate Improvement Criteria 2007.

7.2.2.4. EULAR Response Criteria

Response criteria according to EULAR are measured using DAS28 according to Table 7-2.

Table 7-2 EULAR Response Criteria

	DAS28 Improvement

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

DAS28, disease activity score in 28 joints; EULAR, European League Against Rheumatism.
Reference: Fransen et al 2005

7.2.2.5. Clinical Disease Activity Index and Simplified Disease Activity Index

Clinical and simplified disease activity will be measured using CDAI and SDAI [Aletaha and Smolen 2009] calculated from the formulas presented in Table 7-3.

Table 7-3 Calculation of Disease Activity Indices

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

CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; EGA, evaluator global assessment of disease activity (physician global assessment); PGA, patient global assessment of disease activity; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TJC, tender joint count.
Reference: Aletaha and Smolen 2009.

7.2.2.6. Health Assessment Questionnaire

General health status will be assessed using the Health Assessment Questionnaire (HAQ) (Appendix 10.6). There are 8 categories within the HAQ:

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

7.2.2.7. Short-Form Health Survey (Part 2 only)

General health status will be assessed using the SF-36 (Appendix 10.8). Eight aspects of the health status will be assessed:

- General and mental health
- Physical function

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

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

7.3. Secondary Pharmacodynamic Analysis for both Part 1 and 2

All secondary pharmacodynamic endpoints will be summarized using quantitative descriptive statistics (including geometric mean and CV). PD population will be used for PD analysis.

- RF
- Anti-CCP
- CRP
- ESR

7.4. Tertiary Biomarker Analysis for Part 2

Descriptive analyses will be performed on genotypes (including but not limited to FcγRIIIa) by treatment groups.

7.5. Secondary Safety Analysis for both Part 1 and 2

Safety analysis will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2) by presenting data on:

- Immunogenicity testing
- Hypersensitivity monitoring
- Delayed hypersensitivity monitoring, including serum sickness-like reactions
- Complement (C3, C4) and Total Haemolytic Complement
- Vital sign measurements and weight
- Monitoring of TB signs and symptoms
- Chest x-ray
- Interferon-γ release assay
- Diabetes mellitus assessment
- Congestive heart failure assessment
- Hepatitis B and C and HIV-1 and -2
- Physical examination findings

- ECGs
- AEs including SAEs
- AEs of special interest (infusion related reactions/hypersensitivity/anaphylactic reactions [administration-related reaction], delayed hypersensitivity, injection site reactions, infection and malignancies)
- Clinical laboratory analyses
- Patient's assessment of local site pain
- Pregnancy testing
- Previous and concomitant medications
- Local site pain (VAS)

7.5.1. Demographic, Baseline, and Background Characteristics

Demographics (age, gender, race, and etc.), 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.

7.5.2. 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 v4.03.

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

- Number and percentage of patients reporting at least 1 (TE)AE
- Number and percentage of patients reporting at least 1 (TE)SAE
- Number and percentage of patients discontinuing the study drug due to an TEAE
- Number and percentage of patients with TEAEs of special interest (infusion related reactions/hypersensitivity/anaphylactic reactions [administration-related reaction], delayed hypersensitivity, injection site reactions, infection and malignancies)

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.

7.5.3. Clinical 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.

All laboratory results will be listed.

7.5.4. Immunogenicity

All data will be listed and summarized by treatment group, where appropriate.

7.5.5. Electrocardiograms, Physical Examinations, Vital Signs and Weight

Electrocardiograms, physical examinations, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) and weight will be listed and 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.

7.5.6. Patient's assessment of Local Site Pain

Local site pain measurements by VAS will be assessed at each scheduled collection time and will be summarized by treatment group.

7.5.7. Prior and Concomitant Medications

Prior and concomitant medications will be coded to drug class and preferred term according to WHO Drug Dictionary and will be summarized by treatment group.

7.6. Secondary Usability Analysis for Part 2

7.6.1. PRE- and POST- Self Injection Assessment Questionnaire (SIAQ) Analysis for Part 2

Patient will complete each item of SIAQ on a 5-point (or 6-point semantic Likert-type scale), where a score of 1 corresponds to the patient's worst experience and a score of 5 (or 6) corresponds to the subject's best experience. Item score will be transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item, based on below algorithm:

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

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

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

7.6.2. Successful and Hazard Free Self-injection Analysis for Part 2

The self-injection assessment will be coded as successful if P7, P9, P10 and P11 of the self-injection assessment checklist were checked as Yes. Also, the successful completion of all 14 instructions for AI and all 13 instructions for PFS will be assessed from the self-injection assessment checklist (Appendix 10.11 and 10.12, respectively). Hazard-free injection will be coded as the patient who has none of the hazard (Appendix 10.13). Successful and Hazard-free injection will be summarized using descriptive statistics.

7.7. Sample Size Calculations

For **Part 1**, no formal sample size estimation was performed because no confirmatory analyses are planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) are considered to be sufficient to investigate the primary objective of this study (Section 2.1).

For **Part 2**, the primary endpoint is the mean change from baseline in DAS28 (CRP) at Week 22. A sample size of 174 subjects (87 patients each in the CT-P13 SC and CT-P13 IV treatment groups) provide 80% power to demonstrate noninferiority of CT-P13 SC to CT-P13 IV based on the 97.5% one-sided confidence interval for the difference in the mean change from baseline of DAS28 (CRP) at Week 22. In the sample size calculation, noninferiority margin of -0.6, one-sided alpha level 2.5% and standard deviation of 1.4 were assumed. Considering 20% drop-out rate, total 218 patients (109 patients each in the CT-P13 SC and CT-P13 IV treatment groups) will be randomized.

7.8. Analysis Sets

Intended-to-Treated (ITT) population is defined as all enrolled patients. Five patient populations will be analysed: all-randomized, efficacy, pharmacokinetic, pharmacodynamics and safety populations.

All-Randomized Population: The all-randomized population is defined as all randomly assigned patients at Week 6.

Efficacy Population: The efficacy population is defined as all randomly assigned patients who have at least one efficacy evaluation after receiving at least one full dose of study drug (CT-P13 IV or CT-P13 SC) at Week 6 or thereafter.

Pharmacokinetic (PK) Population: The PK population is defined as all randomly assigned patients who received at least one full dose of study drug at Week 6 or thereafter and who have at least one PK concentration result after Week 6 treatment in all-randomized population. The primary PK endpoint of the AUC_{τ} at steady state between Week 22 and Week 30 will be analysed in patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK population for Part 1.

Pharmacodynamic (PD) Population: The PD population is defined as all randomly assigned patients who receive at least one full dose of study drug at Week 6 or thereafter and who have at least one PD result after Week 6 treatment in all-randomized population.

Safety Population: The safety population is defined as all randomly assigned patients who receive at least one (partial or full) dose of study drug at Week 6 or thereafter.

A major protocol deviation that may affect the interpretation of study results of efficacy will be excluded from efficacy population in Part 2. Final determinations of the efficacy

population in Part 2 will be made at the blinded data review meeting held in accordance with ICH harmonised tripartite guideline E9.

7.9. Description of Subgroups to be Analysed

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

7.10. Interim Analyses

No interim analyses are planned for both Part 1 and Part 2 of the study.

7.11. 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 eCRFs 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 he or she has been contacted by a regulatory agency concerning an upcoming inspection.

8. Investigator’s Obligations

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

8.1. 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 the sponsor, its designee, the regulatory authorities, or the IRB/IEC.

The principal investigator or subinvestigator 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.

8.2. Institutional Review

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(R2): Good Clinical Practice and the Declaration of Helsinki (WMA 2013) will be maintained by the study center and will be available for review by the sponsor or its designee.

All IRB/IEC approvals will 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 principal investigator or subinvestigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The principal investigator or subinvestigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

8.3. Informed Consent

Before being admitted to the clinical study, the patients must have expressed their consent to participate, after clear explanations about the nature, scope, and possible consequences of the clinical study have been given to them by the investigator or designee. Information will be given in both oral and written form. The informed consent information sheet will include all of the elements required by law following the ICH E6(R2) guidelines. The informed consent will be approved by the IRB/IEC (and regulatory authorities) of each study center.

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

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

Adequate time and opportunity to satisfy questions will be given to the patients.

The investigator will be supplied with an adequate number of ICFs to be used. The forms will be signed and dated by both the investigator or subinvestigator and the patient or the patient's legal representatives (according to the local regulations) before the beginning of the study. A copy of the signed form will be given to the patient.

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

8.4. Study Reporting Requirements

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the time line and method outlined in Section 5.5.13.3. In addition, the principal investigator or subinvestigator agrees to submit annual reports to his or her IRB/IEC as appropriate. The principal investigator or subinvestigator also agrees to provide the sponsor with an adequate report shortly after completion of the principal investigator's or subinvestigator's participation in the study.

8.5. Financial Disclosure and Obligations

Principal investigators or subinvestigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements per regional requirements. In addition, the principal investigators or subinvestigators 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 its designee is financially responsible for further testing/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 its designee is financially responsible for further treatment of the patient's disease.

8.6. Investigator Documentation

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

- IRB/IEC approval.
- An original investigator-signed investigator agreement page of the protocol.
- Curriculum vitae for the principal investigator and each subinvestigator. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An 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.
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493.

8.7. Study Conduct

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

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

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

The principal investigator or subinvestigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC.

The principal investigator or subinvestigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

8.8. Data Collection

8.8.1. Electronic Case Report Forms and Source Documents

It is the intent of this study to acquire study data via electronic format. As part of the responsibilities assumed by participating in the study, the principal investigator or 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), enter patient data into the eCRF as accurately as possible, and respond to any reported discrepancies rapidly.

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

Each 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.

8.9. Coding Dictionaries

Medical history, as well as all AEs, will be coded using MedDRA. Previous and concomitant medications will be coded using the WHO Drug Dictionary.

Versions of coding dictionaries will be stated in the study report.

8.10. Adherence to Protocol

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

8.11. Reporting Adverse Events

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the time line and method outlined in Section 5.5.13.3. In addition, the principal investigator or subinvestigator agrees to submit annual reports to the relevant IRB/IEC as appropriate. The principal investigator or subinvestigator also agrees to provide the sponsor with an adequate report shortly after completion of the principal investigator's or subinvestigator's participation in the study.

8.12. Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform his or her institution; the investigator or 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.

8.13. 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 sheets pertaining to the study must be kept on file.

Essential documents will be retained until at least 15 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 15 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 principal investigator or subinvestigator/institution as to when these documents no longer need to be retained.

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

8.14. 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.

8.15. 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.

9. Study Management

9.1. Sponsor

Sponsor Representative

9.2. Vendor Contact

SAE Reporting

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

9.3. Analytical Facilities

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

[redacted]s

9.4. Data Safety Monitoring Board

This study will be monitored by an independent data safety monitoring board (DSMB). DSMB will review and evaluate accumulating safety data to ensure the safety of trial subjects.

During Part 1 of the trial, DSMB will review the PK modelling report data containing PK, efficacy, PD and safety data found over the first 30 weeks from Part 1 and recommend the

optimal dose (dose level and dosing interval) for CT-P13 SC. Part 2 will be initiated based upon the DSMB's recommendation.

Additionally, all clinical study reports for Part 1 and 2 will be reviewed and evaluated by DSMB.

Further details will be provided in the independent data safety monitoring board charter.

9.5. Monitoring

9.5.1. 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 principal investigator or subinvestigator and study facility 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 principal investigator or subinvestigator and staff.

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

9.5.2. Inspection of Records

Principal investigators or subinvestigators 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 principal investigator or subinvestigator agrees to allow the sponsor, representatives of the sponsor, or other regulatory agencies 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.

9.6. Management of Protocol Amendments and Deviations

9.6.1. 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 principal investigator's or subinvestigator's IRB/IEC for approval before patients are enrolled under an amended protocol. This will be fully documented.

The investigator must not implement any deviation from or change to the protocol without discussion and agreement from CELLTRION, Inc. or its designee, and prior review,

documented approval, and favorable opinion of the amendment from the relevant IRB/IEC and/or regulatory authorities, except where it is necessary to eliminate an immediate hazard to patients or where the changes involve only logistical or administrative aspects of the clinical study. The eCRF and source documents will describe any departure from the protocol and the circumstances requiring it.

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

9.6.2. Protocol Violations and Deviations

The principal investigator or subinvestigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The principal investigator or subinvestigator 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 will 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 principal investigator or subinvestigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion, exclusion, or primary endpoint criteria. A protocol violation occurs when there is nonadherence to the protocol by the patient, investigator, or subinvestigator that results in a significant, additional risk to the patient. Protocol violations can include nonadherence to inclusion or exclusion criteria, enrolment of the patient without prior sponsor approval, or nonadherence to regulatory regulations or ICH E6(R2) guidelines.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators or subinvestigators will be notified in writing by the monitor of violations and deviations. The IRB/IEC should be notified of all protocol violations and deviations in a timely manner.

9.7. 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.

The end of the study is defined as the date on which the last patient completes the last visit (includes End-of-Study Visit and AEs/SAEs/SADRs follow-up) if the study is not discontinued by sponsor decision before this date.

9.8. 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 agencies as required by the applicable regulatory requirements. 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.

The sponsor plans to prepare 4 clinical study reports, but if additional clinical study reports are required for regulatory or academic purposes, clinical study reports will be generated:

- To report data for each patient after the completion of all visits in Part 1,
- To report data for each patient up to Week 30 in Part 2
- To report data for each patient up to Week 54 and after the completion of all visits in Part 2

Data for each patient up to Week 30 in Part 1 will be prepared by an abbreviated form of study results report.

10. Appendices

10.1. Study Schedule of Events

Table 10-1 Study Schedule of Events for Part 1

	Screening	Treatment Period												EOS[2]
Study Week		**0**	**2**	**6**	**8[1]**	**10[1]**	**14**	**22**	**PK Monitoring Visit[22]**	**30**	**38**	**46**	**54**	
Study Day	**–21 to –1**	**0**	**14**	**42**	**56**	**70**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**							**± 3 days**	**± 5 days**			
Cohort 1 treatment		**IV**	**IV**	**IV**			**IV**	**IV**		**IV**	**IV**	**IV**	**IV**	
Cohort 2, 3 and 4 treatment[3, 4]				**SC**	**SC[1]**	**SC[1]**	**SC**							
Informed consent	X													
Demography[5]	X													
Medical history[6]	X													
Hepatitis B & C and HIV-1 and -2[7]	X													
Inclusion and exclusion criteria	X	X[8]												
Randomization				X[8]										
Serum pregnancy test	X													X
Urine pregnancy test[9]		X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	
Clinical laboratory tests[10]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Chest x-ray[11]	X													
Interferon-γ release assay[12]	X									X[8]			X[8]	X
Physical examinations	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Vital signs and Weight[13]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
12-lead ECG[14]	X			X			X			X			X	X
Efficacy assessment[15]														
Tender joint count (68 joints/28 joints)	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[16]
Swollen joint count (66 joints/28 joints)	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[16]
VAS pain score	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[16]
VAS global assessment of disease activity (patient/physician) score	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[16]
Health Assessment Questionnaire	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]			X[8]	X[16]
ESR (local)[17]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
CRP[17]	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
VAS local site pain[18]				X			X	X		X			X	
Rheumatoid Factor	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Anti-cyclic citrullinated peptide	X	X[8]	X[8]	X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Immunogenicity[19]		X[8]		X[8]			X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Hypersensitivity monitoring[20]		X	X	X			X	X		X	X	X	X	

	Screening	Treatment Period												EOS[2]
Study Week		**0**	**2**	**6**	**8[1]**	**10[1]**	**14**	**22**	**PK Monitoring Visit[22]**	**30**	**38**	**46**	**54**	
Study Day	**–21 to –1**	**0**	**14**	**42**	**56**	**70**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**							**± 3 days**	**± 5 days**			
Complement (C3, C4) and Total Haemolytic Complement[21]		X[8]												
Pharmacokinetic blood sampling		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	X[22]	X[8]	X[8]	X[8]	X[8]	
Previous/concomitant medications[23]	X													
TB clinical monitoring[24]	X													
AEs monitoring[25]	X													

Abbreviations: ACR, American College of Rheumatology; AE, adverse event; CRP, C-reactive protein; ECG, Electrocardiogram; ESR, erythrocyte sedimentation rate; EOS, end of study; HIV, human immunodeficiency virus; IV, intravenous; N/A; not applicable; PK, pharmacokinetic; QOL, quality of life; SC, subcutaneous; TB, tuberculosis; VAS, visual analogue scale.

1. Visits 4 and 5 (Week 8 and Week 10) will only be made by patients from Cohorts 2, 3 and 4 for additional pharmacokinetic assessment.
2. All EOS assessments will be completed 8 weeks after the last study drug administration.
3. First CT-P13 SC will be administered by PFS at Week 6 and further SC injections will be given every 2 weeks up to Week 54.
4. A dosing window of ±3 days is allowed up to and including Week 30; a dosing window of ±5 days is allowed after Week 30, including EOS.
5. Age, gender, ethnicity and race.
6. At Screening, patients will be assessed for the history of rheumatoid arthritis, respiratory disease, diabetes mellitus, congestive heart failure and etc.
7. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), this patient can be enrolled by the investigator's discretion based on clinical laboratory results and the infection history of hepatitis. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.
8. Assessed prior to study drug administration.
9. A urine pregnancy test for women of childbearing potential who have not been surgically sterilized will be used to confirm patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.
10. Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analysed at the central laboratory. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness.
11. A chest x-ray (both posterior-anterior and lateral views) is not required at Screening if a chest x-ray from within the 42 days prior to the first administration of the study drug (Day 0) is available.
12. The IGRA will be performed at the central laboratory. No further IGRA test is required during Treatment Period for the following patient:
    - Patient who has a history of active TB with sufficient documentation of complete resolution
    - Patient who has a history of latent TB with sufficient documentation of prophylaxis
13. Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented at Screening.
14. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion.
15. It is recommended that the joint count assessments are performed by the same physician when possible.
16. End-of-study assessments will be performed if not done at Week 54.

17. Both ESR rate and CRP are considered to be an efficacy, pharmacodynamics and safety (clinical laboratory test) endpoint. CRP samples should be drawn at the same time as the clinical laboratory blood samples and ESR samples will be analyzed at the local laboratory using kits supplied centrally.
18. Patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug.
19. Serum samples for immunogenicity testing will be drawn before dosing of study drug. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
20. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of the study treatment administration and 1 hour (±10 minutes) after the end of the study drug administration) to monitor for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed. In addition, delayed hypersensitivity will be monitored after 24 hours of study drug administration, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption or edema).
21. Additional serum samples for complement (C3, C4) and total haemolytic complement will be assessed if delayed hypersensitivity occurs after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
22. If the investigator deems hospitalization necessary for the blood sample collection, patients should remain in the hospital until blood samples for pharmacokinetic analysis have been collected. If the investigator deems hospitalization unnecessary and sampling can be adequately obtained without hospitalization, the patient does not have to remain hospitalized. Blood samples for pharmacokinetic analysis will be obtained at following time point;

Visit (Day)	**Cohort 1**	**Cohorts 2, 3 and 4**	
		Group A	**Group B**
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 3, 8 and 24 hr (±15 min) after SOI • 48 hr (±2 hr) after SOI • 96 hr (±4 hr) after SOI • 168 ±6 hr after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 26 (Day 182)	• 28 days (±1 day) after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection

Week 28 (Day 196)	• 42 days (±1 day) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 30 (Day 210)	• Pre-dose* (or 56 days after SOI at Week 22**)	• Pre-dose* (or 14 days after the Week 28 injection**)	

EOI, End of the infusion; hr, hours; min, minutes; SOI, Start of the infusion
* prior to the beginning of study treatment administration on dosing day
** only if patient has not received study treatment at Week 30

23. Use of all prior and concomitant medications for the treatment of rheumatoid arthritis, from the diagnosis of disease until the last assessment date or End-of-Study Visit, will be recorded in the patient's eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) patient enrolment until the last assessment date or End-of-Study Visit, will be recorded.
24. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay or chest x-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
25. Adverse events will be assessed from the date the ICF is signed until the last assessment date or EOS Visit. Where AEs are ongoing at the EOS visit (8 weeks after the last dose is received), the patient should be followed up for a further 30 days) regardless of the relationship to the study drug. The related AEs will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Adverse events of special interest (i.e. administration-related reactions, injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

Table 10-2 Study Schedule of Events for Part 2

	Screening	Treatment Period												EOS[1]
Study Week		**0**	**2**	**6**	**14**	**22**	**PK Monitoring Visit[25]**	**30**	**38**	**46**	**54**	**56**	**64**	
Study Day	**–42 ~**	**0**	**14**	**42**	**98**	**154**		**210**	**266**	**322**	**378**	**392**	**448**	
Visit Window		**N/A**		**± 3 days**										
Arm 1 treatment[2, 3]		**IV**	**IV**	**IV + Placebo SC**	**IV + Placebo SC**	**IV + Placebo SC**	**Placebo SC**	**SC[4]**		**SC via AI[5]**		**SC via PFS[6]**		
Arm 2 treatment[2, 3]				**SC + Placebo IV**	**SC + Placebo IV**	**SC + Placebo IV**	**SC**							
Informed consent	X													
Demography[7]	X													
Medical history[8]	X													
Hepatitis B & C and HIV-1 and -2[9]	X													
Inclusion and exclusion criteria	X	X[10]												
Randomization				X[10]										
Serum pregnancy test[11]	X													X
Urine pregnancy test[12]		X[10]	X[10]	X[810]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	
Clinical laboratory tests[13]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X
Chest x-ray[14]	X													
Interferon-γ release assay[15]	X							X[10]			X[10]			X
Physical examinations	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X
Vital signs and Weight[16]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X[10]	X[10]	X
12-lead ECG[17]	X			X	X			X			X			X
Efficacy assessments:														
Tender joint count[18] (68 joints/28 joints)	X	X[10]	X[10]	X[810]	X[10]	X[10]		X[10]			X[10]			X[19]
Swollen joint count[18] (66 joints/28 joints)	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
VAS pain score	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
VAS global assessment of disease activity (patient and physician) score	X	X[10]	X[10]	X[10]	X[10]	X[810]		X[10]			X[10]			X[19]
Health Assessment Questionnaire	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]			X[10]			X[19]
ESR (local)[20]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[810]			X
CRP[20]	X	X[10]	X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]			X
QOL (SF-36) assessment	X	X[10]		X[10]	X[10]	X[10]		X[10]			X[10]			X[19]

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

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

1. The EOS assessments will be completed 2 weeks after the last dose of CT-P13 SC via PFS is received. For patients who early discontinue the study before Week 30, all EOS assessments will be completed 8 weeks after the last CT-P13 IV or Placebo IV is received (Week 0, 2, 6, 14 and 22). For patients who early discontinue the study on or after Week 30, EOS assessments will be completed 2 weeks after the last CT-P13 SC via PFS or AI is received.
2. During the double-blinded period, SC formulation (either CT-P13 SC or placebo SC) will be injected initially prior to receiving IV infusion (either CT-P13 IV or placebo IV). IV infusion will be initiated immediately within 15 minutes after the completion of SC injection.
3. CT-P13 SC via PFS (or placebo SC via PFS during the double-blinded period) will be injected by a healthcare professional at each site visit (Weeks 6, 14, 22, 24~28 [for patients who will make visit for additional PK assessment], 30 and 38). After proper training in injection technique, patients may self-inject with CT-P13 SC via PFS (or placebo SC via PFS during the double-blinded period) if their investigator determines that it is appropriate at any other weeks (Weeks 8, 10, 12, 16, 18, 20, 24~28 [for patients who will not make visit for additional PK assessment], 32, 34, 36, 40, 42 and 44).
4. CT-P13 IV will be switched to CT-P13 SC via PFS at Week 30 for Arm 1. Further doses of study treatment with CT-P13 SC via PFS every 2 weeks will be given up to Week 44.
5. Patients will be administered CT-P13 SC via AI at Week 46 and every 2 weeks thereafter up to Week 54. CT-P13 SC via AI will be self-injected under observation of healthcare professional at each site visits (Week 46 and 54). Self-injection training will be provided at Week 46 prior to the first AI injection. After proper training in AI injection technique, patient may self-inject with CT-P13 SC via AI at home at any other weeks (Weeks 48, 50 and 52).
6. Switching back to CT-P13 SC via PFS at Week 56 will be implemented at selected sites. At Week 56, patients will be switched back to CT-P13 SC via PFS and self-injection retraining will be provided prior to the Week 56 PFS injection. CT-P13 SC via PFS will be self-injected under observation of healthcare professional at Week 56 and 64. After proper training in PFS injection technique, patient may self-inject with CT-P13 SC via PFS at home at Weeks 58, 60 and 62.
7. Age, gender, ethnicity and race.
8. At Screening, patients will be assessed for the history of rheumatoid arthritis, respiratory disease, diabetes mellitus, congestive heart failure and etc.

9. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), this patient can be enrolled by the investigator's discretion based on clinical laboratory results and the infection history of hepatitis. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.
10. Assessed/performed prior to study drug administration.
11. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS Visit.
12. A urine pregnancy test for women of childbearing potential will be used to confirm patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.
13. Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analysed at the central laboratory. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness.
14. A chest x-ray (both posterior-anterior and lateral views) is not required at Screening if a chest x-ray from within the 42 days prior to the first administration of the study drug (Day 0) is available.
15. The IGRA will be performed at the central laboratory. No further IGRA test is required during Treatment Period and at EOS for the following patient:
    - Patient who has a history of active TB with sufficient documentation of complete resolution
    - Patient who has a history of latent TB with sufficient documentation of prophylaxis
    - Patient with a confirmed latent TB and enrolled after 30 days of latent TB prophylaxis during Screening
    - Patient with positive IGRA result during the study
    - If the patient early discontinued the study at Week 30 and was assessed IGRA, no IGRA test is required at EOS visit.
16. Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented at Screening.
17. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion.
18. An independent joint count assessor will be assigned to each site. It is recommended that the joint count assessments are performed by the same person, when possible, for all patients at each site throughout the entire study period. Standardizing training will be provided to all joint count assessors and evidence of such training will be recorded in the joint assessor's training records. Joint taken any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will not be included in the joint count. For the assessment, independent joint assessor will be informed about history of patient's joint surgery with the name of the surgery, date and location.
19. End-of-study assessment will be performed if the assessment was not done at Week 54, or in patient with discontinuation before Week 54.
20. Both ESR rate and CRP are considered to be an efficacy, pharmacodynamics, and safety (clinical laboratory test) endpoint. CRP samples should be drawn at the same time as the clinical laboratory blood samples and ESR samples will be analysed at the local laboratory using kits supplied centrally.
21. Patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug. During the double-blinded period, local site pain will be assessed at the following time points:
    - Immediately (within 15 minutes) after the end of SC injection (either CT-P13 SC or placebo SC) prior to receiving IV infusion (either CT-P13 IV or placebo IV)
    - Immediately (not exceeding 1 hour) after the end of IV infusion (either CT-P13 IV or placebo IV)
22. Serum samples for immunogenicity testing will be drawn before dosing of study drug. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
23. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of the study treatment administration and 1 hour [±10 minutes] after the end of the study drug administration) to monitor for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed. In addition, delayed hypersensitivity will be monitored after 24 hours of study drug administration, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption or edema).
24. Hypersensitivity will be assessed prior to the beginning of the SC formulation (either CT-P13 SC or placebo SC) injection and 1 hour (±10 minutes) after the end of the IV

formulation (either CT-P13 IV or placebo IV) infusion.

25. Additional serum samples for complement (C3, C4) and total haemolytic complement will be assessed if delayed hypersensitivity occurs after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
26. If the investigator deems hospitalization necessary for the blood sample collection, patients should remain in the hospital until blood samples for pharmacokinetic analysis have been collected. If the investigator deems hospitalization unnecessary and sampling can be adequately obtained without hospitalization, the patient does not have to remain hospitalized.
27. Blood samples for pharmacokinetic analysis will be obtained at the time point specified in Table 10-3.
28. Only for patients who sign a separate informed consent form for the biomarker study (genotypes). Testing will be performed at the assigned testing facilities.
29. PRE-SIAQ will be completed by patient prior to self-injection of CT-P13 SC and POST-SIAQ will be completed by patient after self-injection of CT-P13 SC at every injection (AI: Week 46, 48, 50, 52 and 54; PFS: 56, 58, 60, 62 and 64). Patients will complete PRE-SIAQ immediately (not exceeding 1 hour) before the administration of study drug and POST-SIAQ immediately (not exceeding 1 hour) after the administration of study drug.
30. The healthcare professional will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection at Week 46, 54, 56 and 64. If additional training in either AI or PFS technique is given, checklist should be additionally assessed.
31. Use of all prior and concomitant medications for the treatment of rheumatoid arthritis, from the diagnosis of disease until the last assessment date or EOS Visit, will be recorded in the patient's eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) patient enrolment until the last assessment date or EOS Visit, will be recorded. All concomitant medications will also be recorded when any SADRs occur after the EOS Visit.
32. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay or chest x-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
33. Adverse events will be assessed from the date the ICF is signed until the last assessment date or EOS Visit. Where AEs are ongoing at the EOS visit, the patient should be followed up for a further 30 days regardless of the relationship to the study drug. The related AEs will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Serious adverse drug reactions occurring up to 8 weeks after last dose of study drug will be reported and followed up until 8 weeks after last dose of study drug. In addition, if it is ongoing until 8 weeks after last dose of study drug, it will be followed up for a further 30 days. Adverse events of special interest (i.e. administration-related reactions, injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

Table 10-3 Blood Sampling Times for Part 2 Pharmacokinetic Assessments

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

EOI, End of the infusion; hr, hours; min, minutes; SOI, Start of the infusion
* prior to the beginning of study treatment administration on dosing day
** only if patient has not received study treatment at Week 30

Table 10-4 Blood Sampling Times for Part 2 Pharmacodynamic and Safety Assessments

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

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

1. Pre-treatment: Blood samples will be obtained prior to the study drug administration.
2. Time not specified: Blood samples will be obtained any time during the day.
3. The EOS assessments will be completed 2 weeks after the last dose of CT-P13 SC via PFS is received. For patients who early discontinue the study before Week 30, all EOS assessments will be completed 8 weeks after the last CT-P13 IV or Placebo IV is received (Week 0, 2, 6, 14 and 22). For patients who early discontinue the study on or after Week 30, EOS assessments will be completed 2 weeks after the last CT-P13 SC via PFS or AI is received.

10.2. Diabetes Mellitus Assessment

Diabetes mellitus (is defined by the criteria for the diagnosis of diabetes mellitus according to the American Diabetes Association). Patients are to be excluded from the study if they have uncontrolled diabetes mellitus even after insulin treatment. Details of the American Diabetes Association criteria for the diagnosis of diabetes mellitus are provided in Table 10-5.

Table 10-5 Criteria for the Diagnosis of Diabetes Mellitus

1. Symptoms of diabetes and a casual plasma glucose of 200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. or 2. FPG of 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours. or 3. Two-hour plasma glucose of 200 mg/dL (11.1 mmol/L) during an OGTT. The test will be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

FPG: fasting plasma glucose; OGTT: oral glucose tolerance test

In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

Reference: American Diabetes Association 2006.

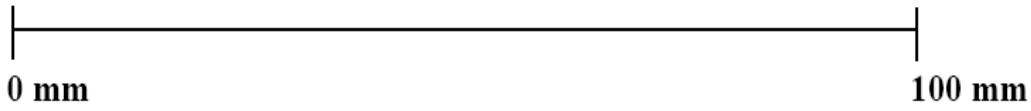
10.3. New York Heart Association Functional Classification

As defined in Raphael et al. 2007, the New York Heart Association (NYHA) classification is used in patients with heart failure.

Class	Symptoms
I (Mild)	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV (Severe)	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

10.4. Visual Analogue Scale (VAS) Patient Assessment of Pain

Patient assessment of pain is measured by the patient indicating the extent of their pain by marking one line (|) 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 case report form.

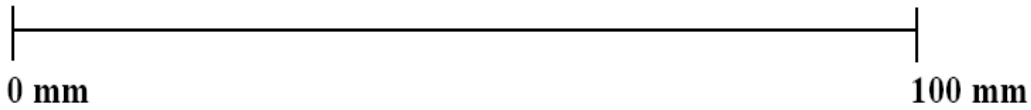


0 mm **100 mm**

None Extreme

10.5. Visual Analogue Scale (VAS) Physician and Patient Global Assessment of Disease Activity

Physician and patient global assessment of disease activity is measured by both the physician and the patient indicating the patient's current disease status by marking one line (|) 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 case report form.



0 mm **100 mm**

None Extreme

10.6. 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

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

_____ Walker

_____ Built up or special utensils

_____ Crutches

_____ Special or built up chair

_____ Wheelchair

_____ Other (Specify:_____)

DRSGASST_____

RISEASST_____

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

_____ Dressing and Grooming

_____ Eating

EATASST_____

_____ Arising

_____ Walking

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_____

10.7. DAS28

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

More information on DAS28 can be found at 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	

MCP, metacarpophalangeal joints; PIP, proximal interphalangeal joints
Reference: http://www.reuma-nijmegen.nl/www.das-score.nl/DAS28frm.doc

10.8. General Health Status (Medical Outcomes Study Short-Form Health Survey, [SF-36])

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.

SF-36 v2.0 Health Survey

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

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

Excellent	Very good	Good	Fair	Poor
○	○	○	○	○

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

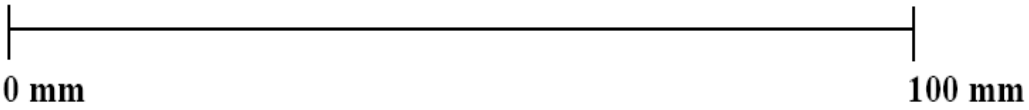
All of the time	Most of the time	Some of the time	A little of the time	None of the time
○	○	○	○	○

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

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

10.9. Visual Analogue Scale (VAS) Local Site Pain

Patient assessment of local site pain is measured by the patient indicating the extent of their pain by marking one line (|) 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 case report form.



None Extreme

10.10. PRE- and POST- Self-Injection Assessment Questionnaire (SIAQ)

SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)

- PRE-Self-Injection -

Domain	Item	Answer category
Feeling about injections	1. In general, how afraid are you of needles? 2. In general, how afraid are you of having an injection? 3. How anxious do you feel about giving yourself an injection?	• Extremely • Very • Moderately • A little • Not at all
Self-confidence	1. How confident are you about giving yourself an injection in the right way? 2. How confident are you about giving yourself an injection in a clean and sterile way? 3. How confident are you about giving yourself an injection safely?	
Satisfaction with self-injection	1. Overall, how satisfied are you with your current way of taking your medication?	• Very satisfied • Satisfied • Neither satisfied nor dissatisfied • Dissatisfied • Very dissatisfied

SELF-INJECTION ASSESSMENT QUESTIONNAIRE (SIAQ)

- POST-Self-Injection –

Domain	Item	Answer category
Feeling about injections	1. In general, how afraid are you of needles? 2. In general, how afraid are you having an injection? 3. How anxious do you feel about giving yourself an injection?	• Extremely • Very • Moderately • A little • Not at all
Self-image	1. How embarrassed would you feel if someone saw you with the self-injection device?	
Self-confidence	1. How confident are you about giving yourself an injection in the right way? 2. How confident are you about giving yourself an injection in a clean and sterile way? 3. How confident are you about giving yourself an injection safely?	
Pain and skin reaction during or after the injection	1. Pain a. Pain? b. Burning sensation? c. Cold sensation? 2. Reaction a. Itching at the injection site? b. Redness at the injection site? c. Swelling at the injection site? d. Bruising at the injection site? e. Hardening at the injection site?	• Extremely • Very • Moderately • A little • Not at all
Ease of use of the self-injection device	1. Remove the cap? 2. Depress the device?* 3. Administer injection without any help? 4. Use the self-injection device?	• Very difficult • Difficult • Somewhat difficult • Somewhat easy • Easy • Very easy
	5. How does the device fit in your hand?	• Very comfortably • Comfortably • Somewhat comfortably • Somewhat uncomfortably • Uncomfortably • Very uncomfortably
Satisfaction with self-injection	1. How easy was it to give yourself an injection?	• Extremely • Very • Moderately

		• A little • Not at all
	2. How satisfied are you with how often you give yourself an injection? 3. How satisfied are you with the time it takes to inject the medication? 4. Overall, how satisfied are you with your current way of taking your medication (self-injection)?	• Very satisfied • Satisfied • Neither satisfied nor dissatisfied • Dissatisfied • Very dissatisfied
	5. Overall, how convenient is the self-injection device?	• Very convenient • Convenient • Neither convenient nor inconvenient • Inconvenient • Very inconvenient
	6. After this study, would you choose to continue self-injecting your medication?	• Yes, definitely • Yes, probably • I don't know • Probably not • Definitely not
	7. After this study, how confident would you be to give yourself injections at home?	• Extremely • Very • Moderately • A little • Not at all

SIAQ, Self-Injection Assessment Questionnaire.

*This question was slightly modified from the SIAQ developed by Keininger and Coteur. It was originally written as: "Depress the plunger or button on the device?

10.11. Self-Injection Assessment Checklist for AI

No.	Instructions for Use	Completion Required for Successful Administration? (Yes/No)
P1	Removed the auto-injector from the outer box	
P2	Checked expiration date on the auto-injector label	
P3	Inspected the auto-injector for damage	
P4	Inspected liquid for discoloration or particles	
P5	Washed hands with soap and water	
P6	Cleaned the injection site	
P7	Removed cap from auto-injector	
P8	Held the auto-injector so that patient could see the window	
P9	Placed the auto-injector at 90° angle on the injection site	
P10	Pressed the auto-injector firmly against the skin to start the injection (1st click), and kept holding the auto-injector firmly against the skin	
P11	After the 2nd loud click, continued to hold the auto-injector firmly against the skin and waited until 5 seconds to ensure the injection was completed	
P12	Checked if the green indicator fills the window completely	
P13	Removed auto-injector from injection site at 90° angle to skin	
P14	Disposed used auto-injector and the cap in a sharps container	

10.12. Self-Injection Assessment Checklist for PFS

No.	Instructions for Use	Completion Required for Successful Administration? (Yes/No)
P1	Removed the PFS from the outer box	
P2	Checked expiration date on the PFS label	
P3	Inspected the PFS for damage	
P4	Inspected liquid for discoloration or particles	
P5	Washed hands with soap and water	
P6	Cleaned the injection site	
P7	Removed cap from PFS	
P8	Gently pinched a fold of skin at the injection site with one hand	
P9	Inserted the needle completely into the fold of the skin at 45° angle	
P10	Pushed the plunger down slowly to start the injection	
P11	Kept pushing the plunger as far as it goes until the syringe was empty	
P12	Removed the needle from injection site at the same angle it was inserted (45° angle to skin)	
P13	Disposed used PFS and the cap in a sharps container	

10.13. Potential Hazard Checklist

No.	Potential Hazard[a]	Yes/No	Specification
H1	Was there a needle stick in a critical area (e.g., eye, carotid artery)?		
H2	Was there a needle stick in a non-critical area?[b]		
H3	Was any part of the device swallowed?[c]		
H4	Was an immediate-type allergic reaction to the device material noticed?		
H5	Was increased pain noticed by the subject due to a bent needle?		
H6	Was a breakage of the device observed?[d]		
H7	Was the swallowing of material debris observed?[c]		
H8	Was any other problem observed?[c]		
H9	Was less than the full dose administered?[e]		

[a] The following potential hazards were not included since these are not observable during self-injection observation: microbiological contamination, wrong drug, transfer of transmissible diseases

[b] Excluding the actual injection into the appropriate injection site of the body

[c] If yes, then it should be specified

[d] If yes, then it should be specified under which circumstances breakage occurs and which parts are affected, and any additional problems (e.g., injuries) due to the breakage are to be specified

[e] If yes, then it should be specified why (e.g., leakage from the injection site, early removal)

11. Reference List

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