Title Page

Protocol Title: A Phase III, Open-label, Single-arm, Multiple-dose Study to Evaluate Usability of Subcutaneous Auto-injector of CT-P17 in Patients with Moderate to Severe Active Rheumatoid Arthritis

Protocol Number: CT-P17 3.2

Sponsor Name and Legal Registered Address:
CELLTRION, Inc.

[redacted]

EudraCT Number: 2019-000660-25

Approval Date: 11 November 2019

Date and Version of Previous Protocol: Version 1.0, dated 30 January 2019

Protocol Approval

Study Title	A Phase III, Open-label, Single-arm, Multiple-dose Study to Evaluate Usability of Subcutaneous Auto-injector of CT-P17 in Patients with Moderate to Severe Active Rheumatoid Arthritis
Protocol Number	CT-P17 3.2
Protocol Date	Protocol version 2.0, 11 November 2019

Protocol accepted and approved by:

[redacted]

11 Nov 2019

Date

Declaration of the Investigator

I have read and understood all sections of the protocol entitled "A Phase III, Open-label, Single-arm, Multiple-dose Study to Evaluate Usability of Subcutaneous Auto-injector of CT-P17 in Patients with Moderate to Severe Active Rheumatoid Arthritis" and the accompanying Investigator Brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the protocol version 2.0, dated 11 November 2019, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without Institutional Review Board/Independent Ethics Committee approval except to eliminate an immediate risk to patients. I agree to administer the study drug only to patients under my personal supervision or the supervision of a sub-Investigator.

I will not supply the study 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 clinical 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

Table of Contents

Protocol Approval 2
Table of Contents 4
Protocol Synopsis 8
1 Introduction 14
1.1 Study Rationale 14
1.1.1 Choice of Study Population 14
1.2 Background 14
1.2.1 Rheumatoid Arthritis 14
1.2.2 CT-P17 15
1.2.3 Non-clinical Studies 16
1.2.4 Clinical Studies 16
1.3 Benefit/Risk Assessment 16
2 Objectives and Endpoints 18
3 Study Design 18
3.1 Overall Study Design 18
3.2 Justification for Dose 20
3.3 Study Duration 20
4 Study Population 20
4.1 Inclusion Criteria 21
4.2 Exclusion Criteria 22
4.3 Study Drug Withdrawal/Discontinuation 25
4.3.1 Recruitment of Additional Patients 25
4.4 Premature Termination of the Study 25
5 Study Treatment 26
5.1 CT-P17 26
5.1.1 Medical Devices 26
5.2 Other Treatments Administered 26
5.2.1 Co-administration of Methotrexate and Folic Acid 26
5.2.2 Premedication 27
5.3 Study Drug Administration 27
5.3.1 Training for Self-Injection of Study Drug 27
5.4 Other Supplies 28
5.5 Management of Clinical Supplies 28

5.5.1 Study Drug Handling and Storage 28
5.5.2 Study Drug Accountability 28
5.6 Treatment Compliance 29
5.7 Prior and Concomitant Medications and Therapy 29
5.7.1 Permitted Concomitant Medication and Therapies 30
5.7.2 Prohibited Therapy 30
5.7.3 Rescue Medication 30
5.8 Dose Modification 31
6 Study Procedures and Assessments 31
6.1 Study Procedures 31
6.1.1 Informed Consent and Enrollment 31
6.1.2 Patient Identification Code 31
6.1.3 Patient Diaries 31
6.2 Usability Assessments 32
6.2.1 PRE- and POST-SIAQ 32
6.2.2 Self-Injection Assessment Checklist 33
6.3 Efficacy Assessments 33
6.3.1 Tender Joint Count (68) and Swollen Joint Count (66) 33
6.3.2 Tender and Swollen Joints Count (28) 33
6.3.3 Disease Activity Score Using 28 Joint Counts 33
6.3.4 Patient's Global Assessment of Disease Activity Measured using VAS 33
6.3.5 C-Reactive Protein and Erythrocyte Sedimentation Rate 34
6.4 Safety Assessments 34
6.4.1 Adverse Events 34
6.4.2 Other Safety Assessments 40
6.5 Sample Collections 46
6.5.1 Interferon-γ Release Assay Blood Sampling 46
6.5.2 Routine Safety Blood Sampling 46
6.6 Labeling of Samples 46
7 Statistical Analysis Plan 46
7.1 Populations for Analyses 47
7.2 Usability Analysis 47
7.2.1 Primary Usability Endpoint 47
7.2.2 PRE- and POST- SIAQ 47
7.3 Secondary Usability Endpoints 47
7.3.1 PRE- and POST- SIAQ 47
7.3.2 Observer Rating of Successful Self-Injection Using Self-Injection Assessment Checklist 48

7.4 Efficacy Analysis 48
7.4.1 DAS28 (CRP) and DAS28 (ESR) 48
7.5 Safety Analyses 48
7.5.1 Demographic, Baseline, and Background Characteristics 48
7.5.2 Adverse Events 49
7.5.3 Clinical Laboratory Analyses, IGRA and Pregnancy 49
7.5.4 Electrocardiogram, Physical Examination, and Vital Signs 49
7.5.5 Prior and Concomitant Medications 49
7.5.6 Other Safety Analyses 49
7.6 Interim Analyses 49
7.7 Handling of Missing, Unused, and Spurious Data 49
7.8 Sample Size Determination 49
8 Supporting Documentation and Operational Considerations 50
8.1 Regulatory, Ethical, and Study Oversight Considerations 50
8.1.1 Regulatory and Ethical Considerations 50
8.1.2 Financial Disclosure 50
8.1.3 Informed Consent Process 50
8.1.4 Data Protection 51
8.1.5 Dissemination of Clinical Study Data 51
8.1.6 Data Quality Assurance 52
8.1.7 Source Documents 53
8.1.8 Study and Site Closure 53
8.1.9 Publication Policy 53
8.1.10 Study Administration 54
8.1.11 Protocol Approval and Amendment and Protocol Deviations 54
8.1.12 Access to Source Data 55
9 Appendices 56
9.1 Appendix 1: Abbreviations 56
9.2 Appendix 2: Schedule of Activities (SoA) 58
9.3 Appendix 3: Self-Injection Checklist 61
9.4 Appendix 4: Self-Injection Assessment Questionnaire 62
10 References 71

List of Tables

Table 1: Details of CT-P17 26
Table 2: Clinical Laboratory Tests 43

Table 3: Eligibility Based on Serologic Markers for Hepatitis B Infection 44

Table 4: Personnel and Organizations Responsible for Study Conduct 54

Table 5: Schedule of Activities 58

List of Figures

Figure 1: Study Design Overview 20

Protocol Synopsis

Protocol Number: CT-P17 3.2

Title: A Phase III, Open-label, Single-arm, Multiple-dose Study to Evaluate Usability of Subcutaneous Auto-injector of CT-P17 in Patients with Moderate to Severe Active Rheumatoid Arthritis

Study Phase: Phase III

Study Centers: Approximately 5 study centers in approximately one country

Test Investigational Drug, Dose and Regimen: CT-P17, 40 mg/0.4 mL (100 mg/mL) by subcutaneous (SC) injection via auto-injector (AI) every other week (EOW) from Week 0 to Week 24, co-administered with methotrexate (MTX) (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or intramuscular [IM], dose and route must be maintained from Screening to end-of-study [EOS]/early discontinuation [ED]) and folic acid (≥5 mg/week, oral).

Objectives:

Primary Objective

- To evaluate usability of CT-P17 AI assessed by patients at Week 4.

Secondary Objectives

- To evaluate change in usability assessed by patients and observer over time up to Week 24.
- To evaluate overall safety and efficacy.

Main selection criteria: Male or female patients with moderate to severe active rheumatoid arthritis (RA) diagnosed according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria, despite ongoing treatment with MTX over at least 12 weeks, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

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

1. Male or female patient between 18 to 70 years of age, inclusive.
2. Patient must be able and willing to self-administer subcutaneous (SC) injections via auto-injector (AI).
3. Patient with a diagnosis of rheumatoid arthritis (RA) according to the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for at least 24 weeks prior to the first administration of the study drug (Day 1).
4. Patient who has active disease as defined by the presence of 6 or more swollen joints (of 66 assessed), 6 or more tender joints (of 68 assessed) and either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a serum C-reactive protein (CRP) concentration >1.0 mg/dL (>10 mg/L) at Screening.
5. Patient who has been receiving oral or intramuscular (IM) methotrexate (MTX) at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, for at least 12 weeks and who has been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug (Day 1).
6. 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) (Système International d'Unités [SI] units: 0.84 mL/second).
    - Serum alanine aminotransferase ≤3.0 × ULN.
    - Serum aspartate aminotransferase ≤3.0 × ULN.
    - Serum total bilirubin ≤1.5 × ULN.
7. Patient has the following hematology laboratory test results at Screening:
    - Hemoglobin >8.0 g/dL (SI units: >80 g/L or 4.96 mmol/L).
    - Absolute neutrophil count ≥1.5 × 10^3 cells/µL (SI units: ≥1.5 × 10^9 cells/L).
    - Platelet count ≥75 × 10^3 cells/µL (SI units: ≥75 × 10^9 cells/L).

8. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side-effects, has the ability to cooperate with the Investigator and is given ample time and opportunity to read and understand verbal and/or written instructions, and signs the written informed consent form (ICF) with date prior to participation in the study.
9. Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 6 months after the last dose of the study drug. Examples include the following:
    - Hormonal contraceptives (combined or progestogen-only) associated with inhibition of ovulation.
    - Intrauterine devices.
    - Sexual abstinence (not periodically, but for the entire period of risk associated with the study drug).

    A man or woman is of childbearing potential if, in the opinion of the Investigator, he or she is biologically capable of having children and is sexually active. Male and female patients and their partners who have been surgically sterilized for less than 24 weeks 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 1 year prior to the date of informed consent to be classified as not of childbearing potential.

Exclusion Criteria:

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

1. Patient who has previously received or plans to receive investigational or licensed product; biologic or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or a tumor necrosis factor (TNF) α inhibitor for any purposes.
2. Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products.
3. Patient who has previous or current use of other SC self-injected drugs (e.g., insulin, MTX).
4. Patient who currently has, or has a history of, any of the following infections:
    - A known infection with hepatitis B (active or carrier of hepatitis B [HBV]), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past HBV is allowed if resolved. Patient will be enrolled based on HBV infection eligibility criteria, specified in Section 6.4.2.8.
    - Hospitalization for treatment of infection within 24 weeks prior to the first administration of the study drug (Day 1).
    - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1).
    - Symptomatic or recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1).
    - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.
5. Patient is ineligible according to the following tuberculosis (TB) screening criteria:
    - Patient who has a history or a current diagnosis of active TB. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.
    - Patient who has had exposure to a person with active TB such as first-degree family members or co-workers.
    - 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 previous diagnosis of latent TB cannot be enrolled despite sufficient documentation of completed TB prophylaxis. 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 indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study.

6. Patient who has current signs or symptoms of liver or renal insufficiency or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances that are severe, progressive, or uncontrolled. Including one or more of the following:
    - Classified as Class II or III obese by World Health Organization classification (body mass index ≥35 kg/m^2).
    - Uncontrolled diabetes mellitus, even after an appropriate treatment.
    - Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥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 the study drug.
    - Significant systemic RA involvement (e.g., Sjögren's syndrome, vasculitis, pulmonary fibrosis), which would put the patient at risk if they are enrolled.
    - A known malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except completely excised and cured squamous carcinoma *in situ* of the uterine cervix *in situ*, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
    - 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 24 weeks prior to the first administration of the study drug (Day 1).
    - History of organ transplantation, including corneal graft/transplantation.
    - Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
    - Any clinically significant respiratory disease, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion.
    - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome.
    - Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) if it could interfere with the Investigator's assessment on disease activity scores (DAS) including joint counts.
    - Any other serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results.
    - History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the Investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion.
7. Patient who has received or plans to receive any of the following prohibited medications or treatment:
    - Intra-articular (IA) corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1). A patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and non-steroidal anti-inflammatory drugs (NSAIDs), if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1). In addition, a patient is permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations as per the instructions on the product label.
    - Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days; must wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug (Day 1).
    - Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer.
    - Alkylating agents within 1 year prior to the first administration of the study drug (Day 1).
    - Traditional Chinese medicine within 4 weeks prior to the first administration of the study drug (Day 1).

- A vaccination (live or live-attenuated) within 4 weeks prior to enrollment or Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to enrollment, or a live or attenuated vaccination planned during the course of the study.
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 1).

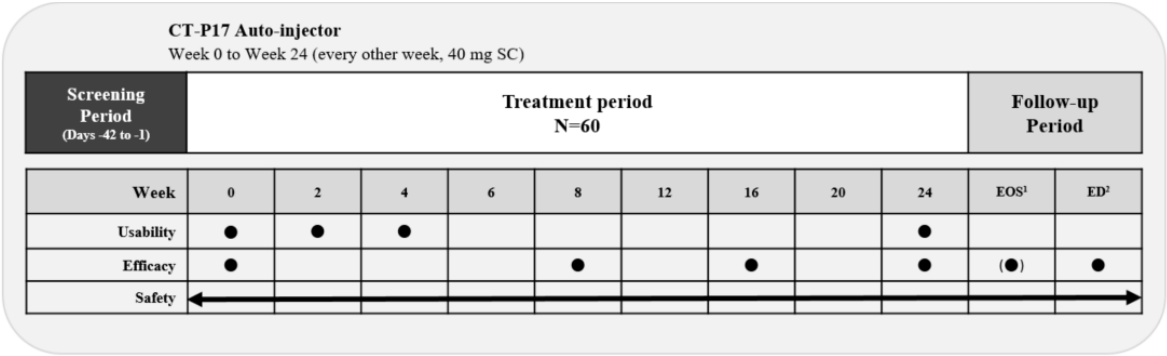
8. Severe physical incapacitation (severely limited in ability to perform routine self-care, has RA ACR global functional status Class IV, or who cannot benefit from medication).
9. Female patient who is currently pregnant or breastfeeding or plans to become pregnant or breastfeed within 6 months after the last dose of study drug.
10. Patient who has current drug or alcohol abuse or dependence, or a history of alcohol or drug abuse within 2 years from the first administration of the study drug (Day 1).
11. Patient who, in the opinion of their general practitioner or the Investigator, should not participate in the study.

Study Design:

This study is a Phase III, open-label, single-arm, multiple-dose study designed to evaluate usability, safety and efficacy of SC AI of CT-P17 (the study drug) in patients with moderate to severe active RA. The study drug will be administered EOW by SC injection via AI from Week 0 to Week 24 in combination with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or IM) and folic acid (≥5 mg/week, oral). The MTX dose and route must be maintained from Screening to EOS/ED visit. Approximately 60 male or female adult patients with moderate to severe active RA will be enrolled.

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

Figure S1: Study Design Overview



Abbreviations: AI=auto-injector; EOS=end-of-study; ED=early discontinuation; N=number of patients; RA=rheumatoid arthritis; SC=subcutaneous.

Note: The investigator or designated study center staff will instruct the patients on the proper administration of CT-P17 via the AI prior to the first self-injection at Week 0. Thereafter, patients will self-inject the study drug at the study center during their scheduled visits under the Investigator or designated study center staff's supervision. Patients will also self-inject the study drug at home at Weeks 10, 14, 18 and 22 according to the treatment schedule.

[1] The EOS assessments need to be completed after 4 weeks from when the last dose (at Week 24) is received or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.

[2] The ED visit needs to be completed after 4 weeks from when the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.

Study Schedule: There will be 3 study periods in the study: Screening Period, Treatment Period, and Follow-up Period.

Screening Period (6 weeks):

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

Treatment Period (24 weeks):

Treatment Period will be from Week 0 to Week 24.

On Day 1 (Week 0), patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. The patients will receive CT-P17 from Week 0 to Week 24 EOW by SC injection via AI, co-administered with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or IM, dose and route must be maintained from Screening to EOS/ED) and folic acid (≥5 mg/week, oral). Patients will comply with all appropriate visits and assessments.

The investigator or designated study center staff will instruct the patients on the proper administration of CT-P17 via the AI prior to the first self-injection on Day 1 (Week 0) visit. Thereafter, patients will self-inject the study drug at the study center during their scheduled visits under the Investigator or designated study center staff's supervision. Patients will also self-inject the study drug at home at Weeks 10, 14, 18 and 22 according to the treatment schedule.

All patients will return to the study center in regular scheduled time intervals for usability and clinical assessments and blood sampling. At each visit, the patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB).

Follow-up Period (4 weeks):

An EOS visit will occur after 4 weeks from when the last dose of study drug is received (at Week 24) or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.

An ED visit will occur after 4 weeks from when the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.

Usability Assessments:

Primary Endpoint

- The usability as assessed by patients rating using PRE- and POST-Self-Injection Assessment Questionnaire (SIAQ) at Week 4.

Secondary Endpoints

- The usability as assessed by patients rating using PRE- and POST-SIAQ at Weeks 0, 2 and 24.
- The observer rating of successful self-injection using self-injection assessment checklist at Weeks 0, 2, 4 and 24.

Efficacy Assessment:

Secondary Endpoint

- Mean change from baseline in disease activity score (DAS)28 (C-reactive protein [CRP]) and DAS28 (erythrocyte sedimentation rate [ESR]) up to Week 24.

Safety Assessments:

Safety Endpoints

Adverse events (including serious AEs [SAEs]), AEs of special interest (AESI) (injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies), hypersensitivity monitoring (via monitoring of vital signs), vital signs measurements, ECGs, physical examination findings, interferon-γ release assay (IGRA), chest X-ray, pregnancy testing, clinical laboratory analyses, signs and symptoms of tuberculosis (TB), and prior and concomitant medications monitored throughout the study. Hepatitis B, hepatitis C, and HIV status will be tested for the patient's eligibility determination.

Sample Size:

Approximately 60 male or female adult patients will be enrolled. In this usability study, a sample size justification based on a formal statistical hypothesis is not relevant, since a formal statistical inference will not be made.

Statistical Analysis:

The statistical analysis will be performed using SAS software Version 9.3 or later (SAS Institute, Inc., Cary, North Carolina). The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to database lock. The data documented in this study and the clinical parameters measured will be described using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for quantitative variables and frequency counts and percentages for qualitative variables.

For purposes of analysis, the following analysis populations are defined:

- *Intent-to-treat (ITT) Population:* The ITT Population includes all enrolled patients to receive a dose of study drug, regardless of whether or not any study drug dosing was completed.

- *Usability Population:* The Usability Population includes all patients in the Safety Population who have evaluable usability measurements at Week 4 and who do not have major deviations that may affect the interpretation of study result. The major protocol deviations will be discussed during the data review meeting and the details of protocol deviations will be defined in the SAP.
- *Safety Population:* The Safety Population includes all patients who receive at least 1 dose (full or partial) of study drug.

Usability Analysis

The primary and secondary usability endpoints will be summarized using the ITT and Usability Population. The following parameters will be summarized: usability of AI assessed by patient using PRE- and POST-SIAQ and assessed by observer rating of successful self-injection using self-injection assessment checklist.

Efficacy Analysis

The efficacy endpoint will be summarized using the ITT Population. The following parameters will be summarized using descriptive statistics: actual value and change from baseline of DAS28 (CRP) and DAS28 (ESR).

Safety Analysis

The safety analysis will be performed on the Safety Population. Adverse events will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and will be coded to system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

1 Introduction

1.1 Study Rationale

CT-P17 is currently being developed by CELLTRION, Inc. (hereafter referred to as the Sponsor) and is intended to be developed as a biosimilar to Humira.

The access to biologicals such as the original product, Humira, is limited in many countries because of the high costs of the treatment, owing to the complex development and manufacturing processes involved in its production. The availability of biosimilar products provides more affordable alternative treatments to patients with rheumatoid arthritis (RA).

Subcutaneous (SC) injection of drugs offers patients the option to self-administer and likely to provide a better treatment experience for them[1]. Removing the need to attend a clinic or hospital for regular injections also brings economic benefits to both the patient and healthcare system[1]. Psychological and social barriers such as injection anxiety, lack of confidence in giving a self-injection, and potential embarrassment associated with self-injecting in public can become problematic in-patient groups that self-inject[1]. There is a need to assess the patients' experience with self-injection and gauge their success in giving self-injections and likelihood of them adhering to self-injection regimen[1].

The purpose of this Phase III study is to evaluate the usability of CT-P17 auto-injector (AI) assessed by patients and observers following the recommendations of the guidance for industry, "Rheumatoid Arthritis: Developing Drug Products for Treatment"[2]. For products intended for self-administration by an RA patient, the device should be durable, and the dexterity and visual acuity required to use the device should be within the capacity of RA patients[2]. In addition, the safety and efficacy of CT-P17 will also be assessed.

1.1.1 Choice of Study Population

International regulations[3,4,5] suggest that proposed biosimilars should be tested in a population representative of approved therapeutic indications of the original product and sufficiently sensitive for detecting potential differences between the biosimilar and the original product.

Consequently, RA has been selected as indication for the CT-P17 3.1 pivotal study (a randomized, active-controlled, double-blind study to compare efficacy and safety of CT-P17 with European Union [EU] approved Humira when co-administered with methotrexate [MTX] in patients with moderate to severe active RA), due to the relatively high magnitude of the treatment effect and immunogenicity rates observed in the Humira clinical studies in this indication.

This study is designed to take into consideration the characteristic of the RA population and their use environment in AI device use by assessing whether usability is within the capability of RA patients[2].

1.2 Background

1.2.1 Rheumatoid Arthritis

Rheumatoid arthritis is the most common autoimmune inflammatory arthritis in adults, occurring in approximately 0.8% of the global population[6,7]. It is characterized by a progressive inflammatory synovitis of the joints, which may result in irreversible joint erosion from as early as 6 months of disease onset[8]. It has a significant negative impact on the

ability to perform daily activities and health related quality of life, and it increases mortality[6]. Therefore, early identification and appropriate treatment should be the primary focus when managing patients with RA to reduce disease progression and loss of function.

Standard anti-rheumatic therapy for RA usually consists of traditional/conventional disease-modifying anti-rheumatic drug (DMARD), low dose corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and analgesics[9]. Methotrexate, a DMARD, has been shown to improve the signs and symptoms of RA and slow the progression of joint destruction in some patients; however, many patients fail to achieve an adequate or sustained response to MTX therapy or even when the patients respond to MTX therapy, patients experience less than 50% improvement[6,10,11].

The proinflammatory cytokine tumor necrosis factor (TNF) α plays a critical role in the pathogenesis of RA and, as such, is a key target for directed biologic therapy[9]. Among its diverse pathologic effects, TNF α induces the production of other proinflammatory cytokines; stimulates endothelial cells to express adhesion molecules that attract leukocytes into affected joints; increases the rate of synthesis of metalloproteinases by synovial macrophages, fibroblasts, osteoclasts, and chondrocytes; and inhibits the synthesis of proteoglycans in cartilage[10]. In recent years, TNF inhibitor biologic agents like adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab and non-TNF biologic agents like abatacept, rituximab, or tocilizumab have been developed for use in RA. Biological DMARDs, such as TNF inhibitors, are recommended when disease activity remains moderate or high despite DMARD monotherapy[7].

Adalimumab, a novel biologic DMARD and the first fully human anti-TNF α monoclonal antibody for RA treatment, has been shown to be effective in the treatment of RA. Adalimumab is structurally and functionally analogous to naturally occurring human immunoglobulin (Ig) G1 and demonstrates a high specificity and affinity for TNF. It does not bind other cytokines such as lymphotoxin[11]. Adalimumab also lyses surface TNF expressing cells *in vitro* in the presence of complement[12]. It is superior to MTX alone in reducing disease activity, arresting structural damage, and decreasing disability over 2 years in patients with RA[13].

1.2.2 CT-P17

CT-P17, containing the active ingredient adalimumab, is a recombinant human monoclonal antibody that is being developed as a similar biological medicinal product to the original product, Humira. The original product was approved in the United States (US) in December 2002 and in the EU in September 2003[14,15,16]. In the EU, Humira is indicated for the following conditions: RA, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis, enthesitis-related arthritis), axial spondyloarthritis (ankylosing spondylitis [AS], axial spondyloarthritis without radiographic evidence of AS), psoriatic arthritis, psoriasis, pediatric plaque psoriasis, hidradenitis suppurativa, Crohn's disease, pediatric Crohn's disease, ulcerative colitis, uveitis and pediatric uveitis; in the US, Humira is indicated for the same conditions except axial spondyloarthritis without radiographic evidence of AS, and pediatric plaque psoriasis[12,16].

CT-P17 is manufactured using a Chinese Hamster Ovary cell line by fed-batch cell culture, followed by harvest, purification, formulation, and subsequent fill-finish operations. The primary amino acid sequences of adalimumab in CT-P17 are identical to that of Humira. Like Humira, CT-P17 will be supplied in a pre-filled syringe (PFS) and AI at a concentration of 100 mg/mL as a clear to opalescent and colorless to brown solution for SC administration.

The CT-P17 will have the same pharmaceutical form and strength as Humira and is intended to have a highly similar quality profile as Humira.

The Sponsor plans to seek approval for all indications for which the innovator product has been approved by demonstrating similarity of CT-P17 with the original product through an extensive array of quality, non-clinical, and clinical comparability assessments.

A detailed description of the chemistry, pharmacology, efficacy, and safety of Humira and further details on CT-P17 are provided in the Investigator Brochure (IB).

1.2.3 Non-clinical Studies

Detailed information regarding the non-clinical pharmacology and toxicology of CT-P17 can be found in the IB.

1.2.4 Clinical Studies

The usability of adalimumab in RA was assessed in a Phase II multicenter, open-label, single-arm, sequential study. The TOUCH study which assessed tolerability and preference of an AI versus a PFS in patients with RA showed that the AI was generally well-tolerated without any new safety signals[17]. A total of 52 patients were enrolled and self-administered adalimumab at each of 3 monitored clinical visits. The first dose was self-administered via the PFS. The second and third doses were self-administered via the AI. The approved adalimumab dose of 40 mg every other week (EOW) was administered. The study demonstrated that patients preferred AI to the PFS, as they found it to be easier to use and more convenient, it had improved safety protection features, and required less time to inject.

There are 4 clinical studies with CT-P17 that are planned or ongoing. Study CT-P17 1.1 is a planned randomized, double-blind, single-dose study to compare the pharmacokinetic (PK) and safety of CT-P17, US-licensed Humira and EU-approved Humira in healthy subjects. Study CT-P17 1.3 is a planned randomized, open-label, 2-arm, parallel group, single-dose study to compare the PK and safety of the AI and PFS in healthy subjects. One Phase III and one Phase I study are ongoing; Study CT-P17 3.1 (see Section 1.1.1) and Study CT-P17 1.2. Study CT-P17 1.2 is a randomized, double-blind, single-dose study to evaluate the safety and PK of CT-P17 and EU-approved Humira in healthy male subjects. Results up to Day 29 showed that CT-P17 and EU-approved Humira were safe and well-tolerated in the healthy male subjects, and the PK result (maximum serum concentration [C_{max}]) of CT-P17 obtained from this study was comparable to that of EU-approved Humira.

1.3 Benefit/Risk Assessment

The CT-P17 will have the same pharmaceutical form and strength as the Humira (40 mg/0.4 mL). The proposed dosing regimen is in line with the approved labeling for Humira[12,16].

The proposed safety monitoring, which includes monitoring the use of the AI, is deemed to be sufficient to monitor potential risks of CT-P17 SC administration by the AI. In view of the structural, biological, and toxicological similarity to Humira, CT-P17 is expected to display a similar safety profile. Humira has been studied extensively and has been shown to be effective at reducing symptoms in patients with inflammatory conditions[12,14]. CT-P17 will be evaluated at the same 40 mg dosage, SC administration route, and EOW dosing schedule as approved for Humira, the original product.

Based upon the clinical evidence (Section 1.2.4) as well as the proven safety profile of Humira, the benefits of the conduct of this proposed clinical study outweigh the associated risks.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of adalimumab are found in the IB.

2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate usability of CT-P17 AI assessed by patients at Week 4.	The usability as assessed by patients rating using PRE- and POST-Self-Injection Assessment Questionnaire (SIAQ) at Week 4.
Secondary	
To evaluate change in usability assessed by patients and observer over time up to Week 24.	The usability as assessed by patients rating using PRE- and POST-SIAQ at Weeks 0, 2 and 24. The observer rating of successful self-injection using self-injection assessment checklist at Weeks 0, 2, 4 and 24.
To evaluate overall efficacy.	Mean change from baseline in disease activity score (DAS)28 (C-reactive protein [CRP]) and DAS28 (erythrocyte sedimentation rate [ESR]) up to Week 24.
To evaluate overall safety.	Adverse events (AEs) (including serious AEs [SAEs]), AEs of special interest (AESIs) (injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies), hypersensitivity monitoring (via monitoring of vital signs), vital signs measurements, ECGs, physical examination findings, interferon-γ release assay (IGRA), chest X-ray, pregnancy testing, clinical laboratory analyses, signs and symptoms of tuberculosis (TB), and prior and concomitant medications monitored throughout the study. Hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) status will be tested for the patient's eligibility determination.

3 Study Design

3.1 Overall Study Design

This study is a Phase III, open-label, single-arm, multiple-dose study to evaluate usability, safety and efficacy of SC AI of CT-P17 (the study drug) in patients with moderate to severe active RA.

The study drug will be administered EOW by SC injection via AI from Week 0 to Week 24 in combination with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or intramuscular [IM]) and folic acid (≥5 mg/week, oral). The patient must have been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug on Day 1. The same dose and route should be maintained throughout the study.

The study will include a Screening Period (6 weeks), a Treatment Period (24 weeks), and a Follow-up Period (4 weeks).

Screening Period **(6 weeks)**:

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

Treatment Period **(24 weeks)**:

Treatment Period will be from Week 0 to Week 24.

On Day 1 (Week 0), patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled in the study. The patients will receive CT-P17 from Week 0 to Week 24 EOW by SC injection via AI, co-administered with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or IM; dose and route must be maintained from Screening to end-of-study [EOS]/early discontinuation [ED]) and folic acid (≥5 mg/week, oral). Patients will comply with all appropriate visits and assessments.

The investigator or designated study center staff will instruct the patients on the proper administration of CT-P17 via the AI prior to the first self-injection on Day 1 (Week 0) visit. Thereafter, patients will self-inject the study drug at the study center during their scheduled visits under the Investigator or designated study center staff's supervision. Patients will also self-inject the study drug at home at Weeks 10, 14, 18 and 22 according to the treatment schedule.

All patients will return to the study center in regular scheduled time intervals for usability and clinical assessments and blood sampling. At each visit, the patients will be questioned about AEs and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB).

Follow-up Period **(4 weeks)**:

An EOS visit will occur after 4 weeks from when the last dose of study drug is received (at Week 24) or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.

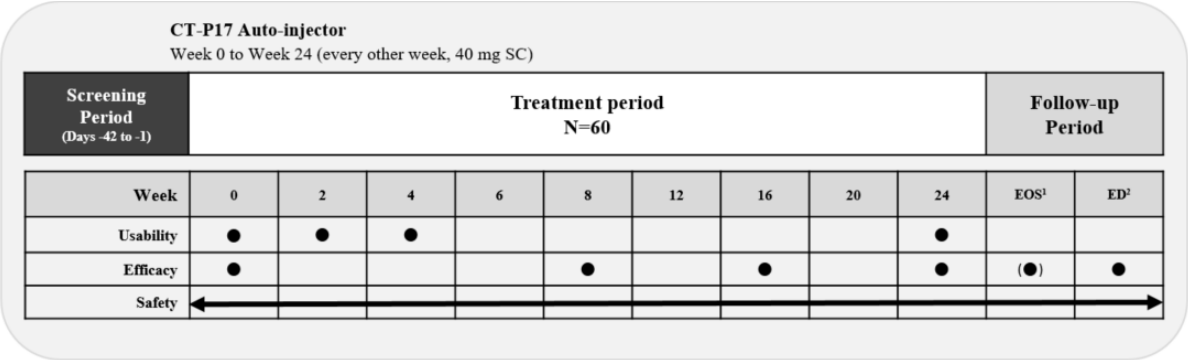
An ED visit will occur after 4 weeks from when the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.

The schedule of activities (SoA) is presented in Table 5.

The Sponsor will not be providing the study drug after the end of the study and the Investigator is responsible for ensuring that consideration for the post-study care of the patient has been given.

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

Figure 1: Study Design Overview



Abbreviations: AI=auto-injector; EOS=end-of-study; ED=early discontinuation; N=number of patients; RA=rheumatoid arthritis; SC=subcutaneous.

Note: The investigator or designated study center staff will instruct the patients on the proper administration of CT-P17 via the AI prior to the first self-injection at Week 0. Thereafter, patients will self-inject the study drug at the study center during their scheduled visits under the Investigator or designated study center staff's supervision. Patients will also self-inject the study drug at home at Weeks 10, 14, 18 and 22 according to the treatment schedule.

[1] The EOS assessments need to be completed after 4 weeks from when the last dose (at Week 24) is received or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.

[2] The ED visit needs to be completed after 4 weeks from when the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.

3.2 Justification for Dose

Humira is supplied in 2 strengths; 50 mg/mL (40 mg/0.8 mL) and 100 mg/mL (40 mg/0.4 mL). The recommended dose of Humira for adult patients with RA is 40 mg of adalimumab administered EOW as a single-dose via SC injection. CT-P17 is being developed to have the same dosage form, route of administration and dosing regimen as the adalimumab (Humira) which is approved in the US and EU. The 40 mg/0.4 mL dose level will be used in this study as the recommended dose in RA treatment.

The doses for MTX and folic acid used in this study are per label instructions for the drugs.

3.3 Study Duration

A patient is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Table 5).

The end of the study is defined as the date of final database lock. An EOS visit will occur 4 weeks after the last dose (at Week 24) is received or prior to the start of new RA therapy, whichever comes earlier.

4 Study Population

Male or female patients between 18 to 70 years of age, inclusive, with moderate to severe active RA diagnosed according to the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria[18] despite previous treatment with MTX (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher

dose, oral or IM) over at least 12 weeks, will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Approximately 60 patients are planned to be enrolled in the study. Only patients with a signed and dated informed consent form (ICF) in compliance with local regulations will be enrolled. Deviations from the inclusion and exclusion criteria could potentially jeopardize the scientific integrity of the study, regulatory acceptability, and, most importantly, patient safety. Therefore, strict adherence to the eligibility criteria as specified in the protocol is essential.

4.1 Inclusion Criteria

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

1. Male or female patient between 18 to 70 years of age, inclusive.
2. Patient must be able and willing to self-administer subcutaneous (SC) injections via auto-injector (AI).
3. Patient with a diagnosis of rheumatoid arthritis (RA) according to the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria[18] for at least 24 weeks prior to the first administration of the study drug (Day 1).
4. Patient who has active disease as defined by the presence of 6 or more swollen joints (of 66 assessed), 6 or more tender joints (of 68 assessed) and either an erythrocyte sedimentation rate (ESR) >28 mm/hour or a serum C-reactive protein (CRP) concentration >1.0 mg/dL (>10 mg/L) at Screening.
5. Patient who has been receiving oral or intramuscular (IM) methotrexate (MTX) at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, for at least 12 weeks and who has been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug (Day 1).
6. 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/minute (by Cockcroft-Gault formula[19]) (Système International d'Unités [SI] units: 0.84 mL/second).
    - Serum alanine aminotransferase ≤3.0 x ULN.
    - Serum aspartate aminotransferase ≤3.0 x ULN.
    - Serum total bilirubin ≤1.5 x ULN.
7. Patient has the following hematology laboratory test results at Screening:
    - Hemoglobin >8.0 g/dL (SI units: >80 g/L or 4.96 mmol/L).
    - Absolute neutrophil count ≥1.5 x 10^3 cells/µL (SI units: ≥1.5 x 10^9 cells/L).
    - Platelet count ≥75 x 10^3 cells/µL (SI units: ≥75 x 10^9 cells/L).
8. Patient (or legal guardian, if applicable) is informed of the full nature and purpose of the study, including possible risks and side-effects, has the ability to cooperate with the Investigator and is given ample time and opportunity to read and understand verbal and/or written instructions, and signs the written informed consent form (ICF) with date prior to participation in the study.
9. Patient and their partner of childbearing potential must agree to use a highly effective method of contraception throughout the study and for 6 months after the last dose of the study drug. Examples include the following:

- Hormonal contraceptives (combined or progestogen-only) associated with inhibition of ovulation
- Intrauterine devices
- Sexual abstinence (not periodically, but for the entire period of risk associated with the study drug)

A man or woman is of childbearing potential if, in the opinion of the Investigator, he or she is biologically capable of having children and is sexually active. Male and female patients and their partners who have been surgically sterilized for less than 24 weeks 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 1 year prior to the date of informed consent to be classified as not of childbearing potential.

4.2 Exclusion Criteria

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

1. Patient who has previously received or plans to receive investigational or licensed product; biologic or targeted synthetic disease-modifying anti-rheumatic drugs (DMARDs) (e.g., tofacitinib, baricitinib) for the treatment of RA and/or a tumor necrosis factor (TNF) α inhibitor for any purposes.
2. Patient who has allergies to any of the excipients of study drug or any other murine and human proteins, or patient with a hypersensitivity to immunoglobulin products.
3. Patient who has previous or current use of other SC self-injected drugs (e.g., insulin, MTX).
4. Patient who currently has, or has a history of, any of the following infections:
    - A known infection with hepatitis B (active or carrier of hepatitis B [HBV]), hepatitis C, or infection with human immunodeficiency virus (HIV). However, a patient with past HBV is allowed if resolved. Patient will be enrolled based on HBV infection eligibility criteria, specified in Section 6.4.2.8.
    - Hospitalization for treatment of infection within 24 weeks prior to the first administration of the study drug (Day 1).
    - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 1).
    - Symptomatic or recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 1).
    - Past or current granulomatous infections or other severe or chronic infections (such as sepsis, abscess, opportunistic infections, or invasive fungal infections such as histoplasmosis). A patient who has a past diagnosis with sufficient documentation of complete resolution of the infection can be enrolled in the study.
5. Patient is ineligible according to the following tuberculosis (TB) screening criteria:

- Patient who has a history or a current diagnosis of active TB. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.
- Patient who has had exposure to a person with active TB such as first-degree family members or co-workers.
- 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 previous diagnosis of latent TB cannot be enrolled despite sufficient documentation of completed TB prophylaxis. 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 indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study.

6. Patient who has current signs or symptoms of liver or renal insufficiency or cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, hematologic, psychiatric, or metabolic disturbances that are severe, progressive, or uncontrolled. Including one or more of the following:
   - Classified as Class II or III obese by World Health Organization classification (body mass index ≥35 kg/m^2).
   - Uncontrolled diabetes mellitus, even after an appropriate treatment.
   - Uncontrolled hypertension (as defined by systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥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 the study drug.
   - Significant systemic RA involvement (e.g., Sjögren's syndrome, vasculitis, pulmonary fibrosis), which would put the patient at risk if they are enrolled.
   - A known malignancy within the previous 5 years prior to the first administration of the study drug (Day 1) except completely excised and cured squamous carcinoma *in situ* of the uterine cervix *in situ*, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
   - 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 24 weeks prior to the first administration of the study drug (Day 1).
   - History of organ transplantation, including corneal graft/transplantation.
   - Hereditary or acquired immunodeficiency disorder, including immunoglobulin deficiency.
   - Any clinically significant respiratory disease, including but not limited to chronic obstructive pulmonary disease, asthma, or pleural effusion.
   - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barre syndrome.

- Any conditions significantly affecting the nervous system (e.g., neuropathic conditions or nervous system damage) if it could interfere with the Investigator's assessment on disease activity scores (DAS) including joint counts.
- Any other serious acute or chronic medical or psychiatric condition that could increase the risk associated with study participation or study drug administration or that could interfere with the interpretation of study results.
- History or evidence of any other clinically significant disorder, condition, or disease that, in the opinion of the Investigator, would pose a risk to patient safety or interfere with the study evaluation, procedures, or completion.

7. Patient who has received or plans to receive any of the following prohibited medications or treatment:
    - Intra-articular (IA) corticosteroids within 4 weeks prior to the first administration of the study drug (Day 1). A patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and non-steroidal anti-inflammatory drugs (NSAIDs), if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1). In addition, a patient is permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations as per the instructions on the product label.
    - Conventional DMARDs, other than MTX, including hydroxychloroquine, chloroquine, or sulfasalazine within 4 weeks prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and had successful chelation with 8 g of cholestyramine (3 times daily) for 11 days; must wait 4 weeks after the last dose of cholestyramine prior to the first administration of the study drug (Day 1). A patient who discontinued leflunomide and did not have cholestyramine washout must wait 12 weeks after the last dose of leflunomide prior to the first administration of the study drug (Day 1).
    - Any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 1) or 5 half-lives, whichever is longer.
    - Alkylating agents within 1 year prior to the first administration of the study drug (Day 1).
    - Traditional Chinese medicine within 4 weeks prior to the first administration of the study drug (Day 1).
    - A vaccination (live or live-attenuated) within 4 weeks prior to enrollment or Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to enrollment, or a live or attenuated vaccination planned during the course of the study.
    - Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug (Day 1).

8. Severe physical incapacitation (severely limited in ability to perform routine self-care, has RA ACR global functional status Class IV[20], or who cannot benefit from medication).
9. Female patient who is currently pregnant or breastfeeding or plans to become pregnant or breastfeed within 6 months after the last dose of the study drug.
10. Patient who has current drug or alcohol abuse or dependence, or a history of alcohol or drug abuse within 2 years from the first administration of the study drug (Day 1).
11. Patient who, in the opinion of their general practitioner or the Investigator, should not participate in the study.

4.3 Study Withdrawal/Study Drug Discontinuation

Patients are free to withdraw from the study at any time for any reason. The Investigator may also discontinue the study drug at any time in the interest of patient safety. The primary reasons for the study withdrawal and the discontinuation of the study drug must be recorded in the patient's source documents and the electronic case report form (eCRF), with any comments (spontaneous or elicited) or complaints made by the patient. Reasons for study drug discontinuation include the following:

- Patient develops signs of disease progression in the judgment of the Investigator.
- Patient withdraws consent or refuses having 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 deviation(s).
- Patient is lost to follow-up.
- Patient dies.
- Study is terminated by the Sponsor.
- Patient is pregnant.
- Investigator's decision.

It is recommended that the Investigator contact the Sponsor or its designee if possible to discuss the particular situation before study withdrawal or study drug discontinuation. All patients who terminate from the study will retain their patient identification code (PIC).

4.3.1 Recruitment of Additional Patients

Patients who receive study drug and discontinue prior to study completion will not be replaced. Patients who failed the Screening, for any reason, can be re-screened only once.

4.4 Premature Termination of the Study

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

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 Treatment

5.1 CT-P17

The study drug administered in this study is CT-P17.

Details of CT-P17 are summarized in Table 1.

Table 1: Details of CT-P17

Study drug Name:	CT-P17.
Dosage Formulation:	Clear to opalescent and colorless to brown solution of adalimumab for subcutaneous (SC) administration, with a pH of approximately 5.2.
Unit Dose Strength(s)/Dosage Level(s):	CT-P17 will be supplied as 40 mg/0.4 mL (100 mg/mL). Each 0.4 mL of CT-P17 contains 40 mg adalimumab, sodium acetate, glycine, and polysorbate 80 with no preservatives.
Route of Administration:	SC injection.
Dosing Instructions:	Every other week (EOW).
Packaging and Labeling:	CT-P17 is supplied as a sterile-use, auto-injector (AI) designed to deliver 0.4 mL (40 mg) of drug product. CT-P17 will be provided in an individual container. Each container will be labeled as required per country requirement.
Manufacturer:	CELLTRION, Inc.
Device:	Auto-Injector (AI).

5.1.1 Medical Devices

The study drug will be administered via an AI provided by the Sponsor. Instructions for use (IFU) and instructions for self-injection of the AI will be provided to each patient and will be included in the study manual provided to all sites.

5.2 Other Treatments Administered

5.2.1 Co-administration of Methotrexate and Folic Acid

All patients will receive MTX and folic acid concomitantly. Patients should have been receiving oral or IM MTX at a dose of between 12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, for at least 12 weeks and have been on a stable dose and route of MTX for at least 4 weeks prior to the first administration of the study drug (Day 1). The same dose and route should be maintained throughout the study. However, the dose of MTX may be reduced for reasons of documented intolerance to MTX (e.g., hepatic or hematologic toxicity or per local requirement).

Patients are required to take folic acid (≥5 mg/week, oral dose) throughout the duration of the study to minimize or prevent AEs related to MTX side-effects[21].

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

5.2.2 Premedication

Patient may also be pre-medicated 30 to 60 minutes prior to the study drug administration for hypersensitivity/allergic reactions and any pre-medications (such as but not limited to antihistamine or paracetamol) can be given at the Investigator's discretion.

5.3 Study Drug Administration

Patients enrolled in the study will receive study drug and only authorized site staff may supply study drugs. The study drug will be self-injected at the study center under the Investigator or designee's supervision.

A fixed dose of the study drug (40 mg) will be administered EOW by SC injection via AI from Week 0 to Week 24 at the study center, under the Investigator or designee's supervision. At Weeks 10, 14, 18 and 22, patients will self-inject at home according to the SoA (Table 5).

For each new injection, a different injection site will be used (e.g., injection site should be rotated). Sites for injection may either be the front of the patient's thighs or lower abdomen (except for the 5 cm around the patient's navel). 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 injection site.

Where the study drug injection is scheduled for the same day as a clinic visit, the visit procedures for the study must be completed before study drug administration and the self-injection must be performed under the supervision of the Investigator or designee.

5.3.1 Training for Self-Injection of Study Drug

The Investigator or designee must have completed training on the self-injection technique before training patients. This training must be documented. Detailed training instructions will be provided in the study manual. After completing their own training, the investigator or designated study center staff will then instruct the patients on the proper administration of the study drug via the AI prior to self-injection on Day 1 (Week 0). Printed IFU and instructions for self-injection of the AI will be provided to each patient. Patients must self-inject at the study center during their visits under the Investigator or designee's supervision to be assessed for their ability of self-administration. The training and performance of self-injection will be documented in the patient's source documents.

If the patient requests it, additional training can be provided during the visits to the study center. Patients will be instructed to contact the Investigator promptly in the event of any signs and symptoms of injection site reactions, hypersensitivity/allergic reactions and anaphylactic reactions when they self-inject at home.

5.4 Other Supplies

As discussed in Section 5.3.1, printed IFU and instructions for self-injection of the AI will be provided to the patients that will serve as their guide while administering the study drug at home.

The following will also be provided to the patient as a combined document form when the Investigator considers the patient eligible for self-injection at home:

- Patient self-injection paper diary to record treatment compliance (see Sections 5.6 and 6.1.3 for details).
- Patient self-reporting of AE paper diary to record any AE including injection site reactions (see Sections 6.1.3 and 6.4.1.4 for details).
- A sharps bin to store used AI. The sharps bin with the used AI will be returned to the study center for disposal.

In addition, a patient card which includes important safety risk and contact information for medical emergency will be provided.

5.5 Management of Clinical Supplies

5.5.1 Study Drug Handling and Storage

The Investigator or designee must maintain a log to confirm appropriate temperature conditions have been maintained during transit for all study drugs received and any discrepancies are reported and resolved before use of the study drugs. All study drugs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. The study drug must be dispensed only at the study center.

The study drug must be kept at a controlled refrigerated temperature between 2°C (36°F) and 8°C (46°F). The study drug must not be frozen: thawed (i.e., previously frozen) study drug must not be used. The study drug must be stored in the original carton until the time of administration to protect from light.

A single study drug AI may be stored at room temperatures of up to a maximum of 25°C (77°F) for a period of up to 14 days. The AI must be protected from light and discarded if not used within the 14-day period. Used AI should be stored in a sharps bin and disposed of via standard procedures.

5.5.2 Study Drug Accountability

The Investigator will maintain records that the study drug was received, including the date received, drug identity code, date of manufacture or expiration date, amount received, and disposition. In addition, records will be maintained that include the PIC, dispensation date, and amount dispensed.

All remaining partially used and/or unused study drug will be returned to the Sponsor or its designee after study completion/termination or destroyed with the permission of the Sponsor in accordance with applicable laws and study center procedures. The used AI can only be destroyed locally if it is written in local standard operating procedures and a specific authorization is given by the Sponsor, which is required prior to study drug administration. Permission will be granted by the Sponsor on a study center-by-study center basis after reviewing the study center destruction policy. The list of destroyed AI 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 the Sponsor.

This is an open-label, single-arm study and patients will not be randomized to treatment. Each eligible patient with a signed ICF, will be assigned a PIC by the Sponsor.

5.6 Treatment Compliance

Patient compliance with the treatment regimen will be monitored by completion of a patient self-injection paper diary detailing the time and date of self-administration of the study drug at home at Weeks 10, 14, 18, and 22. All patients must record study drug administration details in their patient self-injection paper diary for the self-injections performed at home. The study drug container labels from all home injections should be returned and any unused study drug must be accounted for by the patient.

Patients must be instructed to write the date of each injection on the study drug container and to bring all used and dated study drug container labels at each visit for the evaluation of compliance.

Drug accountability details are provided in Section 5.5.2.

If the patient forgets to self-inject the study drug, the patient should inject the dose of study drug as soon as they remember it and contact the Investigator or designated staff to inform the delay in injection and reschedule the next study center visit. The next dosing schedule should be readjusted to every 2 weeks from the time of last study drug administration. Administration of co-administered treatments (MTX and folic acid) will be recorded throughout the study.

5.7 Prior and Concomitant Medications and Therapy

Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS/ED visit, will be recorded in the patient's source documents and the eCRF. Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug until the EOS/ED visit, will be recorded in the patient's source documents and the eCRF. However, in order to check eligibility, prior medications will be reviewed from date specified in exclusion criteria #7 (Section 4.2). This will include all prescription drugs, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's source documents and the eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the Investigator. Local standard of care practices and regulations for the indications being treated must be followed for any allowed concomitant medications. It is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the patient's source documents and the eCRF.

The Sponsor Medical Monitor or its designee should be contacted if there are any questions regarding concomitant or prior medications.

5.7.1 Permitted Concomitant Medication and Therapies

Aside from MTX and folic acid, which should be administered throughout the study as described in Section 5.2.1, a patient is permitted to receive either oral or parenteral glucocorticoids (≤10 mg daily of prednisone/prednisolone or equivalent) and NSAIDs, if they have received a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 1). In addition, the same dose must be maintained until the EOS/ED visit. If there are any changes needed in the dose during the study, they should be reported to and discussed with the Sponsor Medical Monitor or its designee in advance. In addition, patients are permitted to receive low-potency topical, otic, and ophthalmic glucocorticoid preparations provided as per the instructions on the product label.

Killed vaccinations are acceptable during the study.

5.7.2 Prohibited Therapy

Concomitant medications, treatments and procedures not allowed during the study are:

- Intra-articular corticosteroids are discouraged throughout the study; however, limited use of IA corticosteroids may be allowed as treatment for severe RA flares. No more than 1 injection to 1 joint should be injected throughout the study. The injected joint must be considered a non-responder joint during the response evaluation.
- Any conventional DMARDs other than MTX (including but not limited to hydroxychloroquine, leflunomide, sulphasalazine, minocycline, ciclosporin, azathioprine)
- Any other investigational device or medical product
- Alkylating agents
- Traditional Chinese medicine
- Live or live-attenuated vaccines
- Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement)
- Any biologic agent (e.g., TNF inhibitors such as adalimumab, etanercept, infliximab, certolizumab pegol, golimumab or non-TNF inhibitors such as abatacept, rituximab, tocilizumab and belimumab or targeted synthetic DMARDs such as tofacitinib, baricitinib or any anti-rheumatic investigational compounds)
- Narcotic analgesics (except tramadol)

5.7.3 Rescue Medication

Rescue medication is any medication that is used to treat RA in addition to the study drug. The Sponsor will not supply any rescue medication. Acetaminophen/paracetamol and/or tramadol are allowed as rescue medication, but the medication should be stopped at least 24 hours prior to each joint evaluation. However, other narcotic analgesics are not permitted for use. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

The Investigator should contact the Medical Monitor if at any time, a patient needs rescue medication. If necessary, patient's eligibility for continuation of the study drug administration will be determined. If the patient is no longer eligible to continue with the study drug, they should undergo the ED assessments listed in the SoA (Table 5).

5.8 Dose Modification

No dose adjustment of the study drug is allowed during the study. MTX dose may be reduced for reasons of documented intolerance to MTX (e.g., hepatic or hematologic toxicity or per local requirement). The folic acid dose can be increased to counteract the side-effects of MTX (which include nausea, mucositis and headache) as needed. Any dose modifications, and reasons, should be recorded in the patient's source documents and the eCRF.

6 Study Procedures and Assessments

- Study procedures and their timing are summarized in the SoA (Table 5).
- Adherence to the study design requirements, including those specified in the SoA (Table 5), is essential and required for study conduct.

- All Screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for Screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 5).
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

6.1 Study Procedures

6.1.1 Informed Consent and Enrollment

Any patient who provides informed consent (i.e., signs and dates the ICF and assent form, if applicable) is considered a study patient and enrolled in the study. Patients will have the opportunity to have any questions answered prior to signing the ICF. The Investigator must address all questions raised by the patient. The Investigator will also sign the ICF.

6.1.2 Patient Identification Code

Each patient will be assigned a PIC produced by the Sponsor.

All study documents (e.g., eCRFs, clinical documentation, sample containers, drug accountability logs, etc.) will be identified with the PIC.

6.1.3 Patient Diaries

A patient self-injection paper diary will be provided to each patient on Day 1 (Week 0) to record study drug administration performed at home with the following information:

- Study drug administration details such as:
    - Date
    - Time
    - Site of injection
    - Used AI kit information
    - Injection completion status

In addition, patients will also be provided with a patient self-reporting of AE paper diary to record any AEs experienced outside of the study center, including injection site reactions, hypersensitivity/allergic reactions and anaphylactic reactions.

Patients will be trained on use of the patient diaries. The patient diaries will remain with the patient for the duration of the study. The Investigator will review the patient diaries for completeness and request missing information periodically and in a timely manner. Untoward events recorded in the patient diaries will be reported as AEs according to the Investigator's discretion and clinical judgment.

The patient diaries will serve as source documents and remain at the study center at the end of the study. Entries in the patient diaries will be transferred into the appropriate collection device. Any entry in the eCRF that does not correspond with an entry in the patient diaries will be explained by the Investigator in the source documentation.

6.2 Usability Assessments

Usability will be assessed by the evaluation of the patient rating using PRE- and POST-Self-Injection Assessment Questionnaire (SIAQ) and the observer rating of successful self-injection using self-injection assessment checklist at the time points specified in the SoA (Table 5).

6.2.1 PRE- and POST-SIAQ

PRE- and POST-SIAQ will be assessed at the visits specified in SoA (Table 5).

The primary outcome measure is the usability of the study drug as assessed by the patient rating on the PRE- and POST-SIAQ modules at Week 4. PRE- and POST-SIAQ will be completed by the patient prior to and after self-injection of the study drug SC via AI. Patients will complete PRE-SIAQ immediately before the administration of study drug and POST-SIAQ within 20 to 40 minutes after the administration of study drug. This assessment should be recorded in the patient's source documents and the eCRF.

The SIAQ assesses the perceived advantages of self-injection and potential a barrier to self-injection, including psychological barriers, social barriers, and physical barriers, as well as satisfaction with self-injection and willingness to continue the treatment with self-injection[1]. The PRE-SIAQ module is a 7-item questionnaire that investigates feelings about injections, self-confidence (regarding self-administration), and satisfaction with self-injection (each item graded on a 5-point scale). The POST-SIAQ module is a 27-item questionnaire that assesses feelings about injections, self-image, self-confidence (regarding self-administration), pain and skin reactions during or after the injection site reactions, ease of use of the self-injection device, and satisfaction with self-injection (each item graded on either a 5-point or 6-point scale).

The SIAQ is included in Appendix 4.

6.2.2 Self-Injection Assessment Checklist

Self-injection assessment checklist will be assessed at the visits specified in SoA (Table 5). The Investigator or designee will observe the patient's ability to successfully follow the steps to self-administer the study drugs described in the IFU and complete the checklist within 15 minutes after patient's self-injection.

Self-injection assessment checklist is included in Appendix 3.

6.3 Efficacy Assessments

Efficacy will be assessed by the evaluation of DAS28 (DAS28 [CRP], DAS28 [ESR], and individual components) at the time points specified in the SoA (Table 5).

An independent joint count assessor will be assigned in each study center. If possible, it is recommended that the joint assessments should be performed independently by the same person, at each study center throughout the study. Any joint that has undergone any surgical procedure including joint surgery or synovectomy (including joint fusion or replacement) will not be included in the joint count. For assessment, the independent joint assessor will be informed about the history of the patient's joint surgery with the name of the surgery, date, and location. If a patient received IA glucocorticoid injection during study participation, the injected joint must be considered a non-responder joint during the joint assessment.

6.3.1 Tender Joint Count (68) and Swollen Joint Count (66)

Sixty-eight joints will be assessed to determine the number of joints that are considered tender and 66 joints will be assessed for swelling at Screening visit by an independent joint assessor.

6.3.2 Tender and Swollen Joints Count (28)

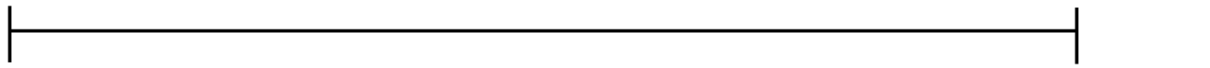
Tender joint counts (TJC) and swollen joint counts (SJC) (28) will be performed by the independent joint assessor at time points specified in the SoA (Table 5).

6.3.3 Disease Activity Score Using 28 Joint Counts

The DAS28 (CRP)[22] is a statistically derived index combining TJC and SJC (28) (Section 6.3.2), CRP (Section 7.4.1), and patient's global assessment of disease activity (PGA) measured using visual analogue scale (VAS) (Section 6.3.4). Similarly, DAS28 (ESR)[23] score is a statistically derived index combining TJC and SJC (28) (Section 6.3.2), ESR (Section 7.4.1), and PGA measured using VAS (Section 6.3.4).

6.3.4 Patient's Global Assessment of Disease Activity Measured using VAS

Patient's global assessment of disease activity will be assessed by VAS at the visits specified in SoA (Table 5). Patients will rate their overall status with respect to RA signs and symptoms and functional capacity by marking one line (|) through the 100-mm line (0 mm equals very well, and 100 mm equals very poor disease activity) in the VAS scale. The length of the line is measured from the left (0 mm) and the value (in mm) recorded in the patient's source documents and the eCRF.



0 mm **100 mm**

Very Well Very Poor

6.3.5 C-Reactive Protein and Erythrocyte Sedimentation Rate

Blood samples for CRP and ESR will be analyzed locally at the time points specified in the SoA (Table 5). A standard ESR kit using the Westergren method of assessment will be supplied to the study centers for use.

6.4 Safety Assessments

Safety evaluations including AEs (including SAEs), AESI (injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies), hypersensitivity monitoring (via monitoring of vital signs), vital signs measurements, ECGs, physical examination findings, IGRA, chest X-ray, pregnancy testing, clinical laboratory analyses, signs and symptoms of TB, and prior and concomitant medications will be monitored throughout the study according to the SoA (Table 5). Hepatitis B, hepatitis C, and HIV status will be tested for the patient's eligibility determination.

6.4.1 Adverse Events

6.4.1.1 Definitions of Adverse Events

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.

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 Investigator at any time after ICF is signed if any symptoms develop (see Section 6.4.1.4). Any new condition noted at Screening will be regarded as an AE, but not a treatment-emergent AE (TEAE).

A TEAE is defined as any event not present prior to exposure to study drug or any event already present that worsens in either severity or frequency after exposure to study drug. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition; abnormal results of diagnostic procedures including laboratory test abnormalities are considered AEs if they fulfill the following:

- Result in discontinuation from the study
- Require treatment or any other therapeutic intervention
- Require further diagnostic evaluation (excluding a repetition of the same procedure to confirm the abnormality)
- Are associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact

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

Diagnostic or therapeutic non-invasive or invasive procedures, such as surgery, should not be reported as AEs. However, they will be recorded as treatment(s) of the AE(s), if medical condition for which the procedure was performed meets the definition of an AE. The event term of primary cause should be recorded and reported instead of the term of surgery, diagnostic procedure, or therapeutic procedure. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

6.4.1.1.1 Adverse Events of Special Interests

The following AESIs will be reported using the same process as for AEs; these events are to be considered serious only if they meet the definition of an SAE.

Injection site reactions

Injection site reactions will be observed after study drug administration and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0. All AEs related to injection site reaction including erythema, itching, hemorrhage, pain, and swelling will be reported.

Hypersensitivity/allergic reactions

All AEs related to hypersensitivity and allergic reactions occurring after the study drug administration will be reported.

Anaphylactic reactions

Anaphylaxis will be identified according to Sampson criteria[24]. Anaphylaxis is likely when any 1 of the 3 criteria are fulfilled.

1. *Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) and at least one of the following:*
    a. Respiratory compromise (e.g., dyspnea, wheeze or bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. *Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):*
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. *Reduced BP after exposure to known allergen for that patient (minutes to several hours):*
    Adults: Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Infections

All AEs related to infection including tuberculosis, sepsis, and other opportunistic infections will be reported.

Malignancy

All AEs related to malignancy including but not limited to the following: hepatosplenic T-cell lymphoma, leukemia, lymphoma, melanoma, and Merkel cell carcinoma will be reported.

6.4.1.1.2 Serious Adverse Events

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

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

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

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

6.4.1.1.3 Unlisted (Unexpected) Serious Adverse Events

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., IB) 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 IB and the label.

6.4.1.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the patient signs the ICF until EOS/ED visit.

All AEs will be followed until resolution or improvement to baseline, death, 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 (e.g., injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies) will be closely monitored.

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

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

6.4.1.3 Reporting Adverse Events

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

Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Adverse events will be recorded according to the CTCAE v.5.0. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

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 Section 6.4.1.7 and 6.4.1.8, respectively.

Adverse events (and SAEs) should be reported until the EOS/ED visit regardless of the relationship to the study drug. After the EOS visit, serious adverse drug reactions will be reported to Sponsor or its designee.

6.4.1.4 Patients' Self-reporting of Adverse Events

A patient self-reporting AE diary will be provided to all patients who will be instructed on how to appropriately complete the diary according to the patient diary instructions.

If there are any signs and symptoms from the time patients leave the study centers until the next visits, patients will record them in the patient self-reporting AE diary and study center staff will review the self-reporting AE diary at each visit throughout the study up to and including EOS/ED visit. However, patients will be advised to contact the Investigator if any severe symptoms develop; the Investigator will determine whether the patient should be referred to the emergency room/hospital or to continue the next dose administration. If needed, the patient will be re-trained on how to complete the self-reporting AE diary. All AEs entered in the self-reporting AE diary will be recorded on the AE page in the eCRF.

6.4.1.5 Reporting Serious Adverse Events

Any AE considered serious by the Investigator or which meets SAE criteria (Section 6.4.1.1.2) must be reported to [redacted] PVG within 24 hours from the time study center staff first learn about the event. The following contact information is to be used for SAE reporting:

[redacted]

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 it 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 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 Investigator or sub-Investigator. All SAEs (regardless of relationship with the study drug) will be followed up until satisfactory resolution or until the Investigator or sub-Investigator deems the event to be chronic or not clinically significant or the patient to be stable.

The Sponsor or its designee is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with European Clinical Trials Directive (Directive 2001/20/EC), International Council for Harmonisation (ICH) guidelines, and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting fatal or life-threatening suspected unexpected serious adverse reaction (SUSARs) (expedited reports) to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of

the event. The Sponsor 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 IRBs/IECs 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 TB unit).

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

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

If a patient is hospitalized purely for convenience (e.g., for easier performance of study assessments), the hospitalization does not qualify as an SAE. If a patient is hospitalized solely due to disease progression without any other adverse events, the hospitalization does not qualify as an SAE.

6.4.1.6 Suspected Unexpected Serious Adverse Reactions

The Sponsor will promptly evaluate all SUSARs against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs/IECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single SAE cases, the Sponsor will assess the expectedness of these events using the applicable reference documents (e.g., study drug IB).

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

6.4.1.7 Assessment of Severity

The severity of an AE refers to the extent to which an AE affects the patient's daily activities. The severity of the AE will be graded based on the CTCAE v5.0, based on the following general guidelines (a semicolon indicates "or" within each description):

Grade 1: Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only; radiographic findings only; marginal clinical relevance).

Grade 2: Moderate AE (minimal intervention; local intervention; non-invasive 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 severity to be performed. If an AE upgrades in severity or changes from a non-serious to a serious event, 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 do not require documentation of onset and duration of each episode.

6.4.1.8 Assessment of Causality

As discussed in Section 6.4.1.3, 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 relationship or association of CT-P17 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, e.g., the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug but could also have been produced by other factors.

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

Definite: This relationship suggests that a definite causal relationship exists between 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. The event reappears or worsens if the study drug is re-administered.

6.4.1.9 Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page in the patient's source documents and the eCRF and followed to satisfactory resolution, until the Investigator deems the event to be chronic or not clinically significant, or until the patient is stable.

6.4.2 Other Safety Assessments

6.4.2.1 Injection Site Reaction

Injection site reactions will be assessed 30 minutes (±10 minutes) after the end of the study drug administration, as specified in the SoA (Table 5).

For injections that will be self-injected at home, patients should be advised to call the study center or get immediate medical help if they experience the symptoms of injection site reactions (Section 6.4.1.1.1).

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

6.4.2.2 Hypersensitivity/Allergic Reactions Monitoring

Hypersensitivity/allergic reactions will be assessed prior to the study drug administration and 1 hour (±10 minutes) after the end of the study drug administration at the study center, as specified in the SoA (Table 5), by additional vital signs measurements including BP, heart and respiratory rates, and body temperature. If a patient has signs and symptoms of hypersensitivity/allergic reactions at home (hives, difficulty breathing, or swelling of face, eyes, lips, or mouth or any symptoms of cardiac origin), the patient should be advised to call the study center or get immediate help.

In addition, hypersensitivity will be monitored by routine continuous clinical monitoring including patient-reported signs and symptoms (see Section 6.4.1.4). In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, artificial

ventilation and ECG equipment must be available at the study center. Any type of ECG can be performed.

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

Details of the event will be recorded in both the patient's source documents and the eCRF.

6.4.2.3 Vital Signs and Weight, and Height

Vital signs measurements will be performed at the time points specified in the SoA (Table 5). Vital signs (including BP, heart and respiratory rates, and body temperature; while sitting) will be measured by the Investigator or designee after 5 minutes of rest. In addition, measurement of height and weight will be documented only at Screening. All measurements will be documented at each study center visit. Details will be recorded in both the patient's source documents and the eCRF.

Vital sign measurements will also be monitored prior to and after study drug administration as part of the hypersensitivity monitoring (Section 6.4.2.2).

6.4.2.4 Electrocardiogram

All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in a supine position. A 12-lead ECG will be performed at the time points specified in the SoA (Table 5) and if the patient experienced cardiac symptoms during study drug administration. If following the ECG review by the Investigator there are any significant ECG findings such as a new or worsening of cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality. The Investigator will then report the event in the patient's source documents and the eCRF. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done based on the Investigator's discretion. In case of hypersensitivity, any type of ECG can be performed (Section 6.4.2.2).

6.4.2.5 Physical Examination

Physical examinations with particular attention to injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancy will be performed prior to study drug administration at the time points specified in the SoA (Table 5).

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

Information about the physical examination will be recorded by the Investigator or designee in both the patient's 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 source documents.

6.4.2.6 Clinical Laboratory Analyses

Patients' blood and urine samples will be collected as specified in the SoA (Table 5). Blood sample does not need to be collected in a fasting state unless required in the opinion of the Investigator according to the laboratory manual. Clinical laboratory (clinical chemistry, hematology and urinalysis) test samples will be analyzed at the local laboratory. If a study center is not equipped to perform the specified tests, this will be discussed and arranged with the Sponsor or its designee.

All abnormal laboratory values will be evaluated for clinical significance by the Investigator. If the abnormality is considered as clinically significant (in the opinion of the Investigator) and meets the AE definition by the Investigator, then the results must be recorded as AE on e-CRF.

Unscheduled clinical laboratory tests will be performed at any time during the study to address any safety concerns.

The clinical laboratory tests to be performed are listed in Table 2 below.

Table 2: Clinical Laboratory Tests

Clinical chemistry	• total protein • serum bilirubin (total, direct) • alanine aminotransferase • aspartate aminotransferase • alkaline phosphatase • γ-glutamyltransferase • blood urea nitrogen • creatinine • creatine kinase • creatine kinase-MB	• albumin • sodium • potassium • calcium • chloride • inorganic phosphorus • glucose • lactate dehydrogenase • total cholesterol • triglyceride • high-density lipoprotein cholesterol
Hematology	• red blood cells • 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 • hematocrit
Urinalysis	• bilirubin • blood • glucose • ketones • leukocytes • nitrite	• pH • protein • specific gravity • urobilinogen • microscopic examination

Creatinine clearance will be calculated using serum creatinine level only at Screening for inclusion and recorded in the patient's source documents and the eCRF.

6.4.2.7 Pregnancy

Women of childbearing potential who have not been surgically sterilized will undergo pregnancy testing in the study center as specified in the SoA (Table 5). Only patients with a negative serum pregnancy test results can be enrolled into the study.

For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted at Screening and EOS/ED visit at the local laboratory. A urine pregnancy test will be used to confirm patients are not pregnant prior to dosing according to SoA (Table 5) or more frequently if required by country-specific legislation. Urine pregnancy test will also be performed locally prior to the study drug administration. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed. If a female patient becomes pregnant, the study drug must be discontinued immediately.

In an event of unexpected pregnancy during study participation and for 6 months after the last dose of study drug, patients will be instructed to inform the Investigator. If a female patient becomes pregnant, the study drug must be discontinued immediately. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to Sponsor and [redacted] Safety Department within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test, female patients must permanently discontinue the study drug and be withdrawn from the study. The study center must complete the pregnancy form provided (female patient or partner of a male patient) and return it to Sponsor and [redacted] Safety Department within 24 hours after receiving the consent for the pregnancy form.

Pregnant patients or the pregnant partners of male patients will be followed until the end of the pregnancy (e.g., delivery, stillbirth, miscarriage) and the mother and the baby will be followed for 1 year after the birth, provided consent is obtained. Any SAE that occurs during pregnancy (e.g., maternal serious complications, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) must be reported within 24 hours in accordance with the procedure for reporting SAEs (Section 6.4.1.5).

6.4.2.8 Hepatitis B, Hepatitis C and HIV Status

At Screening, hepatitis B surface antigen (HbsAg), hepatitis B surface antibody (HbsAb), and hepatitis B core antibody (HbcAb) (total or immunoglobulin G [IgG]) will be assessed in all patients as specified in Table 3.

Table 3: Eligibility Based on Serologic Markers for Hepatitis B Infection

Test Results				Eligibility
HbsAg	**HbsAb**	**HbcAb**	**HBV DNA**	
+	+/–	+/–	Not applicable	Not eligible
–	+/–	+	+	Not eligible
			–	Eligible
–	+/–	–	Not applicable	Eligible

Abbreviations: HbcAb=hepatitis B core antibody; HbsAb=hepatitis B surface antibody; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus.

If the HbsAg test result is positive, the patient will be excluded from the study. If a patient is negative for HbsAg, negative or positive for HbsAb, and positive for HbcAb, a HBV deoxyribonucleic acid (DNA) test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. If hepatitis C or HIV test result is positive, the patient will be excluded from the study. Hepatitis and HIV analysis will be performed at the local laboratory.

6.4.2.9 TB Signs and Symptoms

At Screening, a history of TB or a current diagnosis of TB will result in patient exclusion from the study. A patient who has a previous diagnosis of active TB cannot be enrolled in the study even if there is sufficient documentation of complete resolution of active TB.

A patient who has had exposure to someone with active TB such as first-degree family members or co-workers will not be included in the study.

Additionally, a 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 6.4.2.9.1) with a negative examination of chest X-ray (Section 6.4.2.9.2). 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 indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study. A patient who has a previous diagnosis of latent TB cannot be enrolled even if there is sufficient documentation of completed TB prophylaxis.

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. Tuberculosis clinical monitoring, IGRA testing and chest X-ray will be performed according to the SoA (Table 5). The IGRA or chest X-ray can be performed at the Investigator's discretion based on the judgment on the signs and symptoms of TB monitoring throughout 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 will be referred to the clinician immediately to investigate the presence of active TB based on medical history and any clinical signs and symptoms including chest X-ray result. Even in the absence of clinical suspicion for active TB, study drug administration will be temporarily stopped. It is recommended that study drug administration is resumed, in patients who have received at least 3 weeks of country-specific TB therapy and who intend to complete the entire course of TB therapy. However, study drug administration can be resumed simultaneously with the start of country-specific TB therapy after discussion with the Sponsor Medical Monitors or its designee in advance.

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

No further IGRA testing is required during the Treatment Period and at EOS/ED visit for patients who have at least 1 positive result for IGRA test and have completed the prophylaxis at least for required duration by country-specific legislation.

6.4.2.9.1 Interferon- γ Release Assay

The IGRA is the protocol-required method of Screening for TB. The IGRA testing will be performed at the local laboratory during the Screening Period, EOS and ED.

6.4.2.9.2 Chest X-ray

A chest X-ray (both lateral and posterior-anterior views) must be performed according to local health authority guidance during the Screening Period, EOS and ED. A chest X-ray is not required at Screening if a chest X-ray from within the 42 days prior to the first administration of the study drug (Day 1) is available. All chest X-rays should be available for review by the Investigator before the patient is enrolled into the study.

The chest X-ray must be negative for active TB infection, fungal infections, or any other clinically significant abnormalities for a patient to be considered eligible for the study. All chest imaging must be read by a qualified radiologist/pulmonary physician who is specifically required to look for evidence of active TB or inactive TB.

Radiographic findings suggestive of inactive TB or active TB may include but are not limited to: apical fibrosis, pleural thickening, pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations and pleural effusions, calcified lung nodules, calcified hilar lymph nodes, and pericardial calcification.

The 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 subsequent study drug administration.

6.5 Sample Collections

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

6.5.1 Interferon-γ Release Assay Blood Sampling

Blood samples for IGRA will be obtained at the time points specified in the SoA (Table 5). All samples should be collected at the scheduled time point.

6.5.2 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 SoA (Table 5).

A blood sample for HBV and hepatitis C and HIV testing will be required at Screening. A serum pregnancy test sample will be required at Screening and at the EOS/ED visit for women of childbearing potential who have not been surgically sterilized.

6.6 Labeling of Samples

Each sample tube will be clearly labeled with the following information:

- Study number
- Patient identification number
- Tube identification
- Scheduled sampling time point.

7 Statistical Analysis Plan

The 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 database lock.

The data documented in this study and the clinical parameters measured will be described using descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) for quantitative variables and frequency counts and percentages for qualitative variables.

7.1 Populations for Analyses

For purposes of analysis, the following analysis populations are defined:

Intent-to-Treat (ITT) Population: The ITT Population includes all enrolled patients to receive a dose of study drug, regardless of whether or not any study drug dosing was completed.

Usability Population: The Usability Population includes all patients in the Safety Population who have evaluable usability measurements at Week 4 and who do not have major deviations that may affect the interpretation of study result. The major protocol deviations will be discussed during the data review meeting and the details of protocol deviations will be defined in the SAP.

Safety Population: The Safety Population includes all patients who receive at least 1 dose (full or partial) of study drug.

7.2 Usability Analysis

7.2.1 Primary Usability Endpoint

The primary usability endpoint is the patient rating using PRE- and POST- SIAQ at Week 4 and will be summarized using the ITT and the Usability Population.

7.2.2 PRE- and POST- SIAQ

Patient will complete each item of SIAQ on a 5-point or 6-point (semantic Likert-type scale). Item score will be transformed to obtain a score ranging from 0 to 10 for each item, based on the algorithm below:

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. PRE- and POST-SIAQ will be summarized at Week 4 using the ITT and the Usability Population.

7.3 Secondary Usability Endpoints

The secondary usability endpoints are the patient rating using PRE- and POST-SIAQ and the observer rating of successful self-injection using self-injection assessment checklist at Weeks 0, 2 and 24 and will be summarized using the ITT and the Usability Population.

7.3.1 PRE- and POST- SIAQ

PRE- and POST- SIAQ will be summarized at Weeks 0, 2 and 24 using the ITT and the Usability Population.

7.3.2 Observer Rating of Successful Self-Injection Using Self-Injection Assessment Checklist

The self-injection assessment will be summarized at Weeks 0, 2, 4 and 24 using the ITT and the Usability Population. It will be coded as successful if N7, N9, N10 and N11 of the self-injection assessment checklist are checked as Yes. In addition, the successful completion of all 14 instructions will be assessed from the self-injection assessment checklist (Appendix 3). Successful self-injection will be summarized by scheduled time point as the number and proportion of successful injections and the number and proportion of patients who successfully completed all 4 instructions will be summarized.

7.4 Efficacy Analysis

The efficacy endpoint is the mean change from baseline in DAS28 (CRP) and DAS28 (ESR) up to Week 24 and will be summarized using the ITT Population.

7.4.1 DAS28 (CRP) and DAS28 (ESR)

The following parameters will be summarized using descriptive statistics: actual value and change from baseline of DAS28 (CRP) and DAS28 (ESR) every 8 weeks up to Week 24 using the ITT Population.

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

$$\text{DAS28 (ESR)}=(0.56 \times \sqrt{\text{TJC28}})+(0.28 \times \sqrt{\text{SJC28}})+(0.70 \times \ln[\text{ESR}])+(0.014) \times \text{PGA})$$

Where:

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

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

ESR = ESR measurement (mm/hour)

CRP = CRP measurement (mg/L)

PGA = patient's global disease activity measured on 100 mm VAS

The components of the DAS28 (CRP and ESR) will be summarized.

7.5 Safety Analyses

Safety analysis will be performed on the Safety Population at the time points specified in the SoA (Table 5) by presenting data on AEs (including SAEs), AESI (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies), hypersensitivity monitoring (via monitoring of vital signs), vital signs measurements, ECGs, physical examination findings, IGRA, chest X-ray, pregnancy testing, clinical laboratory analyses, signs and symptoms of TB, and prior and concomitant medications monitored throughout the study. Hepatitis B, hepatitis C, and HIV status will be tested for the patient's eligibility determination.

7.5.1 Demographic, Baseline, and Background Characteristics

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

7.5.2 Adverse Events

Adverse events will be recorded according to the CTCAE v.5.0 and will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA. A TEAE is defined as described in Section 6.4.1.1. The following TEAE summaries will be reported by SOC, PT:

- Number and percentage of patients reporting at least 1 TEAE
- Number and percentage of patients reporting at least 1 treatment-emergent SAE
- Number and percentage of patients discontinuing the study drug due to a TEAE
- Number and percentage of patients with TEAEs of special interest (injection site reactions, hypersensitivity/allergic reactions, infections, and malignancies)

7.5.3 Clinical Laboratory Analyses, IGRA and Pregnancy

Clinical laboratory tests (hematology, clinical chemistry, urinalysis), IGRA, and pregnancy testing will be summarized at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all scheduled collection times after the first administration of study drug.

7.5.4 Electrocardiogram, Physical Examination, and Vital Signs

Individual data and standard summary statistics as well as changes from baseline for 12-lead ECG results, physical examination findings, and vital sign measurements will be presented by study visit. Change from baseline will also be summarized for all scheduled collection times after the first administration of study drug.

7.5.5 Prior and Concomitant Medications

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

7.5.6 Other Safety Analyses

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

7.6 Interim Analyses

Interim analyses are not planned in this study.

7.7 Handling of Missing, Unused, and Spurious Data

No imputation will be conducted for the primary and secondary usability analysis unless additional sensitivity with different imputation methods are requested by the Sponsor.

7.8 Sample Size Determination

Approximately 60 male or female adult patients will be enrolled. In this usability study, a sample size justification based on a formal statistical hypothesis is not relevant, since a formal statistical inference will not be made.

8 Supporting Documentation and Operational Considerations

8.1 Regulatory, Ethical, and Study Oversight Considerations

8.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/ IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.

Overall conduct of the study at the site and adherence to requirements of ICH GCP guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

8.1.2 Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

8.1.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legal guardian will be required to sign and date a statement of informed consent that meets the requirements of local regulations, ICH guidelines, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date of the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legal guardian.

Patients who are re-screened are required to sign and date a new ICF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IEC/IRB and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

8.1.4 Data Protection

Patients will be assigned a unique PIC by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the PIC; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.1.5 Dissemination of Clinical Study Data

All information, including but not limited to information regarding the study drug, the Sponsor's operation (e.g., patent application, formulas, manufacturing process, basic scientific data, prior clinical data, and formulation information) and any data generated as a result of this study, are considered confidential and are the sole property of the Sponsor. The Investigator agrees to maintain this information in confidence and use this information only to accomplish this study. The Investigator will not use this information for other purposes without the Sponsor's prior written approval.

The Investigator understands that the information developed in the clinical study will be used by the Sponsor in connection with the continued development of the study drug, and thus may be disclosed, as required, to other clinical Investigators or regulatory agencies. The Investigator is obligated to provide the Sponsor with all data obtained in the study.

The results of the study will be reported in a clinical study report (CSR) generated by the Sponsor. The Sponsor will also ensure that the CSRs in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of CSRs.

The Sponsor plans to prepare 1 CSR to report: All data after completion of the study.

Additional statistical analysis will be performed for regulatory submission usability data up to Week 4. Details on analysis will be pre-specified in the SAP.

Any work created in connection with the performance of the study and data generated by the study shall be the property of the Sponsor as author and owner of copyright in such work.

8.1.6 Data Quality Assurance

This study will be conducted according to the ICH E6(R2) risk and quality processes described in the applicable procedural documents. The quality management approach to be

implemented in this study will be documented and will comply with the current ICH GCP guidelines on quality and risk management.

All patient data relating to the study will be recorded on the patients' source document and the eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Essential documents should be retained until at least 15 years after the date on which the results of the study are submitted to the regulatory authorities in support of an allocation for a research or marketing permit, or completion date for study by approval or disapproval of any application, whichever is later. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. No records will be destroyed during the retention period without the written approval of the Sponsor. No records will be transferred to another location or party without written notification to the Sponsor.

The specific procedures to be used for data entry and query resolution using the electronic data capture (EDC) system/eCRF will be provided to study centers in a training manual. In addition, site personnel will receive training on the EDC system/eCRF.

8.1.7 Source Documents

Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

8.1.8 Study and Site Closure

The Sponsor designee reserves the right to close the study center or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centers will be closed upon

study completion. A study center is considered closed when all required documents and study supplies have been collected and a study center closure visit has been performed.

The Investigator may initiate study center closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study center by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further study drug development

8.1.9 Publication Policy

The results of this study may be published or presented at scientific meetings.

In these cases, the Sponsor will be responsible for these activities and may work with the Investigators to determine how the manuscript is written and edited, the number and order of authors based on the standard operation process of the Sponsor, the publication to which it will be submitted, and other related issues. The Sponsor has final approval authority over all such issues.

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

8.1.10 Study Administration

A list of personnel and organizations responsible for the conduct of the study (details included in Table 4) will be provided by the Sponsor or its designee to the study center, as part of the Investigator Site File.

Table 4: Organizations Responsible for Study Conduct

Role	Name /Address
Sponsor	CELLTRION, Inc. [redacted]
Contract Research Organization	[redacted]

8.1.11 Protocol Approval and Amendment and Protocol Deviations

8.1.11.1 Protocol and Protocol Amendments

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IEC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC/Competent Authority approval prior to implementation (if appropriate). Protocol amendments will be submitted to the appropriate authorities as required by the applicable regulatory requirements.

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

8.1.11.2 Protocol Deviations

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

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the Sponsor and the IRB/IEC and agreed to by the Investigator. A significant deviation (violation) occurs when there is non-adherence to the protocol by the patient or Investigator that may result in an additional risk to the patient or which may confound analysis of study results. Significant deviations can include enrollment of a patient with non-adherence to inclusion or exclusion criteria, or non-adherence to Food and Drug Administration (FDA) regulations or ICH E6(R2) guidelines and may lead to the patient being withdrawn from the study (see Section 4.3).

Protocol deviations (and violations) will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of deviations. The site must notify the IRB/IEC of all protocol deviations in a timely manner.

8.1.12 Access to Source Data

During the study, a monitor will make site visits to review protocol compliance, compare eCRF entries and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. Electronic case report form entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRF entries for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, IRBs, IECs, and/or the Sponsor's Clinical Quality Assurance Group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures the Sponsor or designee of the necessary support at all times.

9 Appendices

9.1 Appendix 1: Abbreviations

ACR	American College of Rheumatology
AE	adverse event
AI	auto-injector
AESI	adverse events of special interest
BP	blood pressure
CRP	C-reactive protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAS	disease activity score
DMARD	disease-modifying anti-rheumatic drug
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ED	early discontinuation
EOS	end-of-study
EOW	every other week
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen
HbcAb	hepatitis C core antibody
HBV	Hepatitis B virus
HIV	human immunodeficiency virus
IA	intra-articular
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	instructions for use
IGRA	interferon-γ release assay
IM	intramuscular
IRB	Institutional Review Board
ITT	intent-to-treat

MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drugs
PIC	patient identification code
PFS	pre-filled syringe
PGA	Patient's Global Assessment
PK	pharmacokinetic(s)
PT	preferred term
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SIAQ	Self-Injection Assessment Questionnaire
SJC	swollen joint count
SoA	schedule of activities
SOC	system organ class
TB	tuberculosis
TEAE	treatment-emergent adverse event
TJC	tender joint count
TNF	tumor necrosis factor
ULN	upper limit of normal
US	United States
VAS	visual analogue scale

9.2 Appendix 2: Schedule of Activities (SoA)

The schedule of activities (SoA), as outlined in Table 5, consists of a Screening Period, a Treatment Period and a Follow-up Period.

Table 5: Schedule of Activities

	Screening Period	Treatment Period									Follow-up Period	
		Dose 1	Dose 2	Dose 3	Dose 4	Dose 5	Dose 7	Dose 9	Dose 11	Dose 13	EOS[1]	ED[2]
Study visit[3] (Week)	**–6**	**0**	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**	
Study visit[3] (Day)	**–42 to –1**	**1**	**15**	**29**	**43**	**57**	**85**	**113**	**141**	**169**	**197**	
Informed consent	X											
Demographics, height, weight and medical history	X											
Hepatitis B/C and HIV test[4]	X											
Serum pregnancy test[5]	X										X	X
Chest X-ray[6]	X										X	X
IGRA[7]	X										X	X
Inclusion/exclusion criteria	X	X[8]										
Usability assessments												
PRE- and POST-SIAQ[9]		X	X	X						X		
Self-injection assessment checklist by observer[10]		X	X	X						X		
Efficacy assessments[11] – Pre-dose												
Swollen joint count (66 joints)	X											
Tender joint count (68 joints)	X											
Tender joint count and swollen joint count (28 joints)	X	X				X		X		X	(X)	X
CRP and ESR[12]	X	X				X		X		X	(X)	X
VAS global assessment of disease activity (patient) scores	X	X				X		X		X	(X)	X
Safety assessments[11] – Pre-dose												
Physical examination, vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[13]	X	X		X			X			X	X	X
Urine pregnancy test[5]		X	X	X	X	X	X	X	X	X		
12-lead ECG[14]	X	X									X	X
Study drug administration[15,16]		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Hypersensitivity/ allergic reactions[17] and injection site reaction[18] monitoring		X	X	X	X	X	X	X	X	X		
Prior, concomitant medications[19]	X											
TB clinical monitoring[20]	X											
AE[21]	X											

Abbreviations: AE=adverse event(s); AI=auto-injector; CRP=C-reactive protein; ECG=electrocardiogram; eCRF=electronic case report forms; ED=early discontinuation; EOS=end-of-study; EOW=every other week; ESR=erythrocyte sedimentation rate; HIV=human immunodeficiency virus; ICF=informed consent form; igG=immunoglobulin G; IGRA=Interferon-Gamma Release Assays; IM=intramuscular; RA=rheumatoid arthritis; SC=subcutaneous; SIAQ=Self-Injection Assessment Questionnaire; TB=tuberculosis; VAS=visual analogue scale.

Note: Only the study center visits are presented in this table. As the study drug will be administered EOW, the planned injections on Weeks 10, 14, 18 and 22 which are not specified in this table (Dose 6, 8, 10 and 12) will be self-administered at home.

1. An EOS visit will occur 4 weeks after the last dose (at Week 24) is received or prior to the start of new RA therapy, whichever comes earlier. The efficacy assessments will be performed only if the efficacy assessments were not performed at Week 24 as planned.
2. An ED visit will be completed 4 weeks after the last dose is received or prior to the start of new RA therapy, whichever comes earlier, if a patient is discontinued from study prior to Week 24 treatment.
3. A visit window of ±2 days is allowed, based on the previous dosing date, from Week 2 (dose 2) up to the EOS visit.
4. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (total or IgG) will be assessed in all patients. If the HBsAg test result is positive, the patient will be excluded from the study. If a patient is negative for HBsAg, negative or positive for HBsAb, and positive for HBcAb, an HBV DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient will be excluded from the study; if the HBV DNA test result is negative, the patient can be included in the study. If hepatitis C or HIV test result is positive, the patient will be excluded from the study. Hepatitis and HIV analysis will be performed locally.
5. For women of childbearing potential who have not been surgically sterilized, a serum pregnancy test will be conducted locally at Screening and EOS/ED visit. A urine pregnancy test will also be performed locally and will be used to confirm patients are not pregnant prior to dosing on each scheduled visit or more frequently if required by country-specific legislation. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed.
6. A chest X-ray (both lateral and posterior-anterior views) is not required at Screening if a chest X-ray from within the 42 days prior to the first administration of the study drug (Day 1) is available.
7. The IGRA testing will be performed locally. A patient who has a previous diagnosis of latent TB cannot be enrolled even if there is sufficient documentation of completed TB prophylaxis. 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 indeterminate again or positive, the patient will be excluded from the study. If the repeated IGRA result is negative, the patient can be enrolled in the study.
8. Inclusion and exclusion criteria should be confirmed on Day 1 again.
9. PRE- and POST-SIAQ will be completed by patient prior to and after self-injection of CT-P17 SC via AI. Patients will complete PRE-SIAQ immediately before the administration of study drug and POST-SIAQ within 20 to 40 minutes after the administration of study drug.
10. The Investigator or designee will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection.
11. Procedures will be performed at the study center prior to the study drug administration. Where possible, the same Investigator should perform all efficacy assessments for an individual patient.
12. Both CRP and ESR samples will be drawn and analyzed locally at the same time as the clinical laboratory blood samples.
13. Clinical laboratory (clinical chemistry, hematology and urinalysis) test samples will be analyzed locally. See Section 6.4.2.6 for details of the clinical laboratory tests. Creatinine clearance will be calculated using serum creatinine level only at Screening for inclusion and recorded on eCRF.
14. All scheduled 12-lead ECGs will be performed locally after the patient has rested quietly for at least 5 minutes in supine position. If patients have signs and symptoms of cardiac origin, a 12-lead ECG could be performed at any time during the Treatment Period. Regardless of the 12-lead ECG result, further evaluation with a cardiologist can be done depending on the Investigator's discretion.
15. A fixed dose of CT-P17 (40 mg) will be administered EOW by SC injection via AI from Week 0 to Week 24. For each new injection, a different injection site will be used (e.g., 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 injection site. Patients must self-inject the study drug during their study center visits under the Investigator or designated study center staff's supervision at the indicated visits. Patients will self-inject the study drug at home at Weeks 10, 14, 18 and 22.
16. Methotrexate (12.5 to 25 mg/week, or 10 mg/week if intolerant to a higher dose, oral or IM, dose and route must be maintained from Screening to EOS/ED visit) and folic acid (≥5 mg/week, oral) will be administered throughout the study.

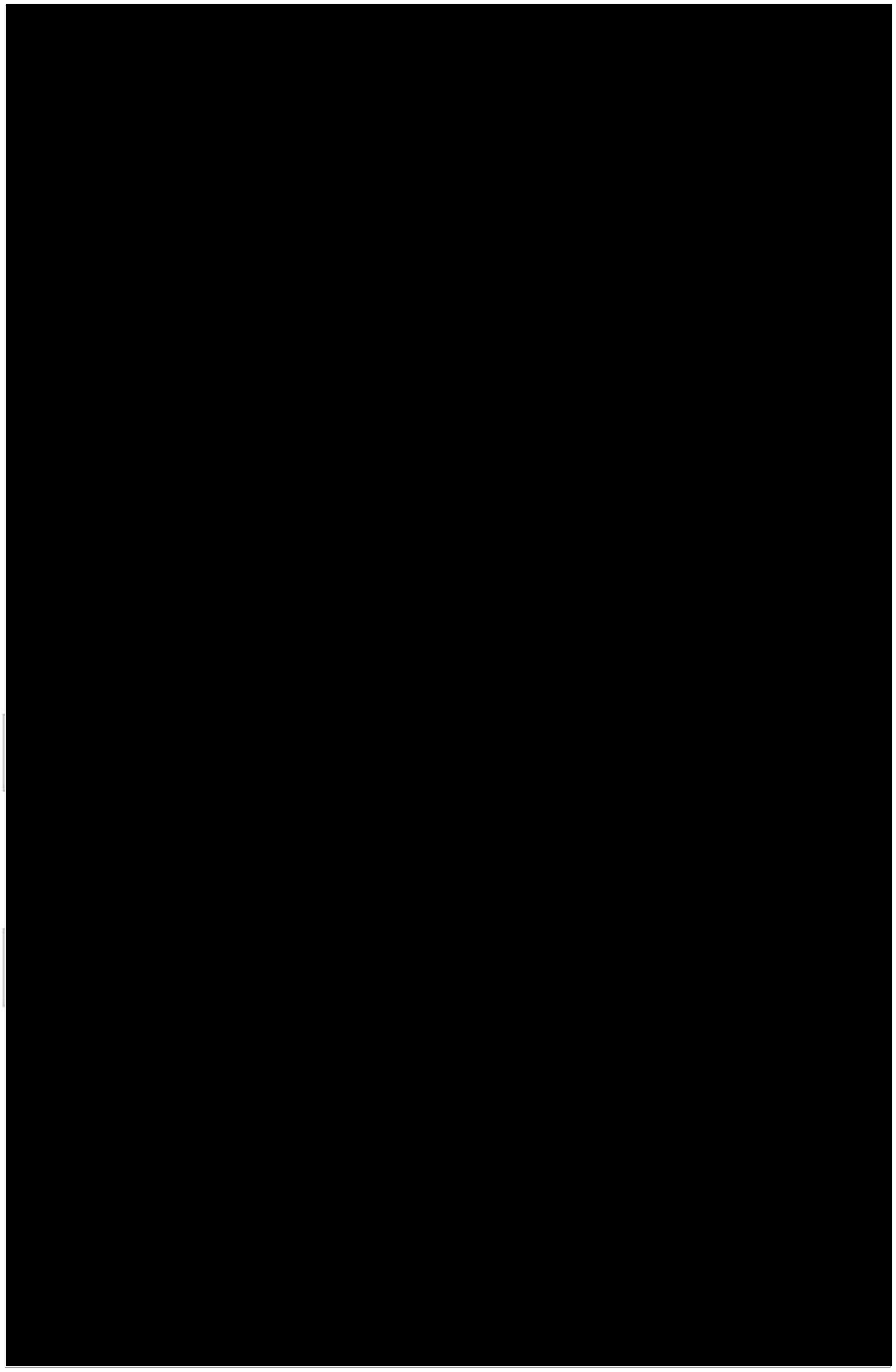
17. Additional vital signs will be monitored for possible hypersensitivity/allergic reactions 1 hour (±10 minutes) after injection of study drug. In case of hypersensitivity, emergency medication and equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, artificial ventilation and ECG equipment must be available at the study center. Any type of ECG can be performed.
18. Injection site reaction will be assessed 30 minutes (±10 minutes) after SC injection of study drug. For injections that will be given at home, injection site reactions will be recorded by the patient in the patient self-reporting of AE diary.
19. Use of all prior and concomitant medications for the treatment of RA, from the diagnosis of disease until the EOS/ED visit, will be recorded in the patient's eCRF. Use of all medications for other purposes, taken from 42 days prior to the first administration of study drug until the EOS/ED visit, will be recorded in the patient's eCRF. However, in order to check eligibility, prior medications will be reviewed from date specified in the exclusion criteria #7 (Section 4.2).
20. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. The IGRA or chest X-ray can be performed at the Investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The Investigator will confirm the absence of active TB prior to subsequent study drug administration.
21. AEs will be assessed from the date the ICF is signed until the EOS/ED visit. After the EOS/ED visit, serious adverse drug reactions will be reported to the Sponsor or its designee. Adverse events of special interest (e.g., injection site reactions, hypersensitivity/allergic reactions, anaphylactic reactions, infections, and malignancies) should be closely monitored.

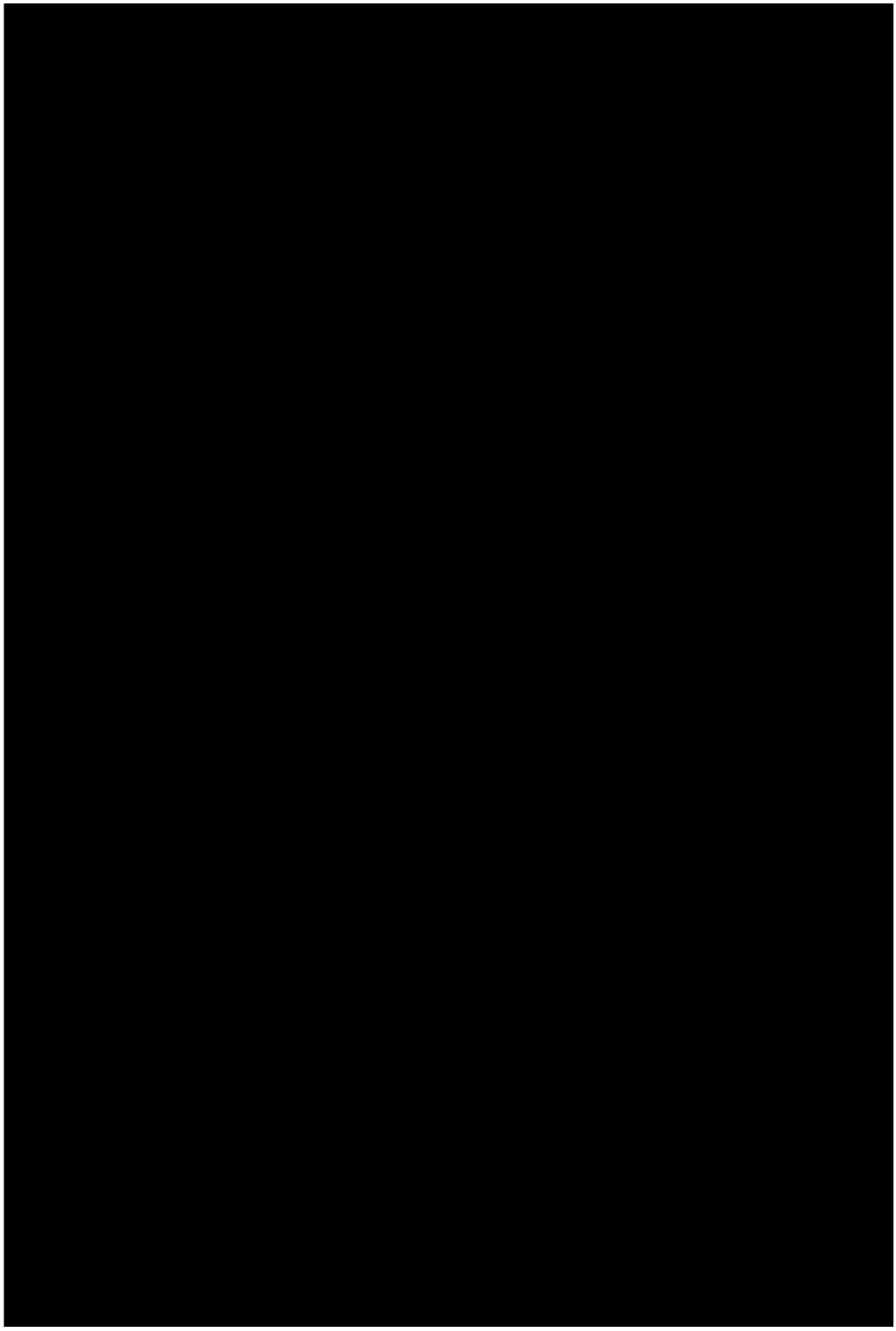
9.3 Appendix 3: Self-Injection Checklist

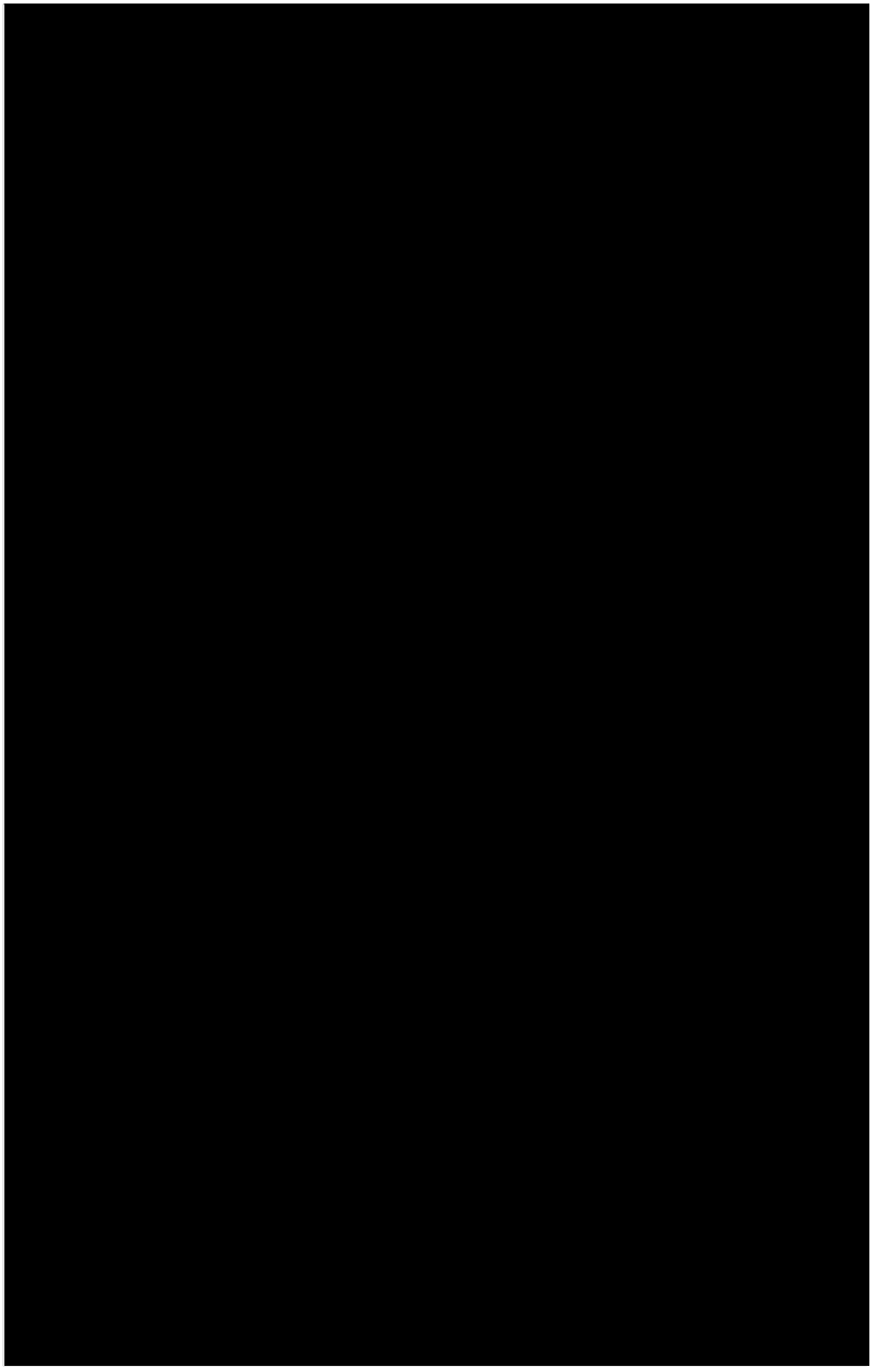
No.	Instructions for Use
1	Removed the auto-injector from the outer carton
2	Checked expiration date on the auto-injector label
3	Inspected the auto-injector for damage
4	Checked liquid for discoloration or particles
5	Washed hands with soap and water
6	Cleaned the injection site
7	**Removed the cap from auto-injector**
8	Held the auto-injector so that patient could see the window
9	**Placed the auto-injector at 90° angle on the injection site**
10	**Pressed the auto-injector firmly against the skin to start the injection (1st loud click), and kept holding the auto-injector firmly against the skin until heard the 2nd loud click**
11	**After the 2nd loud click, continued to hold the auto-injector firmly against the skin and count slowly to five to ensure the injection was completed**
12	Checked if the grey indicator fills the window completely
13	Removed auto-injector from injection site at 90° angle to skin
14	Disposed used auto-injector and the cap in a sharps container

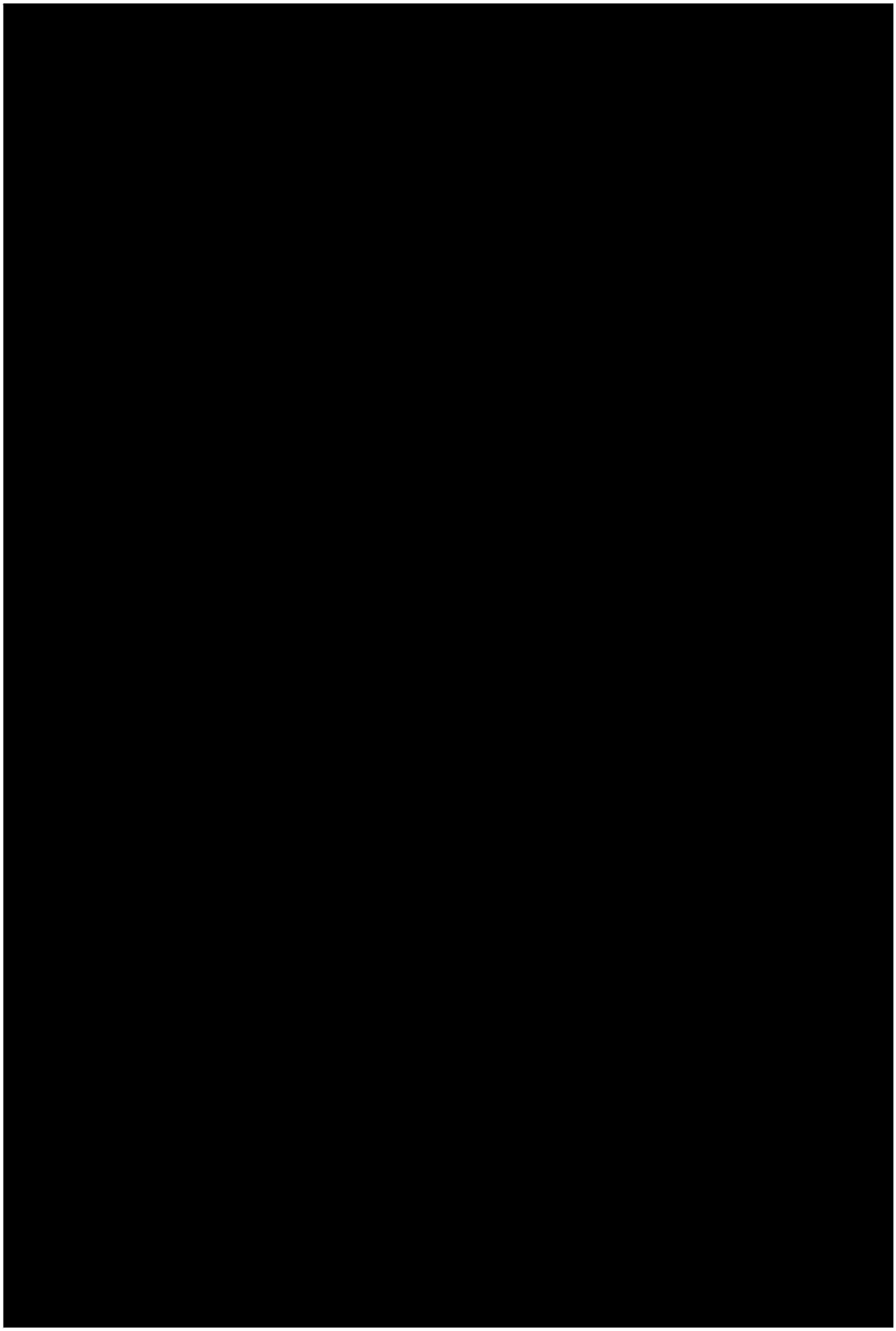
*** The bolded steps are considered as critical steps for the usability assessment.**

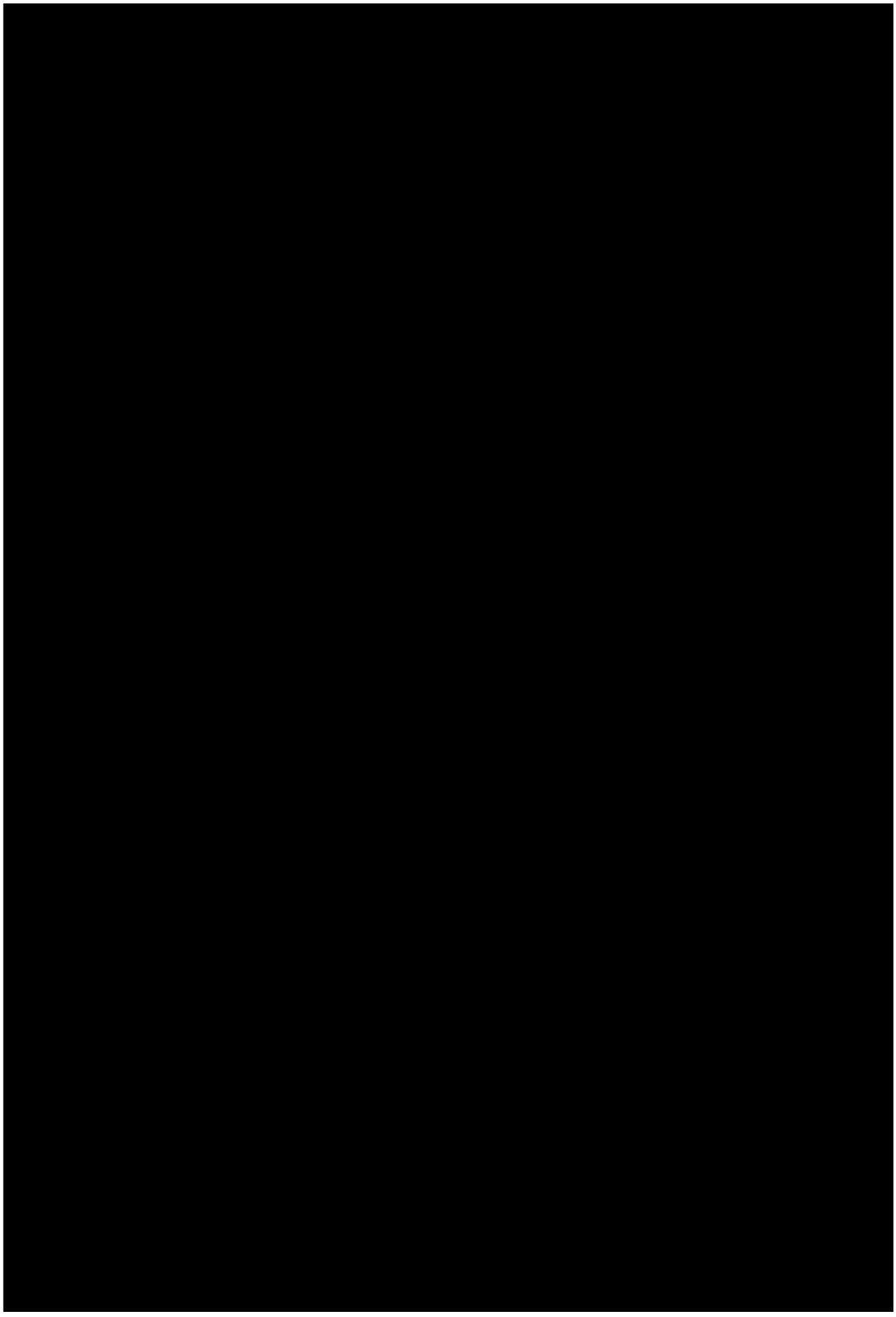
9.4 Appendix 4: Self-Injection Assessment Questionnaire

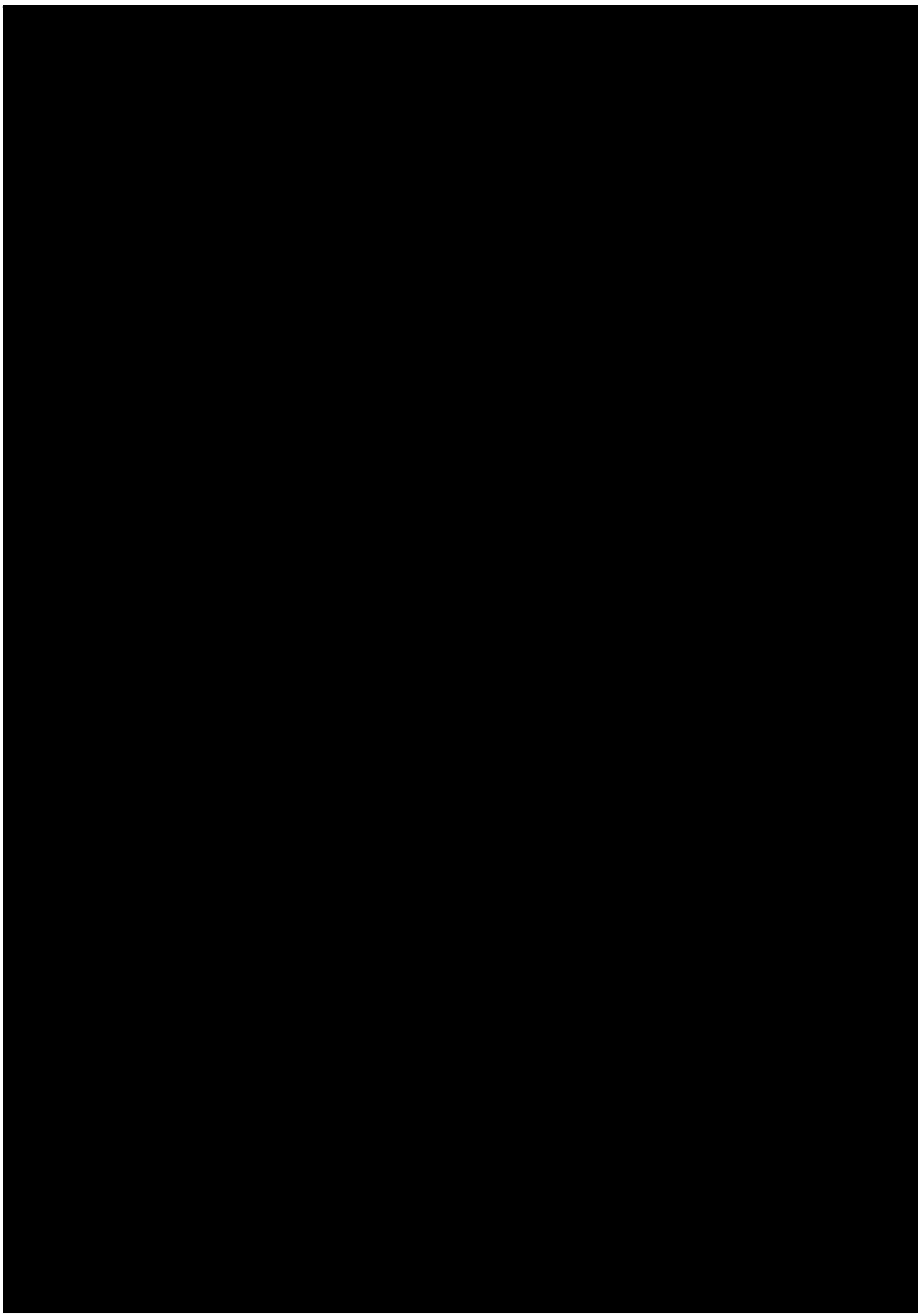


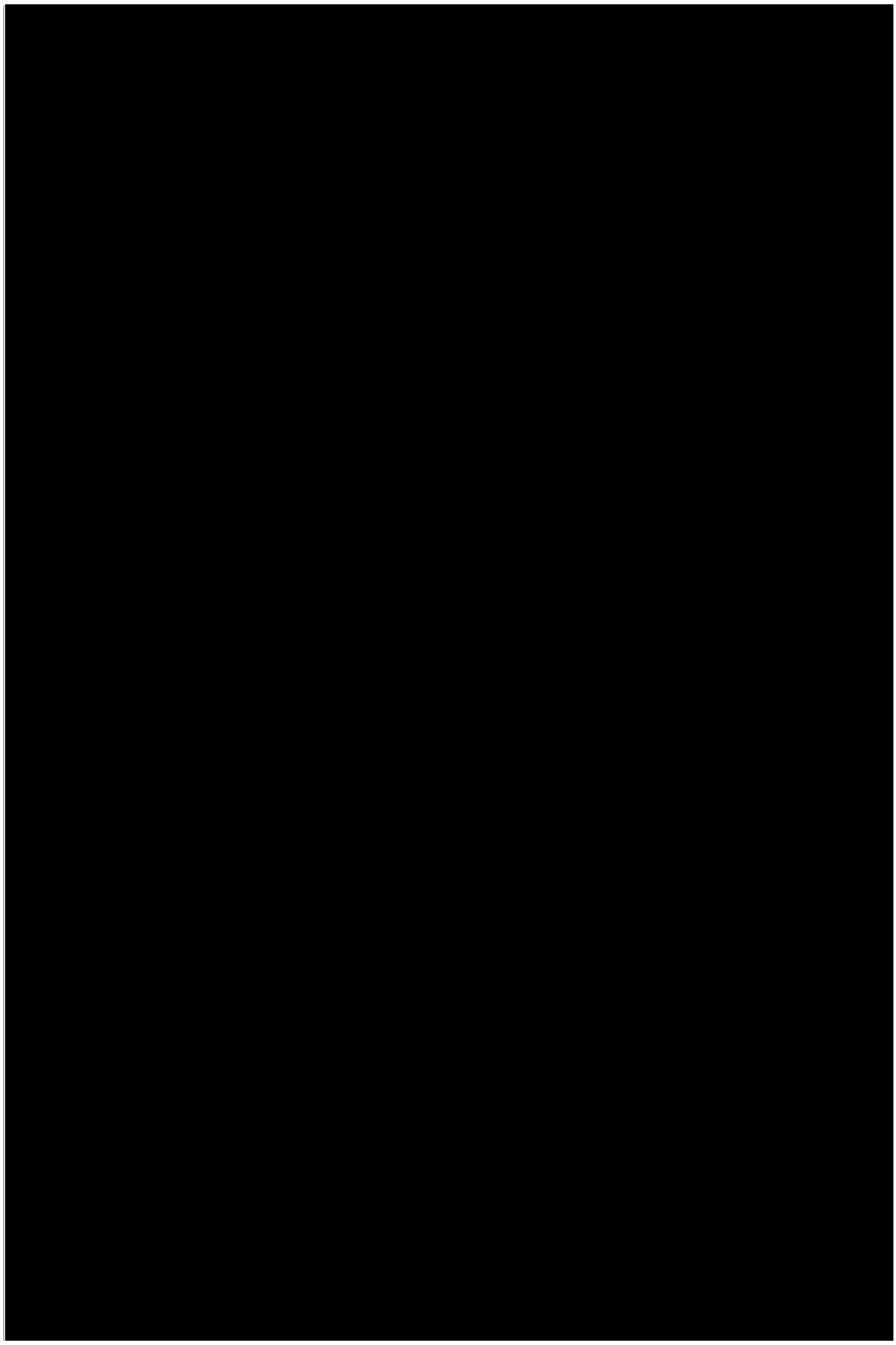


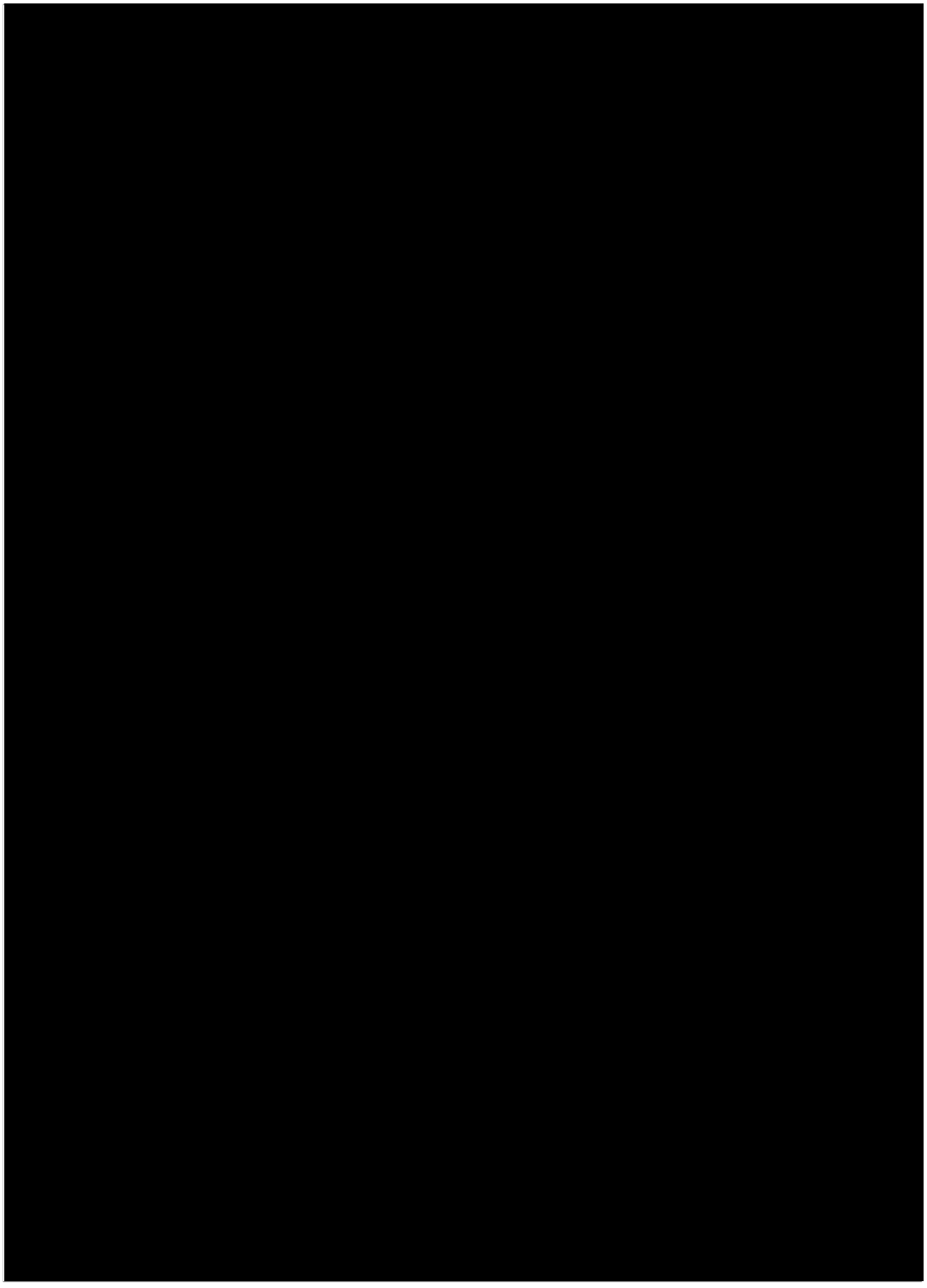












10 References

[1] Keininger D, Coteur G. Assessment of self-injection experience in patients with rheumatoid arthritis: psychometric validation of the Self-Injection Assessment Questionnaire (SIAQ). Health and Quality of Life Outcomes. 2011;9(2): 1-11

[2] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for Industry, Rheumatoid Arthritis: Developing Drug Products for Treatment. Draft Guidance. May 2013. Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM354468.pdf

[3] World Health Organizations (WHO). Expert Committee on Biological Standardization. Guidelines on evaluation of similar biotherapeutic products. 19-23 Oct 2009.

[4] European Medicines Agency. Committee for Medicinal Products for Human Use. Guideline on similar biological medicinal products containing monoclonal antibodies-non-clinical and clinical issues (EMA/CHMP/BMWP/403543/2010). 01 December 2012.

[5] United States Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Scientific considerations in demonstrating biosimilarity to a reference product. Guidance for industry. Apr 2015.

[6] Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. APLAR J Rheumatol. 2007;10 (1):9-16.

[7] Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol. 2016;68(1):1-26.

[8] van der Heijde D, Breedveld FC, Kavanaugh A, et al. Disease activity, physical function, and radiographic progression after longterm therapy with adalimumab plus methotrexate: 5-year results of PREMIER. J Rheumatol. 2010; 37(11):2237-2246.

[9] Furst DE, Shciff MH, Fleischmann RM, et al. Adalimumab, a fully human anti–tumor necrosis factor-α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). J Rheumatol. 2003; 30(12):2563-2571.

[10] Weinblatt ME, Keystone EC, Daniel EF, et al. Adalimumab, a fully human anti–tumor necrosis factor alphamonoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. Arthritis Rheum. 2003; 48(1):35-45.

[11] Keystone EC, Kavanaugh AF, Sharp JT. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. Arthritis Rheum. 2004;50(5):1400-1411.

[12] Humira Prescribing Information (PI). AbbVie Inc, IL, USA; 2019. Available from: http://www.rxabbvie.com/pdf/humira.pdf

[13] Chen DY, Chou SJ, Hsieh TY, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. J Formos Med Assoc. 2009;108(4):310-319.

[14] Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. Application number: 125057/0. Approval letter. Dec 2002. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/BLA_125057_S000_HUMIRA_APPROV.PDF

[15] European Medicines Agency. EPAR Medicine overview. Humira.EMA/722522/2017. EMEA/H/C/000481. Available from: https://www.ema.europa.eu/en/documents/overview/humira-epar-medicine-overview_en.pdf

[16] Humira Summary of Product Characteristics (SmPC); AbbVie Limited, August 2019. Available from: https://www.ema.europa.eu/documents/product-information/humira-epar-product-information_en.pdf

[17] Kivitz A., Cohen S., Dowd J.E et al. Clinical Assessment of Pain, Tolerability, and Preference of an Autoinjection Pen Versus a Prefilled Syringe for Patient Self-Administration of the Fully Human, Monoclonal

Antibody Adalimumab: The TOUCH Trial. Clinical Therapeutics. 2006; 28 (10(: p1619-1629.

[18] Aletaha D, Neogi T, Silman A.J, et al. 2010 Rheumatoid arthritis classification criteria. an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheum2010; 62(9): 2569-2581.

[19] Rostoker G, Andrivet P, Pham I, et al. A modified Cockcroft-Gault formula taking into account the body surface area gives a more accurate estimation of the glomerular filtration rate. J Nephrol. 2007;20(5):576-85.

[20] Hochberg M.C., Chang R.W., Dwosh I. et al. The American College of Rheumatology 1991 Revised Criteria for the Classification of Global Functional Status in Rheumatoid Arthritis. Arthritis Rheum. 1992; 35(5): 498-502.

[21] Whittle SL, Hughes RA. Folate supplementation and methotrexate treatment in rheumatoid arthritis: a review. Rheumatology. 2004; 43(3):267-71.

[22] Prevoo M.L., van 't Hof MA, Kuper HH, et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995; 38(1): 44-48.

[23] DAS28. MW Word DAS28. Available from: https://www.das-score.nl/das28/DAScalculators/DAS28frm%20v26-7-2012.doc

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