CLINICAL STUDY PROTOCOL

A Randomized, Placebo Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis

PROTOCOL NUMBER CT-P13 3.7

EudraCT Number:	2019-003849-15
Test Formulation:	Subcutaneous injection CT-P13 (CT-P13 SC)
Sponsor:	CELLTRION, Inc.
Sponsor Contact:	[redacted]
SAE Reporting:	[redacted]
Version and Date of Protocol:	Protocol Version 5.0, 04 August 2020

Protocol Approval – Sponsor Signatory

Study Title	A Randomized, Placebo Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis
Protocol Number	CT-P13 3.7
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Protocol accepted and approved by:

Head of Clinical Planning Department

[redacted]

Signature Date

Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Randomized, Placebo Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 5.0, dated 04 August 2020, the International Council for Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and the Declaration of Helsinki (WMA2013), and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a subinvestigator.

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

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

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

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Protocol Synopsis

Protocol Number: CT-P13 3.7

Title: A Randomized, Placebo Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients with Moderately to Severely Active Ulcerative Colitis

Clinical Phase: Phase 3

Planned number of centers/countries: The study will be conducted in 230 centers in 27 countries

Test Drug Formulation, Dose and Regimen:

Induction Phase:

Three doses of CT-P13 5 mg/kg by intravenous (IV) infusion administered at Weeks 0, 2, and 6 as a 2-hour infusion per dose will be given initially prior to receiving subcutaneous (SC) injection of CT-P13.

Maintenance Phase:

From Week 10, CT-P13 SC 120 mg will be administered every 2 weeks via pre-filled syringe (PFS) through Week 54.

Extension Phase:

From Week 56, CT-P13 SC 120 mg will be administered every 2 weeks via PFS through Week 102.

Reference Drug, Dose and Regimen:

Induction Phase:

Three doses of CT-P13 (5 mg/kg) by IV infusion administered at Weeks 0, 2 and 6 as a 2-hour infusion per dose will be given initially prior to receiving SC injection of Placebo.

Maintenance Phase:

From Week 10, Placebo SC (matching volume to CT-P13 SC 120 mg) will be administered every 2 weeks via PFS through Week 54.

Objectives:

Primary objective:

- To demonstrate superiority of CT-P13 SC over Placebo SC based on clinical remission at Week 54

Secondary objective:

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

Exploratory objective:

- To evaluate additional efficacy

Sample size:

The sample size of 417 patients (278 in CT-P13 SC group and 139 in Placebo SC group) was estimated to provide 80% statistical power to detect a statistically significant clinical effectiveness of CT-P13 SC in comparison with Placebo SC based on the clinical remission at Week 54 assuming a treatment difference of 15% and placebo rate of 45% at the 1-sided significance level of 2.5%.

Considering a 32% non-responder rate of clinical response at Week 10 before randomization, a total of approximately 615 patients will be enrolled at Week 0. The number of enrolled patients may be adjusted based on the actual number of randomized at Week 10.

A total sample size of 417 patients provides at least 90% statistical power for clinical response at Week 54, one of the key secondary endpoints, under the assumption of a treatment difference of 20% and placebo rate of 50% at the 1-sided significance level of 2.5%. Key secondary endpoints other than clinical response at Week 54 are not applicable for power calculation due to lack of relevant references.

Main selection criteria:

Male or female patients with moderately to severely active ulcerative colitis (UC) who have a modified Mayo score without physician global assessment (PGA) subscore of 5 to 9 points with endoscopic subscore of ≥ 2

points and had an inadequate response to conventional therapy will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion criteria:

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

1. Patient is male or female aged 18 to 75 years, inclusive.
2. Patient has moderately to severely active UC with a modified Mayo score of 5 to 9 points with endoscopic subscore of ≥ 2 points at Screening.
3. Patient with UC, confirmed by endoscopic or radiographic and histological criteria. Histopathology report supporting the diagnosis must be available in the source documents prior to the first administration of the study drug (Day 0).
4. Patient who has been treated for active UC but has not responded despite conventional therapy including corticosteroids alone or in combination with 6-mercaptopurine or azathioprine, or who is intolerant to or has medical contraindications to such therapies.
5. Patient who is receiving stable doses of the following UC treatments or currently not receiving UC treatment during specified time frame:
   - Azathioprine, or 6-mercaptopurine, or methotrexate for at least 8 weeks prior to the first administration of the study drug (Day 0)
   - Oral corticosteroids at the equivalent dose of 20 mg/day or less of prednisone for at least 2 weeks prior to the first administration of the study drug (Day 0)
   - Oral budesonide at the dose of 9 mg/day or less at least for 2 weeks prior to the first administration of the study drug (Day 0)
   - Oral 5-aminosalicylates for at least 4 weeks prior to the first administration of the study drug (Day 0)
   - Antibiotics (e.g., ciprofloxacin, metronidazole) for at least 4 weeks prior to the first administration of the study drug (Day 0).
6. Patient who has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:
   - Serum creatinine < 1.5×upper limit of normal (ULN) or an estimated creatinine clearance level > 50 mL/min (by Cockcroft-Gault formula).
   - Serum alanine aminotransferase < 2.5×ULN
   - Serum aspartate aminotransferase < 2.5×ULN
   - Serum total bilirubin < 2×ULN
7. Patient who has the following clinical hematology results at Screening:
   - Hemoglobin ≥ 8.5 g/dL (SI [Système International d'Unités] units: ≥ 85 g/L or 5.28 mmol/L)
   - White blood cell count ≥ 3.5×10^3 cells/μL (SI units: ≥ 3.5×10^9 cells/L)
   - Neutrophil count ≥ 1.5×10^3 cells/μL (SI units: ≥ 1.5×10^9 cells/L)
   - Platelet count ≥ 100×10^3 cells/μL (SI units: ≥ 100×10^9 cells/L)
8. Patient (or legal guardian, if applicable) who 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 or understand verbal and/or written instructions, and has signed and dated the written informed consent form with date prior to participation in the study.
9. For both male and female patients, the patient and his or her partner of childbearing potential who agree to use one of the following medically acceptable methods of contraception during the course of the study and for 6 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilized):
   - Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
   - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)

- Intrauterine device

Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use any of medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

Exclusion criteria:

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

General Exclusion Criteria:

1. Patient who has previously received 2 or more biologic agents, 2 or more Janus kinase (JAK) inhibitors, or 2 or more both biologic agents and JAK inhibitors.
2. Patient who has previously received either a tumor necrosis factor-alpha (TNFα) inhibitor or biologic agent within 5 half-lives prior to the first administration of the study drug (Day 0).
3. Patient who has previously demonstrated inadequate response or intolerance to TNFα inhibitors for the treatment of UC.
4. Patient who has previously received infliximab for treatment of UC or other disease.
5. Patient who has allergies to any of the excipients of infliximab or any other murine and/or human proteins, or has a hypersensitivity to immunoglobulin products.
6. Patient who has received or has a plan to receive any of following prohibited medications or treatments:
   - Parenteral corticosteroids for the treatment of UC within 2 weeks prior to the first administration of the study drug (Day 0)
   - Rectally administered medications containing corticosteroids or 5-aminosalicylates for the treatment of UC within 2 weeks prior to the first administration of the study drug (Day 0).
   - JAK inhibitors including but not limited to tofacitinib and baricitinib within 4 weeks prior to the first administration of the study drug (Day 0)
   - Alkylating agents within 12 months prior to the first administration of the study drug (Day 0)
   - Cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks prior to the first administration of the study drug (Day 0)
   - Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 0)
   - Abdominal surgery for, including but not limited to, active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection, or intra-abdominal or pancreatic abscess requiring surgical drainage within 6 months prior to the first administration of the study drug (Day 0)
   - Nonautologous stem cell therapy (e.g., Prochymal) within 12 months prior to the first administration of the study drug (Day 0)
   - Apheresis (e.g., Adacolumn apheresis) for the treatment of UC within 3 weeks prior to the first administration of the study drug (Day 0)
   - Use of total parenteral nutrition within a month prior to the first administration of the study drug (Day 0)
   - Use of exclusive enteral nutrition for more than 3 consecutive days within a month or any single day of exclusive enteral nutrition within 2 weeks prior to the first administration of the study drug (Day 0)
7. Patient who has a current or history of any of the following infections:
   - Known infection with hepatitis B or hepatitis C (active or carrier state), or infection with human immunodeficiency virus (HIV). However, a patient who is without cirrhosis of liver and recovered from a past hepatitis B or hepatitis C infection can be enrolled. In the case of hepatitis C infection, a patient who has achieved a sustained virologic response for at least 12 weeks after completing the treatment for hepatitis C infection can be enrolled.
   - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within

4 weeks prior to the first administration of the study drug (Day 0)

- Other serious infection, in the investigator's opinion, within 6 months prior to the first administration of the study drug (Day 0)
- Recurrent herpes zoster or other chronic or recurrent infections, in the investigator's opinion, within 6 weeks prior to the first administration of the study drug (Day 0)
- Past or current granulomatous infections or opportunistic infections (e.g., *Pneumocystis carinii*, aspergillosis, or mycobacteria other than TB) or invasive fungal infection (e.g., histoplasmosis)
- Evidence of infection with cytomegalovirus within 6 months prior to the first administration of the study drug (Day 0)
- Evidence of *Clostridium difficile* toxin within 3 months prior to the first administration of the study drug (Day 0)
- Positive stool examinations for enteric pathogens, pathogenic ova or parasites at Screening

8. Patient who has a medical condition including 1 or more of the following:
   - Ulcerative colitis limited to only the rectum or to less than 15 cm of the colon
   - Evidence of toxic megacolon
   - Diagnosed with Crohn's Disease or indeterminate colitis
   - Extensive colonic resection (subtotal and total colectomy) prior to the first administration of the study drug (Day 0)
   - Evidence of fixed symptomatic stenosis or obstruction of the large intestine
   - Evidence of colonic mucosal dysplasia or adenomatous polyps. However, a patient whose adenomatous polyps are completely removed and free of polyps at Screening can be enrolled.
   - For a patient who has an increased risk for colorectal cancer, a full colonoscopy must be performed at Screening:

     a. If the patient, regardless of age, has extensive colitis for ≥ 8 years.

     However, full colonoscopy at Screening would not be required if there is documented evidence of free of colonic adenomas or dysplasia as a source document:

     b. If the patient is ≥ 45 years of age, a full colonoscopy within 5 years prior to the first administration of the study drug (Day 0) is required to exclude adenomatous polyps. A patient whose adenomas have been completely excised prior to the first administration of the study drug (Day 0) can be enrolled.

     c. If the patient, regardless of age, has disease limited to left side of colon (i.e., distal to splenic flexure) for ≥ 10 years, a full colonoscopy performed within 1 year prior to the first administration of the study drug (Day 0) is required to survey for dysplasia. A patient who does not have an identified dysplasia or cancer on biopsies can be enrolled.
   - Currently require or are anticipated to require surgical intervention for UC during the study
   - Stoma (e.g., ileostomy or colostomy) within 6 months prior to the first administration of the study drug (Day 0)
   - Body mass index ≥ 35 kg/m^2
   - Uncontrolled diabetes mellitus, even after insulin treatment
   - Uncontrolled hypertension (as defined by systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg)
   - A known malignancy within 5 years prior to the first administration of the study drug (Day 0), except completely excised and cured squamous carcinoma in situ of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
   - History of lymphoma, lymphoproliferative disease, or bone marrow hyperplasia
   - New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina, or clinically significant electrocardiogram [ECG] abnormalities), or myocardial

infarction within 6 months prior to the first administration of the study drug (Day 0)
- History of organ transplantation, including corneal graft/transplantation
- Any uncontrolled, clinically significant respiratory disease in the investigator's opinion including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion
- Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain Barré syndrome
- Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage)
- Any other serious, acute, or chronic medical, or psychiatric conditions that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results

9. Patient who has a current or history of drug or alcohol abuse within 12 months prior to the first administration of the study drug (Day 0).
10. Patient who has had treatment with any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 0) or 5 half-lives, whichever is longer.
11. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.
12. Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.

Tuberculosis Exclusion Criteria:

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

Study Design:

This study is a randomized, placebo controlled, double-blind, multicenter, parallel-group, Phase 3 study, designed to evaluate the efficacy, PK, PD and safety of CT-P13 SC as maintenance therapy in patients with moderately to severely active UC who have had an inadequate response to conventional therapy.

Approximately 615 patients with moderately to severely active UC will be enrolled in the open-label Induction Phase. All enrolled patients will receive induction doses of CT-P13 5 mg/kg via IV infusion at Weeks 0, 2, and 6. After the patients receive 3 full doses of CT-P13 via IV infusion, those patients classified as a clinical responder at Week 10 based on modified Mayo score without PGA subscore, and also have no safety concerns

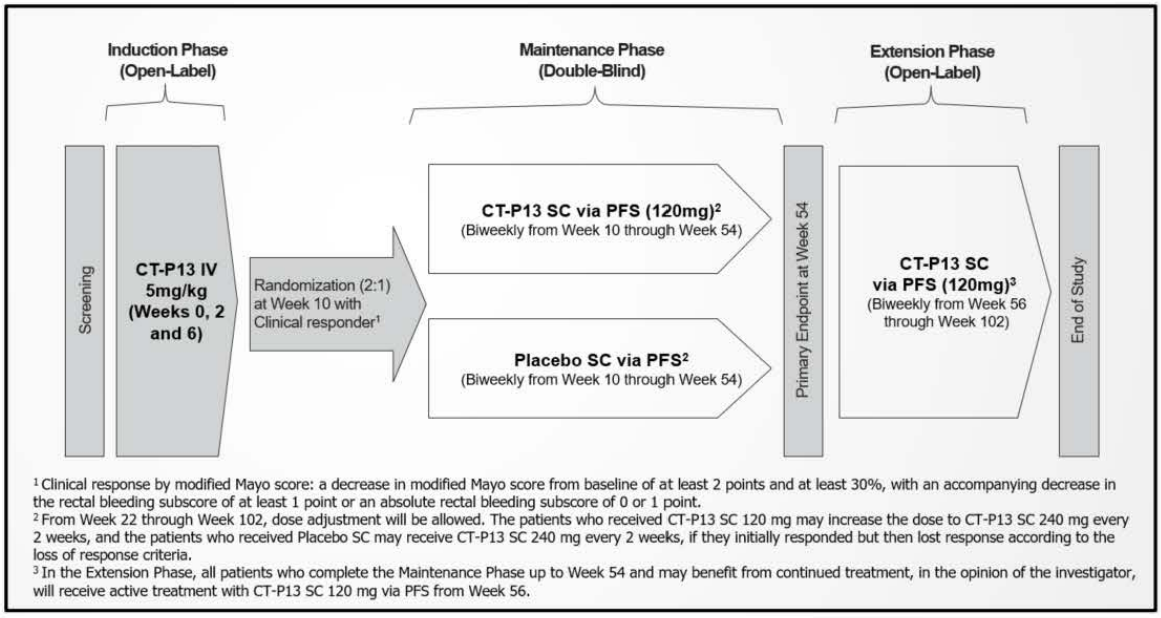
at the investigator's discretion will be randomly assigned before Week 10 treatment in a 2:1 ratio into either CT-P13 SC or Placebo SC treatment groups. Patients classified as non-responders at Week 10 will not continue the study drug treatment. A clinical responder at Week 10 is defined as a patient with a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

It is estimated that at least 417 patients (278 in CT-P13 SC group and 139 in Placebo SC group) will enter the double-blind Maintenance Phase. The Maintenance Phase treatment will continue up to Week 54 and the subsequent open-label Extension Phase treatment will continue up to Week 102. In the open-label Extension Phase, all patients will receive CT-P13 SC.

The duration of the study will be up to 112 weeks, which includes Screening (up to 6 weeks) and Treatment Period (up to the last dosing visit of study drug at Week 102) followed by End-of-Study (EOS) visit (after 4 weeks off dose period). The study will be unblinded to the predefined unblinded teams of CELLTRION, Inc. and [redacted] for reporting purposes after completion of the Week 54 assessments in all patients. However, the treatment assignment for the Maintenance Phase will remain blinded to the investigators, patients, and other teams of CELLTRION, Inc. and [redacted] until the completion of the study.

The overview of study design is presented in **Figure S1**.

Figure S1 Study Design Overview



[1] Clinical response by modified Mayo score: a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.
[2] From Week 22 through Week 102, dose adjustment will be allowed. The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg every 2 weeks, and the patients who received Placebo SC may receive CT-P13 SC 240 mg every 2 weeks, if they initially responded but then lost response according to the loss of response criteria.
[3] In the Extension Phase, all patients who complete the Maintenance Phase up to Week 54 and may benefit from continued treatment, in the opinion of the investigator, will receive active treatment with CT-P13 SC 120 mg via PFS from Week 56.

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

Study Schedule:

The study will comprise 3 study periods including Screening, Treatment Period (Induction Phase, Maintenance Phase and Extension Phase), and EOS visit.

Screening:

Screening will take place between Days –42 and 0 (up to 6 weeks) prior to the first CT-P13 IV infusion during the Induction Phase.

Treatment Period

- Open-label Induction Phase (dosing at Weeks 0, 2, and 6)
- Double-blind Maintenance Phase (dosing from Week 10 through Week 54)
- Open-label Extension Phase (dosing from Week 56 through Week 102)

In the open-label Induction Phase, the patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled on Day 0 (Week 0). All enrolled patients will receive a 2-hour CT-P13 IV (5 mg/kg)

infusion at Weeks 0, 2, and 6 as induction treatments. At Week 8, only endoscopy and biopsy for histologic assessment will be performed for the evaluation of Mayo score and mucosal healing at Week 10. The endoscopy result at Week 8 will be used for randomization at Week 10. Patients who are classified as a clinical responder at Week 10 based on modified Mayo score after receiving 3 full doses of CT-P13 IV infusion and for whom there are no safety concerns based on the investigator's discretion will be randomly assigned to receive either CT-P13 SC or Placebo SC before treatment on Day 70 (Week 10). A clinical responder at Week 10 is defined as a patient with a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

The randomization of treatment assignment will be stratified by the following:

- Previous exposure to biologic agent and/or JAK inhibitors (used or not used)
- Use of treatment with oral corticosteroids at Week 0 (used or not used)
- Clinical remission at Week 10 (remitter or non-remitter by modified Mayo score)

The double-blind Maintenance Phase will consist of further doses of CT-P13 SC or Placebo SC with the last dose administered no later than Week 54.

- Treatment group 1, CT-P13 SC: from Week 10, CT-P13 SC 120 mg will be administered every 2 weeks via PFS through Week 54.
- Treatment group 2, Placebo SC: from Week 10, Placebo SC (matching volume to CT-P13 SC 120 mg) will be administered every 2 weeks via PFS through Week 54

In the open-label Extension Phase, all patients who complete the Maintenance Phase up to Week 54 and may benefit from continued treatment, in the opinion of the investigator, will receive active treatment with CT-P13 SC 120 mg via PFS from Week 56. The patients who received the adjusted dose of CT-P13 SC 240 mg in the Maintenance Phase will continue receiving the same doses of CT-P13 SC for the study treatment in the Extension Phase. The Extension Phase will continue up to Week 102. From Week 22 through Week 102, dose adjustment will be allowed as follows:

- The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
- The patients who received Placebo SC may receive CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.

Loss of response is defined as follows: an increase in modified Mayo score $\geq$ 2 points and $\geq$ 30% from the Week 10 modified Mayo score with actual value of $\geq$ 5 points, and endoscopic subscore of $\geq$ 2 points.

On the day of initiation of dose adjustment, blood samples for PK and immunogenicity analysis will be collected before study drug administration. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter or non-responder at Week 54 in the analysis of the primary endpoint and key secondary endpoints.

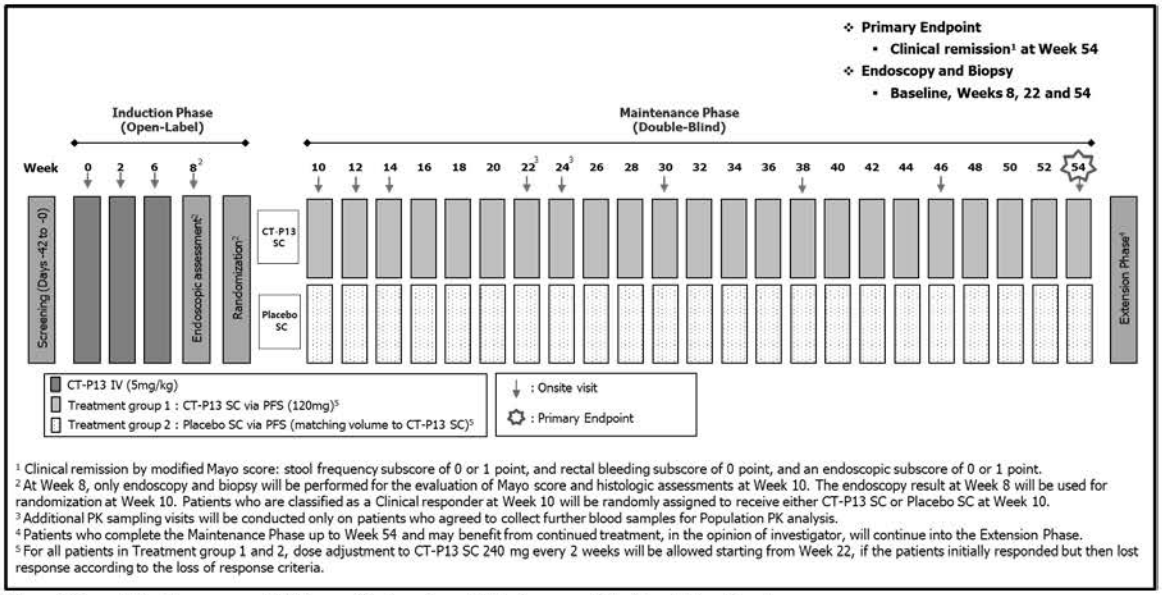
Patients may also be premedicated 30 to 60 minutes prior to the start of infusion of CT-P13 IV and any premedications such as, but not limited to, antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. The patients who receive CT-P13 SC or Placebo SC may also be treated with premedications at the investigator's discretion.

Patients will comply with all appropriate visits and assessments. Patients will return to the study center at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of TB and/or cardiovascular disease.

End of Study visit: The EOS visit will occur 4 weeks after the last dose of study drug is received. For patients who early discontinue study drug before administration of CT-P13 SC or Placebo SC at Week 10, the EOS visit will occur 8 weeks after the last dose of CT-P13 IV is received.

The study design for each treatment phase is illustrated in **Figure S2** and **Figure S3**.

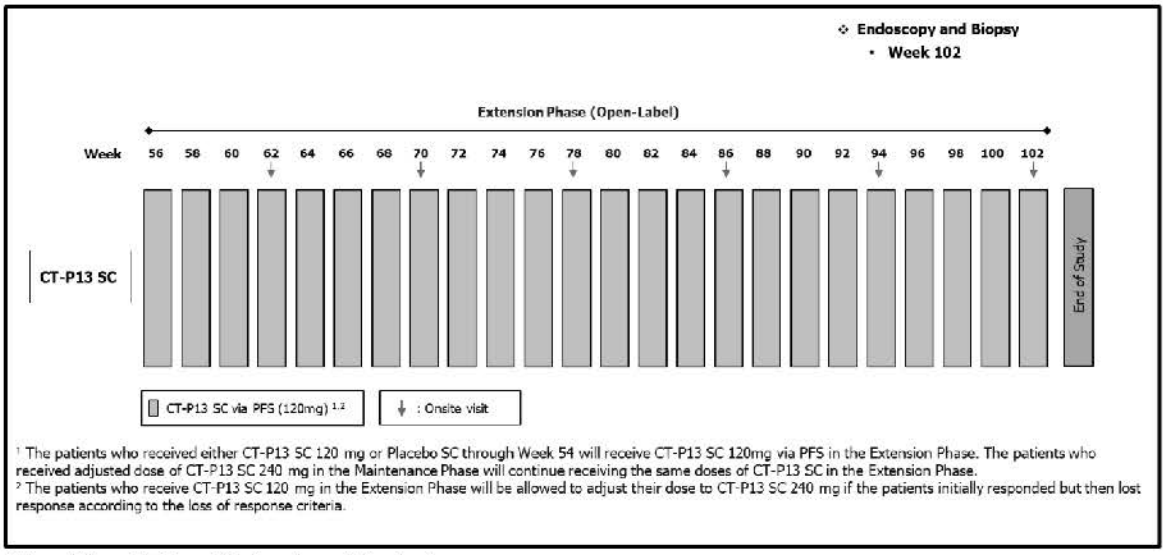
Figure S2 Study Design for Induction and Maintenance Phase



[1] Clinical remission by modified Mayo score: stool frequency subscore of 0 or 1 point, and rectal bleeding subscore of 0 point, and an endoscopic subscore of 0 or 1 point.
[2] At Week 8, only endoscopy and biopsy will be performed for the evaluation of Mayo score and histologic assessments at Week 10. The endoscopy result at Week 8 will be used for randomization at Week 10. Patients who are classified as a Clinical responder at Week 10 will be randomly assigned to receive either CT-P13 SC or Placebo SC at Week 10.
[3] Additional PK sampling visits will be conducted only on patients who agreed to collect further blood samples for Population PK analysis.
[4] Patients who complete the Maintenance Phase up to Week 54 and may benefit from continued treatment, in the opinion of investigator, will continue into the Extension Phase.
[5] For all patients in Treatment group 1 and 2, dose adjustment to CT-P13 SC 240 mg every 2 weeks will be allowed starting from Week 22, if the patients initially responded but then lost response according to the loss of response criteria.

Abbreviations: IV, intravenous; PFS, pre-filled syringe; PK, pharmacokinetics; SC, subcutaneous

Figure S3 Study Design for Extension Phase



[1] The patients who received either CT-P13 SC 120 mg or Placebo SC through Week 54 will receive CT-P13 SC 120mg via PFS in the Extension Phase. The patients who received adjusted dose of CT-P13 SC 240 mg in the Maintenance Phase will continue receiving the same doses of CT-P13 SC in the Extension Phase.
[2] The patients who receive CT-P13 SC 120 mg in the Extension Phase will be allowed to adjust their dose to CT-P13 SC 240 mg if the patients initially responded but then lost response according to the loss of response criteria.

Abbreviations: PFS, pre-filled syringe; SC, subcutaneous

Efficacy Assessments:

Primary endpoint:

- Clinical remission at Week 54, defined as the following modified Mayo score:
  (1) Stool frequency subscore of 0 or 1 point, and
  (2) Rectal bleeding subscore of 0 point, and
  (3) Endoscopic subscore of 0 or 1 point

Key Secondary endpoints:

- Clinical response at Week 54, defined as a decrease in modified Mayo score from baseline of at least

2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point

- Mucosal healing at Week 54, defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute Robarts Histopathology Index (RHI) score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point
- Corticosteroid-free remission at Week 54, defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline

Other Secondary endpoints:

- Clinical remission assessed at Weeks other than Week 54, defined as the following modified Mayo score:
  (1) Stool frequency subscore of 0 or 1 point, and
  (2) Rectal bleeding subscore of 0 point, and
  (3) Endoscopic subscore of 0 or 1 point
- Maintenance of clinical remission at Week 54, defined as being in clinical remission by modified Mayo score, among the patients in clinical remission by modified Mayo score at Week 10
- Sustained clinical remission at both Week 22 and Week 54, defined as a stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0
- Clinical response assessed at Weeks other than Week 54, defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Mucosal healing assessed at Weeks other than Week 54, defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute RHI score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point
- The scores and change from baseline in Short Inflammatory Bowel Disease Questionnaire

Exploratory endpoints:

- Clinical remission with normalization of stool frequency at Week 54, defined as following modified Mayo score:
  (1) Stool frequency subscore of 0 point, and
  (2) Rectal bleeding subscore of 0 point, and
  (3) Endoscopic subscore of 0 or 1 point
- Total clinical remission, defined as a total Mayo score (stool frequency, rectal bleeding, endoscopic, and PGA subscores) of 2 points or lower with no individual subscore exceeding 1 point
- Total clinical response, defined as a decrease in total Mayo score from baseline of at least 3 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Partial clinical remission, defined as a partial Mayo score (stool frequency, rectal bleeding, and PGA subscores) of 1 point or lower
- Partial clinical response, defined as a decrease in partial Mayo score from baseline of at least 2 points, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1 point

Pharmacokinetic Assessments:

Secondary endpoints:

For all patients, trough concentration (C_{trough} [concentration before the next study drug administration]) will be assessed up to Week 100 and observed maximum serum concentration (C_{max}) will be assessed at Week 6. Blood samples for PK analysis will be collected at pre-dose (prior to the beginning of study drug administration) at Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102, and within 15 minutes after the end of the

study drug infusion of Week 6. On the day of initiation of dose adjustment, blood samples for PK analysis will be collected at pre-dose.

For patients who agreed to collect further blood samples, additional blood samples for further Population PK analysis will be collected at the following time points:

- Any time between 48 hours and 72 hours after study drug administration of Week 22
- Any time between 120 hours and 168 hours after study drug administration of Week 22
- Pre-dose of Week 24

Pharmacodynamic Assessments:

Secondary endpoints:

- Fecal calprotectin
- C-reactive protein

Safety Assessments:

Secondary endpoints:

Safety assessments will be performed on immunogenicity, hypersensitivity monitoring (including delayed hypersensitivity monitoring), vital sign measurements (including blood pressure, heart and respiratory rates, and body temperature) and weight, 12-lead ECGs, monitoring of TB signs and symptoms, chest X-ray, IGRA, diabetes mellitus assessment, monitoring of cardiovascular disease related signs and symptoms, NYHA functional classification assessment, hepatitis B and C and HIV-1 and -2 status, stool microbiology, anti-double-stranded DNA assessment, physical examination findings, AEs (including serious AEs), AEs of special interest (infusion-related reaction/systemic injection reaction [hypersensitivity/anaphylactic reaction], delayed hypersensitivity, localized injection site reaction, infection, malignancy), pregnancy testing, clinical laboratory analyses, monitoring of drug-induced liver injury, local site pain using 100 mm Visual Analogue Scale, and prior and concomitant medications.

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

- Immunogenicity
- Clinical laboratory analyses
- Complement (C3, C4) and total hemolytic complement

Data Analysis:

Statistical analysis:

Statistical analysis will be performed using [redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to locking of the database. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report. The randomization will be stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used), and clinical remission at Week 10 (remitter or non-remitter).

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

Final determination of the major protocol deviations that can affect the data analysis will be made at the blinded data review meeting held in accordance with International Council for Harmonisation Technical Requirements for Registration of Pharmaceuticals for Human Use harmonised tripartite guideline E9.

Population of analyses:

- The intent-to-treat (ITT) population is defined as all enrolled patients.
- The all-randomized population is defined as all randomly assigned patients at Week 10. The all-

randomized population will be used for analysis of primary and key secondary endpoints.

- The per-protocol (PP) population is defined as all randomly assigned patients who receive all doses (full) of study drug prior to Week 54 and who have at least 1 efficacy evaluation after Week 10 treatment and who do not have any major protocol deviation that is relevant to efficacy analysis. The PP population will also be used to provide supportive results of primary and key secondary endpoints.
- The PK population is defined as all randomly assigned patients who receive at least 1 dose (full) of study drug at Week 10 or thereafter and who have at least 1 PK result after Week 10 treatment.
- The PD population is defined as all randomly assigned patients who receive at least 1 dose (full) of study drug at Week 10 or thereafter and who have at least 1 PD result after Week 10 treatment.
- The safety population is defined as all randomly assigned patients who receive at least 1 dose (full or partial) of study drug at Week 10 or thereafter.

Efficacy analysis:

Primary: The primary endpoint will be tested at the 1-sided significance level of 2.5% on the all randomized population using the p-value from Fisher's exact test. If the p-value is ≤ 0.025, the statistical significance of the primary endpoint will be concluded. If the primary endpoint is significant, the fixed sequence procedure will be used for key secondary endpoints in order to preserve the Type I error. The supportive analysis for the primary endpoint will be performed in the PP population.

The primary endpoint, sensitivity analyses, will be performed using the logistic regression model and Cochran-Mantel-Haenszel test stratified by randomization factors on the all-randomized population. To evaluate the effect of missing data on the primary endpoint, tipping point analysis will be conducted on the all-randomized population. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter at Week 54 in the analysis of the primary endpoint.

Secondary: The key secondary endpoints will be tested at the 1-sided significance level of 2.5% on the all-randomized population using the p-value from Fisher's exact test. The first key secondary endpoint will be tested only if the primary endpoint is statistically significant, and the next key secondary endpoint will be tested only if the previous key secondary endpoint is statistically significant. The supportive analysis for the key secondary endpoints will be performed in the PP population. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter or non-responder at Week 54 in the analysis of key secondary endpoints. The secondary endpoints will be summarized using descriptive statistics or frequency tables.

Pharmacokinetic analysis:

Pharmacokinetic parameters will be computed by noncompartmental methods using appropriate validated software [redacted]

The PK parameters and concentrations at each time point will be presented in listings and summarized in tables. The summary tables will display the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum, geometric mean, and the coefficient of variation. The PK parameters and concentrations will be summarized in the PK population.

Pharmacodynamic analysis:

The PD endpoints will be presented in listings and summarized in tables. In addition to the standard summary statistics, the geometric mean and coefficient of variation will also be presented at each time point. The PD endpoints will be analyzed in the PD population.

Safety analysis:

Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities v22.1 or the most recent version. Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events v5.0. Prior and concomitant medications will be coded to drug class and preferred term according to the World Health Organization Drug Dictionary Sep 2019 or later. All safety data will be listed and summarized by treatment group as appropriate in the safety population.

List of Abbreviations

Abbreviation	Definition
5-ASA	5-aminosalicylates
6-MP	6-mercaptopurine
ADE	adverse device effect
ADR	adverse drug reaction
AE	adverse event
AI	auto-injector
ALT	alanine aminotransferase
Anti-ds	anti-double stranded
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AZA	azathioprine
CD	Crohn's disease
CFR	Code of Federal Regulations
CRP	C-reactive protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
C_{max}	observed maximum serum concentration
C_{trough}	trough concentration
DILI	drug-induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
EOS	End-of-Study
ESR	erythrocyte sedimentation rate
FDA	United States Food and Drug Administration
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Definition
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IGRA	interferon-γ release assay
INR	international normalized ratio
IRB	institutional review board
ITT	intent-to-treat
IV	intravenous
IWRS	interactive web response system
JAK	Janus kinase
MedDRA	Medical Dictionary for Regulatory Activities
MTX	methotrexate
NYHA	New York Heart Association
PD	pharmacodynamics(s)
PFS	pre-filled syringe
PGA	physician global assessment
PK	pharmacokinetic(s)
PP	per-protocol
PT	preferred term
PVG	pharmacovigilance
RA	rheumatoid arthritis
RHI	Robarts Histopathology Index
SADE	Serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SI	Système International d'Unités
SIBDQ	Short Inflammatory Bowel Disease Questionnaire

Abbreviation	Definition
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SVR	sustained virologic response
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor-alpha
UC	ulcerative colitis
ULN	upper limit of normal
VAS	Visual Analogue Scale
WHO	World Health Organization

1 Introduction

1.1 Background

Tumor necrosis factor-alpha (TNFα), a proinflammatory cytokine, is a key mediator of inflammation shown to be a central factor in inflammatory immune response [Hanauer et al. 2002; Hsia et al. 2006]. In general, TNFα is produced mainly by macrophages, but also by a broad variety of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts, and neuronal tissue. It has a wide spectrum of activities including coordinating host immune and inflammatory response to infectious, malignant, and autoimmune conditions. There are 2 types of TNF receptors, p55 and p75, which are part of a large family of structurally related cell-surface receptors [Bazzoni F, Beutler B 1996]. There is evidence that the p75 receptor stimulates T cell proliferation and suppresses TNFα-mediated inflammatory responses, whereas the p55 receptor appears to be critical in triggering host defense and inflammatory responses [Tartaglia et al. 1993; Peschon et al. 1998].

Large amounts of TNFα are released in response to lipopolysaccharide, other bacterial products, and interleukin-1. TNFα induces proinflammatory cytokines such as interleukin-1 and interleukin-6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue-degrading enzymes produced by synoviocytes or chondrocytes or both. Whereas, initial TNFα expression in response to infection or injury is beneficial; elevated concentrations of TNFα have been found in involved tissues and fluids of patients with rheumatoid arthritis (RA), Crohn's disease (CD), ulcerative colitis (UC), ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.

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

Ulcerative colitis is an idiopathic, chronic inflammatory disease of the large intestine including rectum and generally extends to part of, or the entire, colon [Ordás et al. 2012]. Patients often require corticosteroids to control symptoms but corticosteroid causes steroid dependent or refractory disease even after steroid treatment [Faubion et al. 2001]. For treatment of UC, infliximab as an anti-TNFα agent has shown efficacy in inducing and maintaining clinical remission in patients with moderately to severely active UC [Rutgeerts et al. 2005].

1.2 CT-P13

CT-P13 intravenous (IV) is an approved biosimilar to US-licensed Remicade and EU-approved Remicade. Remicade was constructed by combining the antigen-binding variable regions of

the A2 mouse monoclonal antibody with the constant regions of both human immunoglobulin G kappa heavy and light chain [Cohen RB, Dittrich KA 2001]. CT-P13 IV is produced by a recombinant cell line cultured by fed batch and is purified by a series of steps that includes measures to inactivate and remove viruses. CT-P13 IV has an identical primary sequence to that of US-licensed Remicade and EU-approved Remicade.

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

A new formulation of CT-P13 for subcutaneous (SC) administration is under development as a liquid type, filled aseptically into a 1 mL pre-filled syringe (PFS) or auto-injector (AI). Each PFS and AI contains 120 mg of active substance (1 mL fill volume) and the excipients [redacted] sodium acetate, 4.5% (w/v) sorbitol, and [redacted] polysorbate 80 [redacted] No preservatives are present.

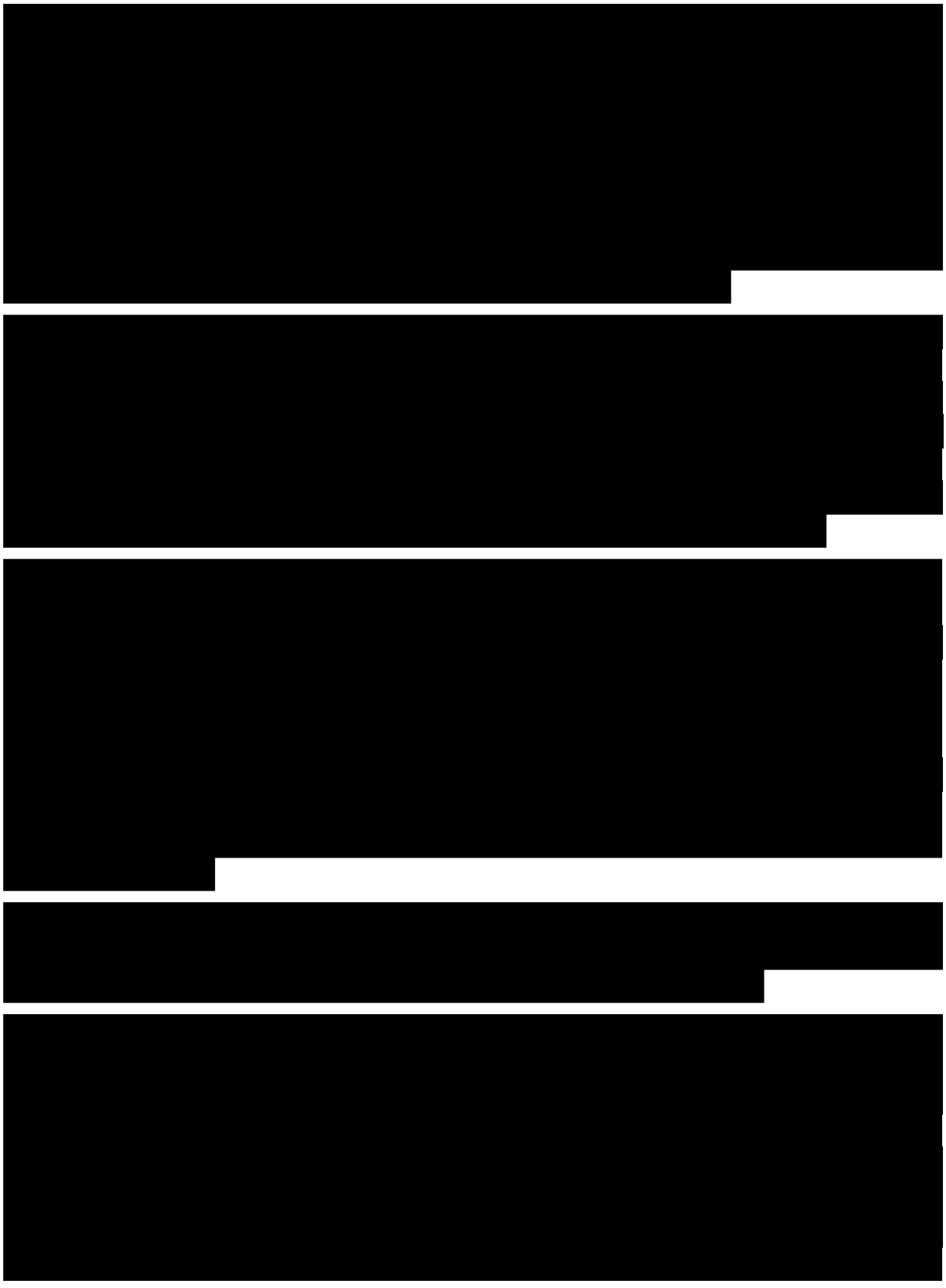
Unless otherwise specified, the name 'CT-P13 IV' will be used throughout the document to indicate the product initially developed for IV infusion. The SC formulation of CT-P13 will use the name 'CT-P13 SC'.

1.3 Non-clinical Studies

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

1.4 Clinical Studies

[redacted]



[redacted]

1.5 Study Rationale

Infliximab was initially developed for IV infusion, administered as a 2-hour infusion in previous studies. A new SC formulation of infliximab is being developed by CELLTRION, Inc. as an alternative to the IV regimen, as the injection typically takes less than 2 minutes. Potential benefits of such administration include improved patient convenience, better compliance, reduced pharmacy preparation times, and optimization of medical resources. The availability of an SC formulation of infliximab will increase the treatment options available to patients, particularly those wishing to self-administer their therapy [Jackisch et al. 2014]. This Phase 3 randomized, placebo controlled, double-blind, multicenter, parallel-group study is designed to evaluate the efficacy and safety of CT-P13 SC as a maintenance therapy in patients with moderately to severely active UC.

1.5.1 Dose Selection

From Study CT-P13 SC 1.6, it was demonstrated that administration of CT-P13 SC of 120 mg and 240 mg had sufficient efficacy without any sign of unexpected safety issues in adult patients with CD and UC. Thus, PK-PD modeling and simulation has been conducted to select the optimal dosing regimen to be used in this study.

The results from PK-PD modeling and simulation suggested that all dosage regimens of CT-P13 SC would achieve sufficient efficacy without any unexpected safety signal in CD and

UC patients. Simulations were then successfully employed to guide the optimal CT-P13 SC dosage regimens for future implementation in CD and UC treatment. It was concluded that the CT-P13 SC dosage regimen of 120 mg every 2 weeks is considered best for further evaluation in this study in patients with CD and UC.

The dosing regimen for the IV induction period for this study is the same as the currently approved induction dosing regimen for IV infliximab, and the SC dosing will start at Week 10, which is 4 weeks after the last IV induction dose at Week 6. This timing of first SC dose was chosen to ensure trough concentration (C_{trough}) levels remained close to the steady state plasma concentration throughout the SC dosing regimen, minimizing low plasma levels and thereby prevent enhancing potential for immunogenicity.

In conclusion, the dosing regimen of 3 IV induction doses of CT-P13 5mg/kg at Weeks 0, 2, and 6 followed by maintenance doses of CT-P13 SC 120 mg every 2 weeks starting at Week 10 is selected for this study.

2 Study Objectives

2.1 Primary Objective

The primary objective of this study is to demonstrate superiority of CT-P13 SC over Placebo SC based on clinical remission at Week 54.

2.2 Secondary Objective

The secondary objective of this study is to evaluate additional efficacy, PK, PD, and overall safety including immunogenicity.

2.3 Exploratory Objective

The exploratory objective of this study is to evaluate additional efficacy.

3 Investigational Plan

3.1 Study Design

This is a randomized, placebo controlled, double-blind, multicenter, parallel-group, Phase 3 study to evaluate the efficacy, PK, PD, and safety of the SC injection of CT-P13 (CT-P13 SC) as maintenance therapy in patients with moderately to severely active UC who have had an inadequate response to conventional therapy. Approximately 615 patients with moderately to severely active UC will be enrolled in the open-label Induction Phase. All enrolled patients will receive induction doses of CT-P13 5 mg/kg via IV infusion at Weeks 0, 2, and 6. After the patients receive 3 full doses of CT-P13 via IV infusion, those patients classified as a clinical responder at Week 10 based on modified Mayo score without physician global assessment (PGA) subscore, and also have no safety concerns at the investigator's discretion will be randomly assigned before Week 10 treatment in a 2:1 ratio into either CT-P13 SC or Placebo SC treatment groups. Patients classified as non-responders at Week 10 will not continue the study drug treatment. A clinical responder at Week 10 is defined as a patient with a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

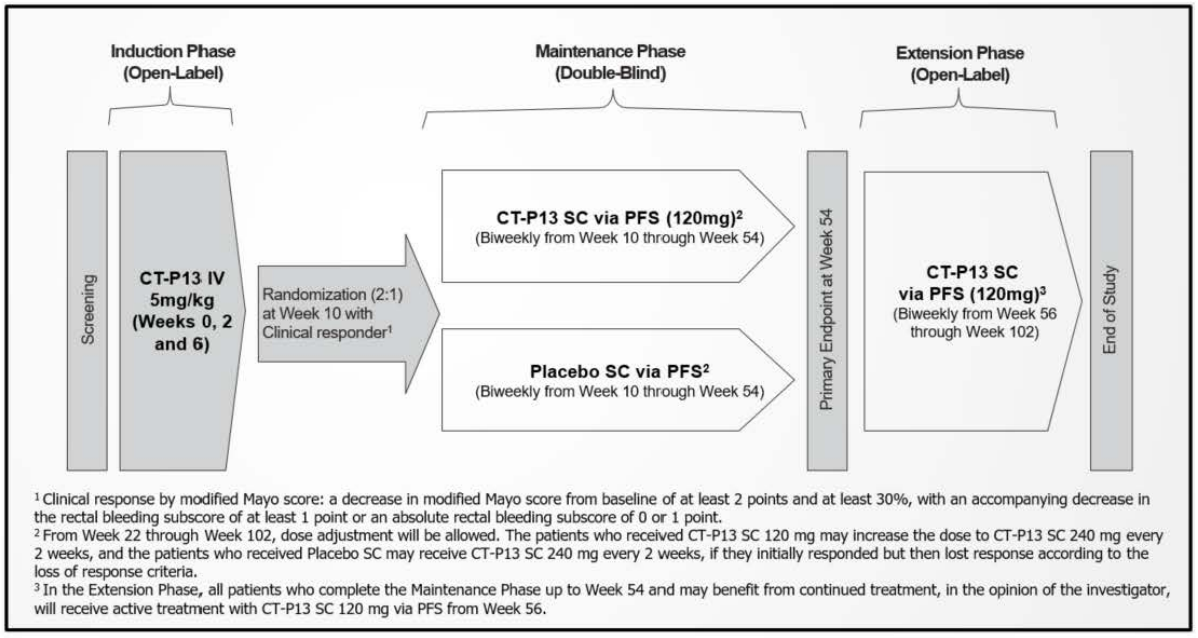
It is estimated that at least 417 patients (278 in CT-P13 SC group and 139 in Placebo SC group) will enter the double-blind Maintenance Phase. The Maintenance Phase treatment will continue up to Week 54 and the subsequent open-label Extension Phase treatment will continue up to Week 102. In the open-label Extension Phase, all patients will receive CT-P13 SC.

The duration of the study will be up to 112 weeks, which includes Screening (up to 6 weeks) and Treatment Period (up to the last dosing visit of study drug at Week 102) followed by End-of-Study (EOS) visit (after 4 weeks off-dose period).

The study will be unblinded to the predefined unblinded teams of CELLTRION, Inc. and [redacted] for reporting purposes after completion of the Week 54 assessments in all patients. However, the treatment assignment for the Maintenance Phase will remain blinded to the investigators, patients, and other teams of CELLTRION, Inc. and [redacted] until the completion of the study (Section 5.6).

The overview of study design is presented in Figure 3-1.

Figure 3-1 Study Design Overview



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

3.2 Study Overview

This study will comprise 3 study periods including Screening, Treatment Period (Induction Phase, Maintenance Phase, and Extension Phase), and EOS visit.

Screening: Screening will take place between Days –42 and 0 (up to 6 weeks) prior to the first CT-P13 IV infusion during the Induction Phase.

Treatment Period:

- Open-label Induction Phase (dosing at Weeks 0, 2, and 6)
- Double-blind Maintenance Phase (dosing from Week 10 through Week 54)
- Open-label Extension Phase (dosing from Week 56 through Week 102)

In the open-label Induction Phase, the patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled on Day 0 (Week 0). All enrolled patients will receive a 2-hour CT-P13 IV infusion (5 mg/kg) during onsite visits at Weeks 0, 2, and 6 as induction treatments. At Week 8, only endoscopy and biopsy for histologic assessment will be performed for the evaluation of Mayo score and mucosal healing at Week 10. The endoscopy result at Week 8 will be used for randomization at Week 10. Patients who are classified as a clinical responder at Week 10 based on modified Mayo score after receiving 3 full doses of CT-P13 via IV infusion and for whom there are no safety concerns based on the investigator's discretion will be randomly assigned to receive either CT-P13 SC or Placebo SC, before treatment on Day 70 (Week 10). A clinical responder at Week 10 is defined as a patient with a

decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point.

The randomization of treatment assignment will be stratified by the following:

- Previous exposure to biologic agent and/or Janus kinase (JAK) inhibitors (used or not used)
- Use of treatment with oral corticosteroids at Week 0 (used or not used)
- Clinical remission at Week 10 (remitter or non-remitter by modified Mayo score)

The double-blind Maintenance Phase will consist of further doses of CT-P13 SC or Placebo SC with the last dose administered no later than Week 54.

- Treatment group 1, CT-P13 SC: from Week 10, CT-P13 SC 120 mg will be administered every 2 weeks via PFS through Week 54.
- Treatment group 2, Placebo SC: from Week 10, Placebo SC (matching volume to CT-P13 SC 120 mg) will be administered every 2 weeks via PFS through Week 54.

In the open-label Extension Phase, all patients who complete the Maintenance Phase up to Week 54 and may benefit from continued treatment, in the opinion of the investigator, will receive active treatment with CT-P13 SC 120 mg via PFS from Week 56. The patients who received the adjusted dose of CT-P13 SC 240 mg in the Maintenance Phase will continue receiving the same doses of CT-P13 SC for the study treatment in the Extension Phase. The Extension Phase will continue up to Week 102.

From Week 22 through Week 102, dose adjustment will be allowed as follows:

- The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
- The patients who received Placebo SC may receive CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.

Loss of response is defined as follows: an increase in modified Mayo score $\geq$ 2 points and $\geq$ 30% from the Week 10 modified Mayo score with actual value of $\geq$ 5 points, and endoscopic subscore of $\geq$ 2 points (Section 5.2).

On the day of initiation of dose adjustment, blood samples for PK and immunogenicity analysis will be collected before study drug administration. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter or non-responder at Week 54 in the analysis of the primary endpoint and key secondary endpoints.

Patients may also be premedicated 30 to 60 minutes prior to the start of infusion of CT-P13 IV and any premedications such as, but not limited to, antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. The patients who receive CT-P13 SC or Placebo SC may also be treated with premedications at the investigator's discretion.

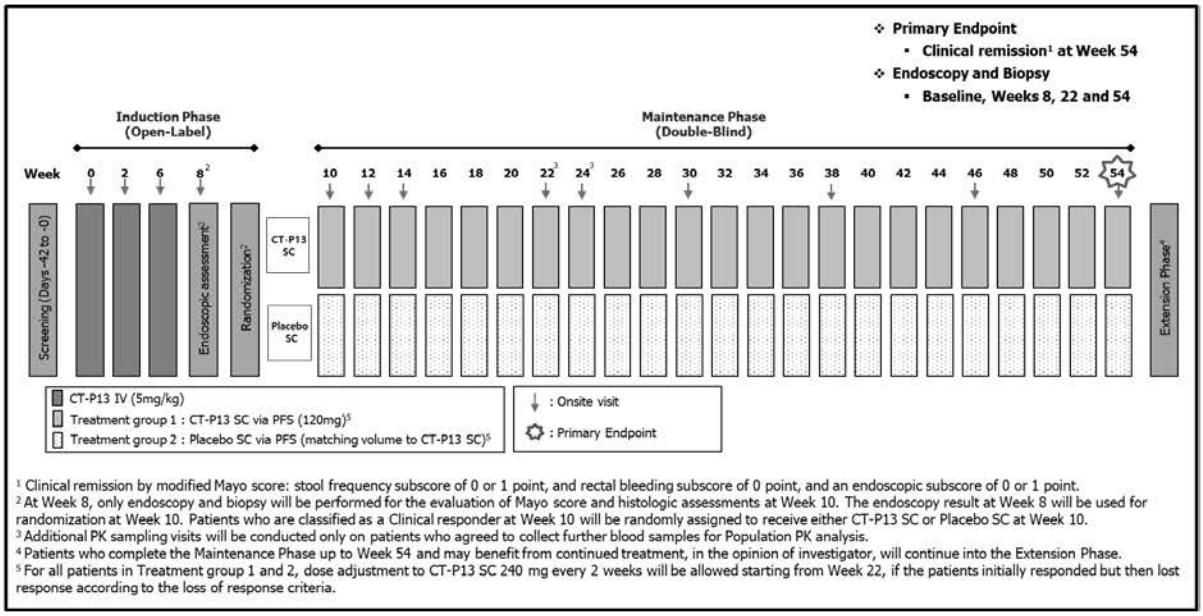
Patients will comply with all appropriate visits and assessments (Section 5.7). Patients will return to the study center at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB) and/or cardiovascular disease. The efficacy, PK, PD, and safety assessments will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

The CT-P13 SC or Placebo SC via PFS will be injected by the investigator or designee at Weeks 10 and 12, or until the patient (or caregiver, if needed) is properly trained and confident to administer the study drug at home, or until the investigator considers patient self-injection (or injection by caregiver, if needed) is appropriate. After proper training in PFS injection technique, patients (or caregiver, if needed) may self-inject with CT-P13 SC or Placebo SC via PFS at home or the study center at the scheduled administration week if their investigator determines that it is appropriate. CT-P13 SC or Placebo SC via PFS can be administered by another person, such as a family member or friend who is trained properly by the investigator or designee (Section 5.2.2).

End-of-Study visit: The EOS visit will occur 4 weeks after the last dose of study drug is received. For patients who early discontinue the study drug before administration of CT-P13 SC or Placebo SC at Week 10, the EOS visit will occur 8 weeks after the last dose of CT-P13 IV is received.

The study design for each treatment phase is illustrated in Figure 3-2 and Figure 3-3.

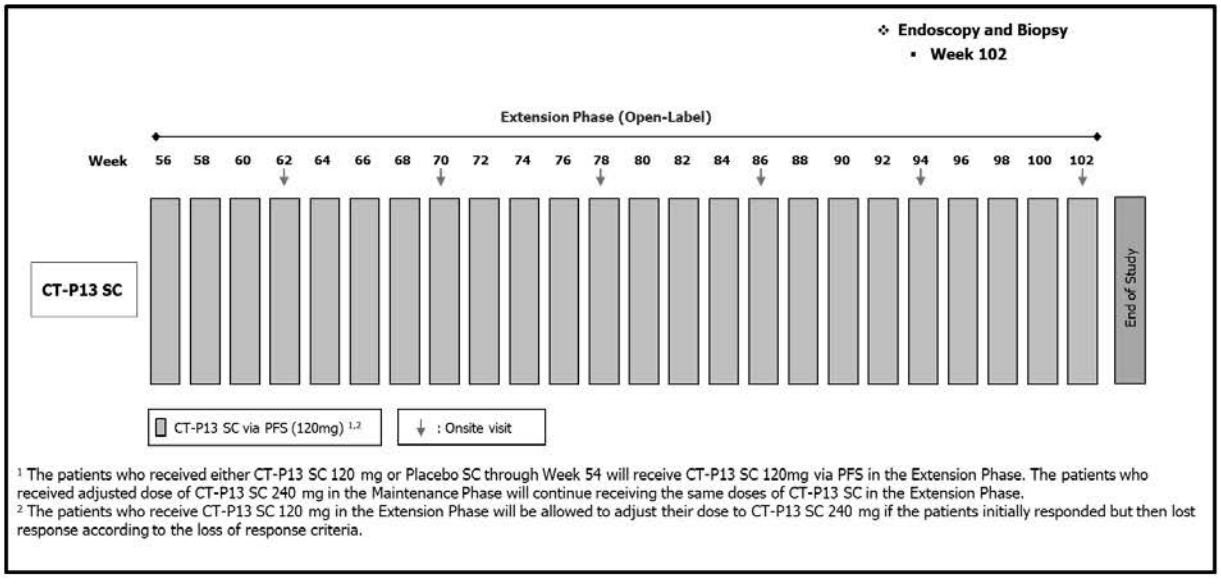
Figure 3-2 Study Design for Induction and Maintenance Phase



[1] Clinical remission by modified Mayo score: stool frequency subscore of 0 or 1 point, and rectal bleeding subscore of 0 point, and an endoscopic subscore of 0 or 1 point.
[2] At Week 8, only endoscopy and biopsy will be performed for the evaluation of Mayo score and histologic assessments at Week 10. The endoscopy result at Week 8 will be used for randomization at Week 10. Patients who are classified as a Clinical responder at Week 10 will be randomly assigned to receive either CT-P13 SC or Placebo SC at Week 10.
[3] Additional PK sampling visits will be conducted only on patients who agreed to collect further blood samples for Population PK analysis.
[4] Patients who complete the Maintenance Phase up to Week 54 and may benefit from continued treatment, in the opinion of investigator, will continue into the Extension Phase.
[5] For all patients in Treatment group 1 and 2, dose adjustment to CT-P13 SC 240 mg every 2 weeks will be allowed starting from Week 22, if the patients initially responded but then lost response according to the loss of response criteria.

Abbreviations: IV, intravenous; PFS, pre-filled syringe; PK, pharmacokinetics; SC, subcutaneous

Figure 3-3 Study Design for Extension Phase



[1] The patients who received either CT-P13 SC 120 mg or Placebo SC through Week 54 will receive CT-P13 SC 120mg via PFS in the Extension Phase. The patients who received adjusted dose of CT-P13 SC 240 mg in the Maintenance Phase will continue receiving the same doses of CT-P13 SC in the Extension Phase.
[2] The patients who receive CT-P13 SC 120 mg in the Extension Phase will be allowed to adjust their dose to CT-P13 SC 240 mg if the patients initially responded but then lost response according to the loss of response criteria.

Abbreviations: PFS, pre-filled syringe; SC, subcutaneous

4 Subject Selection and Withdrawal Criteria

4.1 Selection of Study Population

Approximately 615 patients will be enrolled at 230 centers in 27 countries. Male or female patients with moderately to severely active UC who have a modified Mayo score without PGA subscore of 5 to 9 points with endoscopic subscore of ≥ 2 points and had an inadequate response to conventional therapy will be considered for enrollment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.2 Inclusion Criteria

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

1. Patient is male or female aged 18 to 75 years, inclusive.
2. Patient has moderately to severely active UC with a modified Mayo score of 5 to 9 points with endoscopic subscore of ≥ 2 points at Screening.
3. Patient with UC, confirmed by endoscopic or radiographic and histological criteria. Histopathology report supporting the diagnosis must be available in the source documents prior to the first administration of the study drug (Day 0).
4. Patient who has been treated for active UC but has not responded despite conventional therapy including corticosteroids alone or in combination with 6-mercaptopurine (6-MP) or azathioprine (AZA), or who is intolerant to or has medical contraindications to such therapies.
5. Patient who is receiving a stable dose of the following UC treatments or currently not receiving UC treatment during the specified time frame:
    - Azathioprine, or 6-MP, or methotrexate (MTX) for at least 8 weeks prior to the first administration of the study drug (Day 0)
    - Oral corticosteroids at the equivalent dose of 20 mg/day or less of prednisone for at least 2 weeks prior to the first administration of the study drug (Day 0)
    - Oral budesonide at a dose of 9 mg/day or less for at least 2 weeks prior to the first administration of the study drug (Day 0)
    - Oral 5-aminosalicylates (5-ASA) for at least 4 weeks prior to the first administration of the study drug (Day 0)
    - Antibiotics (e.g., ciprofloxacin, metronidazole) for at least 4 weeks prior to the first administration of the study drug (Day 0)
6. Patient who has adequate renal and hepatic function at Screening as defined by the following clinical chemistry results:

- Serum creatinine < 1.5×upper limit of normal (ULN) or an estimated creatinine clearance level > 50 mL/min (by Cockcroft-Gault formula)
- Serum alanine aminotransferase (ALT) < 2.5×ULN
- Serum aspartate aminotransferase (AST) < 2.5×ULN
- Serum total bilirubin < 2×ULN

7. Patient who has the following clinical hematology results at Screening:
   - Hemoglobin ≥ 8.5 g/dL (SI [Système International d'Unités] units: ≥ 85 g/L or 5.28 mmol/L)
   - White blood cell count ≥ 3.5×10^3 cells/μL (SI units: ≥ 3.5×10^9 cells/L)
   - Neutrophil count ≥ 1.5×10^3 cells/μL (SI units: ≥ 1.5×10^9 cells/L)
   - Platelet count ≥ 100×10^3 cells/μL (SI units: ≥ 100×10^9 cells/L)
8. Patient (or legal guardian, if applicable) who 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 or understand verbal and/or written instructions, and has signed and dated the written informed consent form (ICF) prior to participation in the study.
9. For both male and female patients, the patient and his or her partner of childbearing potential who agree to use one of the following medically acceptable methods of contraception during the course of the study and for 6 months following discontinuation of study drug (excluding women who are not of childbearing potential and men who have been sterilized):
   - Barrier contraceptives (male condom, female condom, or diaphragm with a spermicidal gel)
   - Hormonal contraceptives (implants, injectables, combination oral contraceptives, transdermal patches, or contraceptive rings)
   - Intrauterine device

   Male and female patients and their partners who have been surgically sterilized for less than 6 months prior to the date of informed consent must agree to use any of the medically acceptable methods of contraception. Menopausal females must have experienced their last period more than 12 months prior to the date of informed consent to be classified as not of childbearing potential.

4.3 Exclusion Criteria

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

4.3.1 General Exclusion Criteria

1. Patient who has previously received 2 or more biologic agents, 2 or more JAK inhibitors, or 2 or more both biologic agents and JAK inhibitors.
2. Patient who has previously received either a TNFα inhibitor or biologic agent within 5 half-lives prior to the first administration of the study drug (Day 0).
3. Patient who has previously demonstrated inadequate response or intolerance to TNFα inhibitors for the treatment of UC.
4. Patient who has previously received infliximab for treatment of UC or other disease.
5. Patient who has allergies to any of the excipients of infliximab or any other murine and/or human proteins, or has a hypersensitivity to immunoglobulin products.
6. Patient who has received or has a plan to receive any of following prohibited medications or treatments:
    - Parenteral corticosteroids for the treatment of UC within 2 weeks prior to the first administration of the study drug (Day 0)
    - Rectally administered medications containing corticosteroids or 5-ASA for the treatment of UC within 2 weeks prior to the first administration of the study drug (Day 0).
    - JAK inhibitors including but not limited to tofacitinib and baricitinib within 4 weeks prior to the first administration of the study drug (Day 0)
    - Alkylating agents within 12 months prior to the first administration of the study drug (Day 0)
    - Cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil within 8 weeks prior to the first administration of the study drug (Day 0)
    - Live or live-attenuated vaccine within 4 weeks prior to the first administration of the study drug (Day 0)
    - Abdominal surgery for, including but not limited to, active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection, or intra-abdominal or pancreatic abscess requiring surgical drainage within 6 months prior to the first administration of the study drug (Day 0)

- Nonautologous stem cell therapy (e.g., Prochymal) within 12 months prior to the first administration of the study drug (Day 0)
- Apheresis (e.g., Adacolumn apheresis) for the treatment of UC within 3 weeks prior to the first administration of the study drug (Day 0)
- Use of total parenteral nutrition within a month prior to the first administration of the study drug (Day 0)
- Use of exclusive enteral nutrition for more than 3 consecutive days within a month or any single day of exclusive enteral nutrition within 2 weeks prior to the first administration of the study drug (Day 0)

7. Patient who has a current or history of any of the following infections:
   - Known infection with hepatitis B or hepatitis C (active or carrier state), or infection with human immunodeficiency virus (HIV). However, a patient who is without cirrhosis of liver and recovered from a past hepatitis B or hepatitis C infection can be enrolled. In the case of hepatitis C infection, a patient who has achieved a sustained virologic response (SVR) for at least 12 weeks after the completing the treatment for hepatitis C infection can be enrolled. (Section 6.4.12)
   - Acute infection requiring oral antibiotics within 2 weeks or parenteral injection of antibiotics within 4 weeks prior to the first administration of the study drug (Day 0)
   - Other serious infection, in the investigator's opinion, within 6 months prior to the first administration of the study drug (Day 0)
   - Recurrent herpes zoster or other chronic or recurrent infections, in the investigator's opinion, within 6 weeks prior to the first administration of the study drug (Day 0)
   - Past or current granulomatous infections or opportunistic infections (e.g., *Pneumocystis carinii*, aspergillosis, or mycobacteria other than TB) or invasive fungal infection (e.g., histoplasmosis)
   - Evidence of infection with cytomegalovirus within 6 months prior to the first administration of the study drug (Day 0)
   - Evidence of *Clostridium difficile* toxin within 3 months prior to the first administration of the study drug (Day 0)
   - Positive stool examinations for enteric pathogens, pathogenic ova or parasites at Screening
8. Patient who has a medical condition including 1 or more of the following:
   - Ulcerative colitis limited to only the rectum or to less than 15 cm of the colon

- Evidence of toxic megacolon
- Diagnosed with CD or indeterminate colitis
- Extensive colonic resection (subtotal and total colectomy) prior to the first administration of the study drug (Day 0)
- Evidence of fixed symptomatic stenosis or obstruction of the large intestine
- Evidence of colonic mucosal dysplasia or adenomatous polyps. However, a patient whose adenomatous polyps are completely removed and free of polyps at Screening can be enrolled.
- For a patient who has an increased risk for colorectal cancer, a full colonoscopy must be performed at Screening:

  a. If the patient, regardless of age, has extensive colitis for ≥ 8 years.

  However, full colonoscopy at Screening would not be required if there is documented evidence of free of colonic adenomas or dysplasia as a source document:

  b. If the patient is ≥ 45 years of age, a full colonoscopy within 5 years prior to the first administration of the study drug (Day 0) is required to exclude adenomatous polyps. A patient whose adenomas have been completely excised prior to the first administration of the study drug (Day 0) can be enrolled.

  c. If the patient, regardless of age, has disease limited to left side of colon (i.e., distal to splenic flexure) for ≥ 10 years, a full colonoscopy performed within 1 year prior to the first administration of the study drug (Day 0) is required to survey for dysplasia. A patient who does not have an identified dysplasia or cancer on biopsies can be enrolled.

- Currently require or are anticipated to require surgical intervention for UC during the study
- Stoma (e.g., ileostomy or colostomy) within 6 months prior to the first administration of the study drug (Day 0)
- Body mass index ≥ 35 kg/m^2
- Uncontrolled diabetes mellitus, even after insulin treatment
- Uncontrolled hypertension (as defined by systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg)

- A known malignancy within 5 years prior to the first administration of the study drug (Day 0), except completely excised and cured squamous carcinoma in situ of the uterine cervix, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma.
- History of lymphoma, lymphoproliferative disease, or bone marrow hyperplasia
- New York Heart Association (NYHA) class III or IV heart failure, severe uncontrolled cardiac disease (unstable angina or clinically significant electrocardiogram [ECG] abnormalities), or myocardial infarction within 6 months prior to the first administration of the study drug (Day 0)
- History of organ transplantation, including corneal graft/transplantation
- Any uncontrolled, clinically significant respiratory disease in the investigator's opinion, including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion
- Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain-Barré syndrome
- Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage)
- Any other serious, acute, chronic medical, or psychiatric conditions that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results

9. Patient who has a current or history of drug or alcohol abuse within 12 months prior to the first administration of the study drug (Day 0).
10. Patient who has had treatment with any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 0) or 5 half-lives, whichever is longer.
11. Female patients who are currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.
12. Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.

4.3.2 Tuberculosis Exclusion Criteria

1. Patient who has a current diagnosis of active TB or a history of active TB. A patient who has any evidence of history of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.

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

4.4 Withdrawal of Patients from the Study

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

When possible, the sponsor should be notified of the withdrawal of a patient from the study. For patients who withdraw for any reason, all study procedures should be performed on the day of withdrawal (or the day after withdrawal) and all attempts should be made to complete all EOS assessments at planned time points of the EOS visit. Any comments (spontaneous or elicited) or complaints made by the patient, together with the reason for withdrawal from the study, and the date of cessation of study drug must be recorded in the eCRF and source documents. As it is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE in every case, efforts must be made to undertake protocol-specified safety and follow-up procedures.

Patients who meet the individual withdrawal criteria indicated in Appendix 10.8, which are based on the safety concerns, should be withdrawn from the study. Reasons for withdrawal include the following:

- Patient develops signs of disease progression in the investigator's judgement
- 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 pregnant
- Investigator's decision
- Patient withdraws consent or refuses to continue treatment and/or procedures/observations
- Patient is lost to follow-up
- Patient dies
- Study is terminated by the sponsor
- Non-responder at Week 10

If necessary, the investigator may discuss with CELLTRION, Inc., or its designee any patient's reason for withdrawal. CELLTRION, Inc. may be contacted if clarification is required on a case-by-case basis. All withdrawn patients will retain their study number with the reason for withdrawal from the study.

4.4.1 Recruitment of Additional Patients

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

4.5 Premature Discontinuation of the Study

Reason for premature discontinuation of this study may include failing to meet the requirements of regulatory authority, change in opinion of the institutional review board (IRB)/ independent ethics committee (IEC), unexpected or significant safety risk, or at the discretion of CELLTRION, Inc.

An independent data safety monitoring board will thoroughly review and evaluate the safety data of study patients, and provide recommendations regarding the acceptability of continuing the study based on safety monitoring (see Section 9.4).

CELLTRION, Inc. 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 CELLTRION, Inc., all patients will be kept fully informed and an appropriate follow-up examination of the patients will be arranged. The investigator will inform the IRB or IEC of any premature termination or suspension of the study, where applicable.

5 Study Treatments

5.1 Method of Assigning Subjects to Treatment Groups

For initiating the double-blind Maintenance Phase, an interactive web response system (IWRS) will be used for the randomization. Biostatistician will generate the randomization schedule for the IWRS, which will link sequential patient randomization numbers to treatment codes. Patients classified as a clinical responder by modified Mayo score at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and have no safety concern based on the investigator's discretion will be randomized in a 2:1 ratio to receive either CT-P13 SC or Placebo SC, before starting treatment Day 70 (Week 10). The randomization will be stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score). Permuted block design will be used to randomize patients to treatment groups, where within each block the same pre-specified ratio of patients will be allocated to the treatment groups. The block size will not be revealed.

5.2 Treatments Administered

CT-P13 IV will be administered as a 2-hour (+15 minutes) IV infusion and CT-P13 SC or Placebo SC via PFS will be injected at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

The CT-P13 SC or Placebo SC via PFS will be injected by the investigator or designee at Weeks 10 and 12, or until the patient (or caregiver, if needed) is properly trained and confident to administer the study drug at home, or until the investigator considers patient self-injection or injection by caregiver is appropriate. After proper training in PFS injection technique, patients (or caregiver, if needed) may self-inject with CT-P13 SC or Placebo SC via PFS at home or the study center at the scheduled administration week if their investigator determines that it is appropriate. CT-P13 SC or Placebo SC via PFS can be administered by another person, such as a family member or friend who is trained properly by the investigator or designee (Section 5.2.2). CT-P13 SC or Placebo SC via PFS will be injected at a slow, steady rate at any one of the following sites:

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

For each subsequent SC injection, a different injection site will be used (i.e., injection site should be rotated). For example, if 2 injections will be injected on the same day, different sites for each injection will be used. If both arms were the last injection sites for multiple injections, subsequent injections will be injected on different sites such as the abdomen or the front of the

middle thighs. 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 a new injection should be given at least 3 cm away from the most recent area injected.

CT-P13 SC and Placebo SC should sit at room temperature for at least 30 minutes prior to injection and they must not be warmed in any other way.

From Week 22 through Week 102, dose adjustment will be allowed as follows:

- The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
- The patients who received Placebo SC may receive CT-P13 SC 240 mg (double injection [2 shots] of CT-P13 SC 120 mg) every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.

Loss of response is defined as follows: an increase in modified Mayo score $\geq$ 2 points and $\geq$ 30% from the Week 10 modified Mayo score with actual value of $\geq$ 5 points, and endoscopic subscore of $\geq$ 2 points.

5.2.1 Premedication

Patients may be premedicated 30 to 60 minutes prior to the start of infusion of CT-P13 IV and any premedications such as, but not limited to, antihistamine (at an equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at an equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. The patients who receive CT-P13 SC or Placebo SC may also be treated with premedications by investigator's discretion.

5.2.2 Training for Self-Injection of Study Drug

The investigator or designee will be trained about SC administration of study drug via PFS. This training must be documented. Detailed training instructions will be provided in the study manual. The trained investigator or designee will be responsible for training each individual patient (or caregiver, if needed) about proper SC administration of study drug via PFS. Printed instructions for use of PFS, and the patient's self-injection diary for PFS will be provided to the patient that will serve as a guide while administering the study drug.

Initial training for self-injection of CT-P13 SC or Placebo SC via PFS will be conducted at Weeks 10 and 12. If needed, the patient or caregiver will be retrained during the study on how to perform the injection of the study drug.

To assess how well the patient learned the SC injection of study drug and how well that information was retained, an actual patient injection of the study drug may be performed during a study center visit. During that visit, the investigator or designee will observe the patient as

they perform the injection without assistance or guidance provided from the investigator or designee.

Patients will be instructed to contact the investigator promptly in the event of any signs and symptoms of localized injection site reactions and/or infusion-related reaction/systemic injection reaction (hypersensitivity/anaphylactic reactions).

As discussed in Section 3.2, patients will return to the study center at regular scheduled time intervals for clinical assessments and blood sampling.

5.3 Identity of Investigational Product

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

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

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

CT-P13 IV will be prepared as detailed in the summary of product characteristics of Remsima [Remsima summary of product characteristics, 2019] and prescribing information of Inflectra [Inflectra US prescribing information, 2019].

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

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

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

As CT-P13 (infliximab) vials do not contain preservatives, the solution for infusion should be used as soon as possible and within 3 hours of reconstitution and dilution (a maximum of 1-hour interruption is permitted during administration [Section 5.7]). Including the maximum interruption allowed, the solution for infusion must be used within 4 hours of reconstitution and dilution. Any unused portion should be discarded. An infusion pump or gravity method will be used to administer the investigational product.

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

The CT-P13 SC drug product includes [redacted] sodium acetate, 4.5% (w/v) sorbitol, and [redacted] polysorbate 80 [redacted].

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

The following drug products will be used in the study:

Product	Supplied as:
CT-P13 IV	Vials containing 100 mg of CT-P13
CT-P13 SC	PFS containing 120 mg of CT-P13

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

5.4 Identity of CT-P13 Placebo Product

CT-P13 SC Placebo is formulated to include [redacted] sodium acetate, 4.5% (w/v) sorbitol, and [redacted] polysorbate 80 at a [redacted] as a sterile and liquid formulation in a PFS. It is a colorless, clear solution and free of visible particles. A 1.0 mL volume of CT-P13 SC Placebo presented as a liquid formulation is filled into a 1 mL PFS for SC administration.

CELLTRION, Inc. will provide adequate supplies of CT-P13 SC Placebo product for distribution to the centers.

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

Product	Supplied as:
CT-P13 SC Placebo	PFS containing CT-P13 SC formulation buffer without CT-P13

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

5.5 Management of Clinical Supplies

5.5.1 Study Drug Packaging and Storage

The clinical supplies group will provide prepacked supplies for each patient. Kits will be allocated to each patient via the IWRS system at each visit.

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

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

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

5.5.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and also that the inventory results are recorded in the drug accountability form maintained at the study center. The drug accountability will be verified by the monitor during onsite monitoring visits. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

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

The investigator will retain and store all original containers until these containers are inventoried by CELLTRION, Inc. Patients will return all the unused and empty syringes and containers. Unless otherwise instructed by CELLTRION, Inc., the investigator agrees at the end of the study to return all original containers containing unused study drug to CELLTRION, Inc. and containers (outer carton box) for used IV and SC study drugs will be destroyed once accountability is confirmed by the monitor.

The used vials and PFSs can only be destroyed if it is written in local standard operating procedures and a specific authorization is given by CELLTRION, Inc. Permission will be granted by CELLTRION, Inc. on a study-center-by-study-center basis after reviewing the study center destruction policy. This authorization may also be granted to destroy used vials, and PFSs immediately after administering to patients. Authorization from CELLTRION, Inc. is required before a patient is enrolled. The list of destroyed vials, and PFSs must be recorded. The investigator agrees to neither dispense the study drug from, nor store it at, any study center other than the study centers agreed upon with CELLTRION, Inc.

5.6 Blinding

As this study has a double-blind Maintenance Phase, the treatment assignment for the Maintenance Phase will be blinded to the investigators, patients and predefined CELLTRION, Inc. and [redacted] blinded teams until the final clinical study report (CSR) is generated.

5.6.1 Breaking the Blind for Maintenance Phase

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

The date, time, and reason for the unblinding must be documented in the appropriate field of the eCRF and source documents. The medical monitor must be informed as soon as possible. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the medical monitor and CELLTRION, Inc. Any patients for whom the blind is broken may continue in the study and receive the study drug at the investigator's discretion. Suspected unexpected serious adverse reactions (SUSAR), which are subject to expedited reporting, should be unblinded before submission to the regulatory authorities if required.

The overall randomization code will be broken only for reporting purposes. This will occur after the database is locked for the data of all patients collected up to Week 54. The unblinded team will be predefined prior to performing the analyses. The study drug assignment for the Maintenance Phase will remain blinded to the investigators, patients, and predefined CELLTRION, Inc. and [redacted] blinded teams until the final CSR is generated.

5.7 Treatment Compliance

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

CT-P13 SC or Placebo SC will be injected at a slow, steady rate (Section 5.2). The date and time of the injection visit as well as any deviations from the planned injection visit will be recorded in both the source documents and/or the eCRF.

After proper training in injection technique, patients may inject with CT-P13 SC or Placebo SC if their investigator determines that it is appropriate at the scheduled administration week.

At each instance of CT-P13 SC or Placebo SC self-injection, patients should record details of the injection in their patient diary including the date and time of injection, kit number of each syringe, the number of syringes administered, and administration sites. At each visit date, the investigator or designee will review the patient diary and check the number of returned syringes (unused) to judge the patient's dosing compliance and the source data will be recorded in the eCRF.

Every effort will be made to encourage patients' compliance with the study day visits and self-injection schedule. A dosing window of ±3 days is allowed, including self-injection. The minimal dose interval of 11 days is allowed from Week 10.

Patients will contact the investigator or designee at any time if he/she missed a dose or a dosing was out of window.

5.8 Prior, Concomitant, and Subsequent Medications

Use of all prior and concomitant medications for the treatment of UC, from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF (Section 6.4.21).

5.8.1 Azathioprine, or 6-Mercaptopurine, Methotrexate

Immunomodulators such as AZA, or 6-MP, or MTX will be allowed if patients have maintained stable doses for at least 8 weeks prior to first administration of the study drug (Day 0) (Section 4.2).

A stable dose of immunomodulators should be maintained throughout Week 54. Any change of doses for immunomodulators should be discussed with the medical monitors of CELLTRION, Inc. or its designee in advance.

5.8.2 Corticosteroids

Oral corticosteroids at the equivalent dose of 20 mg/day or less of prednisone will be allowed if the patient has received a stable dose for at least 2 weeks prior to the first administration of the study drug (Day 0) (Section 4.2).

For patients receiving corticosteroids at the first administration of the study drug (Day 0), corticosteroid treatment should be kept up to Week 10 at the same dose level. After Week 10, the dose will be tapered, and the following tapering regimen will be recommended: tapering rate of 2.5 mg/week is recommended at the maximum rate of 5 mg/week if current corticosteroids dose is > 10 mg/day equivalent dose of prednisone. In case of corticosteroids dose of ≤ 10 mg/day as equivalent dose of prednisone, tapering rate is recommended as 2.5 mg/week.

Oral budesonide at a dose of 9 mg/day or less will be allowed if the patient has received a stable dose for at least 2 weeks prior to the first administration of the study drug (Day 0) (Section 4.2). For patients receiving budesonide at the first administration of the study drug (Day 0), budesonide treatment should be kept up to Week 10 at the same dose level. After Week 10, the dose will be tapered and tapering rate of 3 mg every 2 weeks is recommended. The investigators may also follow local clinical practice for the tapering regimen.

Any dose increase of corticosteroids needs to be discussed with the medical monitors of CELLTRION, Inc. or its designee in advance.

5.8.3 5-Aminosalicylates

Only oral 5-ASA will be allowed if patients have maintained stable doses for at least 4 weeks prior to the first administration of study drug (Day 0) (Section 4.2).

A stable dose of oral 5-ASA should be maintained throughout Week 54.

5.8.4 Antibiotics

Antibiotics (e.g., ciprofloxacin, metronidazole) for the treatment of UC will be allowed if patients have maintained a stable dose for at least 4 weeks prior to the first administration of the study drug (Day 0) (Section 4.2).

For patients receiving antibiotics for the treatment of UC at the first administration of the study drug (Day 0), antibiotics treatment should be maintained up to Week 10 at the same dose level. After Week 10, continuing the usage of antibiotics for the treatment of UC needs to be discussed with the medical monitors of CELLTRION, Inc. or its designee in advance.

5.9 Prohibited Therapy

The following medications and treatments are prohibited during the study. Patients who have received or plan to receive these prohibited medications or treatments will not be enrolled in the study (see Exclusion criteria 6, Section 4.3.1, for complete list). Killed vaccines are acceptable during the study.

- Any other investigational device or medical product
- Any biologic agents or JAK inhibitors for the treatment of UC
- Anakinra, Abatacept, or Tocilizumab
- Parenteral corticosteroids for the treatment of UC
- Rectally administered medications containing corticosteroids or 5-ASA for the treatment of UC
- Any TNFα inhibitor, except for study drug
- Alkylating agents
- Cyclosporine, tacrolimus, sirolimus, or mycophenolate mofetil
- Live or live-attenuated vaccine
- Abdominal surgery for, including but not limited to, active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection or intra-abdominal or pancreatic abscess requiring surgical drainage
- Nonautologous stem cell therapy (e.g., Prochymal)
- Apheresis (e.g., Adacolumn apheresis) for the treatment of UC
- Use of exclusive enteral or total parenteral nutrition

6 Study Assessments and Procedures

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

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

6.1 Efficacy Assessments

Efficacy will be assessed by the evaluation of the Mayo score, mucosal healing and Short Inflammatory Bowel Disease Questionnaire (SIBDQ). All patients will have efficacy assessments performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

6.1.1 Mayo Score Assessment

Clinical response and remission will be assessed by the Mayo score (Appendix 10.5). The Mayo score will be calculated at the time points specified in the schedule of events (Table 10-1 and Table 10-2) prior to study drug administration. The Mayo score is composed of the patient's Mayo score diary entries and assessments performed by the site investigator including PGA and flexible proctosigmoidoscopy. At every study center visit, the Mayo score diary will be collected and reviewed before study drug administration; the investigator will review the Mayo score diary for these patient-reported outcomes to evaluate the efficacy of study drug treatment. To ensure quality of data and consistency, it is recommended that Mayo score assessments including flexible proctosigmoidoscopy are performed by the same physician at each center throughout the entire study period if possible. Source data related to the Mayo score should be recorded in relevant eCRF pages.

The total Mayo score is composed of the stool frequency, rectal bleeding, endoscopic and PGA subscores. The modified Mayo score is composed of the 3 components of the total Mayo score excluding PGA subscore, and the partial Mayo score is composed of the 3 components of the total Mayo score excluding endoscopic subscore. Among the components of the Mayo score, rectal bleeding and endoscopic subscores are modified in accordance with United States Food and Drug Administration (FDA) guidance (see Appendix 10.5).

Patients will complete a Mayo score diary according to patient diary instruction. To determine eligibility, the Mayo score diary will be completed within 3 days immediately prior to the first administration of the study drug (Day 0), and the Mayo score will be calculated at Day 0. With the exception of Screening, the Mayo score diary will be collected by patients for 7 days immediately prior to the Mayo score assessment and the most recent 3 days (not necessarily

consecutive days) within the 7 days will be used to calculate the Mayo score. If the Mayo score assessment is performed at the same date as the flexible proctosigmoidoscopy or full colonoscopy procedure, the 3 days overlapping with endoscopy procedure (i.e., from the day before and up to the next day of the endoscopy procedure) will not be used to calculate the Mayo score.

The stool frequency and rectal bleeding subscores will be calculated using the average of the daily scores over the 3 days.

Flexible proctosigmoidoscopy (endoscopic examination of the inside of the rectum and lower part of the colon) will be assessed according to endoscopic subscore criteria of the Mayo score. Flexible proctosigmoidoscopy will be performed in all patients at Screening and at the time points specified in the schedule of events (Table 10-1 and Table 10-2). At Screening, full colonoscopy will be performed, instead of flexible proctosigmoidoscopy, for the patients who had an increased risk of colorectal cancer according to the exclusion criteria 8 or who require full colonoscopy at the investigator's discretion for the reasons including suspected extensive colitis or pancolitis. For the patients who had been performed full colonoscopy at Screening, full colonoscopy will be performed at Week 54. Full colonoscopy may also be performed based on the investigator's discretion at other time points after Screening. If full colonoscopy has been performed, it can replace flexible proctosigmoidoscopy. Flexible proctosigmoidoscopy (or full colonoscopy) for endoscopic subscore assessment will be performed within 14 days prior to the Mayo score assessment. Flexible proctosigmoidoscopy (or full colonoscopy) can be performed whenever needed based on investigator's discretion including determination of loss of response. Endoscopic subscore of the Mayo score by flexible proctosigmoidoscopy (or full colonoscopy) will be evaluated at the central level by an independent reviewer blinded to treatment allocation to confirm eligibility, determine loss of response and for reporting purposes. The local endoscopic subscore will be considered during evaluation of the endoscopic subscore at the central level.

6.1.2 Mucosal healing

Mucosal healing will be assessed by endoscopic subscore of the Mayo score (Appendix 10.5) and histologic assessment by the Robarts Histopathology Index (RHI) (Appendix 10.6).

The endoscopic subscore of the Mayo score evaluates the degree of endoscopic rectal inflammation based on a 4-point scale according to flexible proctosigmoidoscopy findings. Details of flexible proctosigmoidoscopy are presented in Section 6.1.1.

The histologic assessment by RHI score evaluates the degree of histologic inflammation using a categorical system containing 4 microscopic features of UC. Histologic assessment will be evaluated at the central level by an independent reviewer blinded to treatment allocation for reporting purposes. Biopsy for histologic assessment will be performed on all patients at

Screening and at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Biopsy will be performed within 14 days prior to the histologic assessment.

6.1.3 Short Inflammatory Bowel Disease Questionnaire

The SIBDQ is a quality-of-life questionnaire for patients with inflammatory bowel disease (Appendix 10.4). It has 10 questions measuring physical, social, and emotional status. Scores for this questionnaire range from 1 (poorest quality of life) to 7 (best quality of life). The SIBDQ will be assessed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

6.2 Pharmacokinetic Assessments

For all patients, C_{trough} will be assessed up to Week 100 and C_{max} will be assessed at Week 6. Blood samples for PK analysis will be collected at pre-dose (prior to the beginning of study drug administration) of Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102, and within 15 minutes after the end of the study drug infusion of Week 6. On the day of initiation of dose adjustment, blood samples for PK analysis will be collected at pre-dose.

For patients who agreed to collect further blood samples, additional blood samples for further Population PK analysis will be collected at the following time points:

- Any time between 48 and 72 hours after study drug administration of Week 22
- Any time between 120 and 168 hours after study drug administration of Week 22
- Pre-dose of Week 24

PK-PD modeling can be conducted including the patients who agreed to collect further blood samples, if it is required from a regulatory or medical perspective.

Details of the PK endpoints and PK analysis are presented in Section 7.2.

Actual sampling times for each patient will be recorded in the patient's eCRF and individual source documents. See Section 6.5.1 for further information on sample collection for PK analysis.

6.3 Pharmacodynamic Assessments

Samples for PD assessments (C-reactive protein [CRP] and fecal calprotectin) will be collected prior to study drug administration at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

Details of the PD endpoints and PD analyses are presented in Section 7.3.

Actual sampling date for each patient will be recorded in the patient's eCRF and individual source documents. See Section 6.5.2 for further information on sample collection for PD analysis.

6.4 Safety Assessments

6.4.1 Patient's Self-Reporting of Adverse Events

A patient diary will be distributed to all patients at the first administration of the study drug (Day 0), and patients will be instructed on how to appropriately complete the diary according to patient diary instruction.

If there are any signs and/or symptoms after study drug administration, the patient will record them in the patient diary and the investigator or designee will review the diary at each visit throughout the study up to and including the EOS visit. However, patients will be advised to contact the investigator at any time after the first administration of the study drug (Day 0) if any severe symptoms develop and the investigator will determine whether the patient should be referred to a specialist or continue the next dose administration. If needed, the patient or caregiver will be re-trained on how to complete the diary. All AEs entered in the diary will be recorded on the AE page in the eCRF.

6.4.2 Immunogenicity Testing

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

According to Section 6.4.3.1, additional immunogenicity testing will be performed if a patient experiences any delayed hypersensitivity after study drug administration.

On the day of initiation of dose adjustment, serum samples for immunogenicity analysis will be collected before study drug administration.

Anti-CT-P13 antibodies will be assessed by a validated immunoassay. Samples that are positive in the anti-CT-P13 antibody assay will be analyzed further in anti-CT-P13 neutralizing antibody assays.

Analysis will be performed at the central laboratory.

6.4.3 Hypersensitivity Monitoring

Hypersensitivity monitoring (including delayed hypersensitivity) will be assessed by vital signs (including blood pressure, heart and respiratory rates, and body temperature) at the following time points at each visit specified in the schedule of events (Table 10-1 and Table 10-2):

- Prior to the beginning of study drug administration

- Within 15 minutes after the end of study drug administration
- 1 hour (+ 10 minutes) after the end of study drug administration

If patients have signs and symptoms of hypersensitivity at home (such as but not limited to skin rash, hives, difficulty breathing, or swelling of face, lips, or mouth, or swelling of the hands, feet, or ankles), patients or caregivers 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 (Section 6.4.1). In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation, must be available; in addition, 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 must be withdrawn from the study.

6.4.3.1 Delayed Hypersensitivity Monitoring

In the case of delayed hypersensitivity, including serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption, or edema), the patient will be asked to visit the study center and additional serum samples for complement (C3, C4) and total hemolytic complement will be assessed to determine serum sickness during the study period. The following analysis will be performed at the central laboratory in the case of delayed hypersensitivity:

- Immunogenicity
- Clinical laboratory analyses
- Complement (C3, C4) and total hemolytic complement

6.4.4 Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, and body temperature) will be measured at all visits by the investigator or designee after 5 minutes of rest (sitting). Vital signs and weight will be measured before the beginning of study drug administration (at the same visit as study drug administration) at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

All measurements will be documented at each visit. Vital sign measurements will also be monitored as part of the hypersensitivity monitoring (Section 6.4.3). In addition, height will be documented once at Screening. Details will be recorded in both the source documents and the eCRF.

6.4.5 Electrocardiogram

All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). If there are any ECG findings that would indicate cardiac insufficiency or QT prolongation based on the ECG review by the investigator, the patient will be referred to a cardiologist to confirm the abnormality. Afterwards, the investigator will report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the investigator's discretion. In the case of hypersensitivity, any type of ECG can be performed (Section 6.4.3).

6.4.6 Tuberculosis Assessment

A patient who has a current diagnosis of active TB or a history of active TB at Screening will be excluded from the study. A patient who has any evidence of history of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.

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

Latent TB is defined as the presence of a positive IGRA (Section 6.4.8) with a negative examination on chest X-ray (Section 6.4.7).

A patient who has a past diagnosis of latent TB cannot be enrolled. However, a patient who has sufficient documentation of completing TB prophylaxis, or has received at least the first 3 weeks of country-specific TB prophylaxis and intends to complete its entire course can be enrolled. A patient who has a current diagnosis of latent TB at Screening without a history of active TB or latent TB cannot be enrolled. However, a patient who has received at least the first 3 weeks of country-specific TB prophylaxis during Screening and intends to complete its entire course can be enrolled.

A patient who is without a history of active TB or latent TB and has an indeterminate result of IGRA with a negative examination of chest X-ray at Screening cannot be enrolled. If the result of the IGRA is indeterminate at Screening, 1 retest will be allowed during the Screening period. If the repeated IGRA result is negative, the patients can be enrolled. If the repeated IGRA result is positive, the patient who has received at least the first 3 weeks of country-specific TB prophylaxis during Screening and intends to complete its entire course can be enrolled. If the repeated IGRA result is again indeterminate, the patient cannot be enrolled.

Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the

absence of active TB prior to the subsequent dose administration. Patients with active TB based on the chest X-ray result and/or the clinical signs and symptoms must be withdrawn from the study.

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

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

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

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

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

6.4.7 Chest X-ray

A chest X-ray (both posterior-anterior and lateral views) should be taken during Screening and locally read by a qualified radiologist or pulmonary physician to specifically look for evidence of current active TB or prior inactive TB.

If a chest X-ray result from within the 42 days prior to the first administration of the study drug (Day 0) is available, a chest X-ray is not required at Screening and the result will be recorded

in both the source documents and the eCRF. The chest X-ray will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

Radiographic findings suggestive of healed TB or active TB may include but are not limited to pulmonary nodules, fibrotic scars, calcified granulomas, upper lobe infiltrates, cavitations, and pleural effusions. Any abnormal X-ray changes should be discussed with the medical monitor before the first administration of the study drug (Day 0). The chest X-ray results should be available to the investigator for review before the first administration of the study drug (Day 0) of the patient.

6.4.8 Interferon-γ Release Assay

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

As described in the literature (Park et al. 2009), IGRA can be used as a method of identifying patients with a false negative response to latent TB infections or new TB infections in patients treated with infliximab. Specifically, these assays detect cell-mediated immune responses to TB infections by quantifying interferon-γ in the presence of specific antimicrobial agents. Samples for this analysis will be obtained at the time points specified in schedule of events (Table 10-1 and Table 10-2). The IGRA analysis will be performed at the central laboratory. During the treatment period, samples will be obtained before study drug administration.

6.4.9 Diabetes Mellitus Assessment

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

6.4.10 Cardiovascular Disease Assessment

At Screening, patients will be assessed for the presence of heart failure according to the NYHA functional classification (Section 6.4.11). Patients with heart failure of NYHA class III or IV, severe uncontrolled cardiac disease (unstable angina or clinically significant ECG abnormalities), or myocardial infarction within the 6 months prior to the first administration of the study drug (Day 0) will be excluded from the study. If a patient has current or history of any cardiovascular disease at Screening, the evidence of diagnosis such as but not limited to echocardiogram result and/or coronary angiography interpretation may be required by the Sponsor and it will be recorded in the source documents.

Throughout the study, patients will be monitored for cardiovascular disease related signs and symptoms such as but not limited to shortness of breath, palpitations, chest pain, chest discomfort, and/or fainting.

6.4.11 New York Heart Association Functional Classification

Throughout the study, NYHA functional classification (Appendix 10.3) assessment will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

6.4.12 Hepatitis B and C and Human Immunodeficiency Virus-1 and -2 Screening

At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient cannot be enrolled.

If a patient has results of HBsAg (negative), HBsAb (negative or positive), and HBcAb (positive), a hepatitis B virus (HBV) DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient cannot be enrolled. If the HBV DNA test result is negative and the patient does not have any evidence of liver cirrhosis, the patient can be enrolled. For patients enrolled based on the HBV DNA test, the tests for HBsAg, HBsAb, HBV DNA, AST, ALT, and total bilirubin will be additionally performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). In patients who develop hepatitis B reactivation, study drug should be stopped, and the patient must be withdrawn from the study.

At Screening, hepatitis C antibody and hepatitis C virus (HCV) RNA must be assessed in all patients (mandatory). If the HCV RNA test result is positive, the patient cannot be enrolled.

If the hepatitis C antibody and HCV RNA test results are both negative, the patient can be enrolled. If the hepatitis C antibody result is positive and HCV RNA test result is negative, the patient can be enrolled as long as the patient does not have liver cirrhosis and achieved SVR for at least 12 weeks after completing the hepatitis C infection treatment. For enrolled patients who have a result of hepatitis C antibody (positive), the tests for HCV RNA, AST, ALT and total bilirubin will be additionally performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). In patients who develop hepatitis C activation, study drug should be stopped, and the patient must be withdrawn from the study.

Human immunodeficiency virus-1 and -2 must be assessed at Screening in all patients (mandatory). If HIV-1 or -2 test results are positive, the patient must be excluded from the study.

Hepatitis and HIV analysis will be performed at the central laboratory.

6.4.13 Stool Microbiology

Stool microbiology (enteric pathogens, ova and parasites, and *Clostridium difficile* toxin test) will be performed at Screening and at any point in the study when a patient becomes

symptomatic, including worsening or return of disease activity, at the investigator's discretion. Analysis will be performed at the central laboratory (Table 10-1 and Table 10-2).

6.4.14 Anti-Double-Stranded DNA Assessment

An anti-double-stranded (anti-ds) DNA test will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

If during the course of the study, a patient develops the signs or symptoms of systemic lupus erythematosus or lupus-like disease, the investigator may obtain unscheduled anti-ds DNA and other tests to aid in the evaluation. If systemic lupus erythematosus or lupus-like disease is diagnosed, the patient must be withdrawn from the study, and the EOS assessments should be performed, including an anti-ds DNA test in addition to any other tests deemed medically appropriate. Analysis will be performed at the central laboratory.

6.4.15 Physical Examinations

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

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

Information about the physical examinations will be recorded by the investigator or designee in both the source documents and the eCRF. Any abnormalities will be recorded in the source documents. Significant findings and illnesses reported after the start of the study that meet the definition of an AE will be recorded as such in the source documents and eCRF.

6.4.16 Adverse Events

6.4.16.1 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.

Adverse Event

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug or device. Patients will be instructed to contact the investigator at any time after the ICF is signed if any symptoms develop (Section 6.4.1). Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or worsening of the underlying disease or of

other pre-existing conditions will be reported. In addition, changes in vital signs, physical examination, and laboratory tests will be recorded as (S)AE(s) in the eCRF if they are judged clinically significant by the investigator.

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

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

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

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

Abnormal Laboratory Value

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

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study drug
- Accompanies or induces symptoms or signs

- Is judged by the investigator as clinically significant; laboratory abnormalities due to underlying disease (UC) are not to be recorded as AEs based on the investigator's judgement

Adverse Events of Special Interest

Adverse events of special interest should be closely monitored.

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

Infusion-related reaction/systemic injection reaction (hypersensitivity/anaphylactic reaction)

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

Delayed hypersensitivity

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

Localized injection site reaction

Localized injection site reactions will be observed after the administration of study drug and assessed based on Common Terminology Criteria for Adverse Events (CTCAE) v5.0. AEs related to localized injection site reaction include but are not limited to the following: erythema, pain, pruritus, hematoma, hemorrhage, swelling, urticaria, induration, bruising, irritation, paresthesia, rash, tenderness with or without symptoms (e.g., warmth, erythema, itching), lipodystrophy, edema, ulceration, necrosis, and severe tissue damage.

Infection

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

Malignancy

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

Serious Adverse Event

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; or results in a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Unlisted (Unexpected) Serious Adverse Event

An unlisted or unexpected SAE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., investigator's brochure) for an unapproved investigational product or the label (e.g., package leaflet or summary of product characteristics/US prescribing information) for an approved product. Assessment of expectedness will be made with the use of the investigator's brochure and the summary of product characteristics.

Adverse Device Effect

An Adverse Device Effect (ADE) is defined as any AE related to the use of an investigational medical device. This includes AEs resulting from insufficient or inadequate instructions for use, the operation, any malfunction of the device or any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effect

A Serious Adverse Device Effect (SADE) is defined as an AE of which has resulted in any of the consequences characteristic of a SAE.

Unanticipated (Unexpected) Serious Adverse Device Effect

An unanticipated or unexpected SADE is defined as a SADE which the nature, severity is not consistent with the applicable product information (e.g., investigator's brochure) for an unapproved investigational product or the label (e.g., package insert or summary of product characteristics/US product insert) for an approved product. Assessment of expectedness will be made with the use of the investigator's brochure and the summary of product characteristics.

6.4.16.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the date the patient signs the ICF until the last assessment date or EOS visit. Where an adverse drug reaction (ADR) (i.e., related to study drug) is ongoing at the EOS visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure.

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

In addition to patient's self-reporting AEs (Section 6.4.1), all AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings) or other documents relevant to patient safety.

6.4.16.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug or device, time to resolution of the event, seriousness, as well as action taken with study drug or device, any required treatment or evaluations, and outcome. All AEs will be followed up to adequate resolution. The Medical Dictionary for Regulatory Activities (MedDRA v22.1 or the most recent version) will be used to code all AEs. Adverse events will be graded for severity according to the CTCAE v5.0.

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

The investigator's assessment of an AE's relationship to study drug or device 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 or device in causing or contributing to the AE or ADE will be characterized as defined in Section 6.4.16.4 and Section 6.4.16.5, respectively.

After the EOS visit, serious adverse drug reactions (SADRs) will be reported to CELLTRION, Inc. or its designee.

Serious Adverse Events

Any AE considered serious by the investigator or that meets SAE criteria (Section 6.4.16.1) must be reported to the [redacted] Pharmacovigilance (PVG) Department within 24 hours from the time the investigator or designee first learns about the event and during normal business hours. The following contact information is to be used for SAE reporting:

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax to [redacted] PVG within 24 hours of awareness of the event. The remote data capture system should be updated as soon as it is available. If the patient is hospitalized during the course of an SAE or because of an SAE, a copy of the hospital discharge summary will be faxed to [redacted] PVG as soon as it becomes available. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator. All SAEs (regardless of relationship with the study drug) will be followed up until satisfactory resolution or until the investigator deems the event to be chronic or not clinically significant or the patient to be stable.

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

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

regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. CELLTRION, Inc. or its designee should report other relevant SAEs associated with the use of the study drug to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 15 calendar days of notification. CELLTRION, Inc. or its designee should report other relevant SAEs associated with device to the appropriate competent authorities (according to local guidelines), investigators, and central ethics committees by a written safety report within 10 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 a psychiatric wing to a medical floor, from a medical floor to a coronary care unit, from a 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 with a 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, which should be noted in the baseline documentation for the entire protocol and/or for the individual patient

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

6.4.16.4 Assessment of Severity

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

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

Grade 2: Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])

Grade 3: Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)

Grade 4: Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, or sepsis; life-threatening physiological consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy, or operation)

Grade 5: Death related to AE

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. If an AE upgrades in intensity or changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in intensity, it should not be reported as a new AE. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

6.4.16.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event will be reported.

The relationship or association of CT-P13 IV, CT-P13 SC, or Placebo SC in causing or contributing to the AE will be characterized using the following classification and criteria:

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

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

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. 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 study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

6.4.16.6 Follow-Up of Patients Reporting Adverse Events

Where an ADR (i.e., related to study drug) is ongoing at the EOS visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure (Section 6.4.16.2).

6.4.17 Pregnancy

A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS visit. Patients who are of childbearing potential with only negative results from a serum pregnancy test can be enrolled. A urine pregnancy test for women of childbearing potential will be used to confirm that patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation (Table 10-1 and Table 10-2). A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.

In an event of unexpected pregnancy during study participation, patients will be counselled to inform the investigator of any pregnancy that occurs during the study and for 6 months after the last dose of study drug. If a female patient becomes pregnant, the study drug must be discontinued immediately. If a female patient or the partner of a male patient becomes pregnant, the pregnancy must be reported to CELLTRION, Inc. and [redacted] PVG within 24 hours of the study center's knowledge of the pregnancy while confirmation is pending. Once the pregnancy is confirmed with a serum pregnancy test for female patients, study drug will be permanently discontinued and the patient will be withdrawn from the study. The study center must complete the supplied pregnancy form (female patient or partner of a male patient) and return it to [redacted] PVG within 24 hours.

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

6.4.18 Clinical Laboratory Analyses

Blood and urine samples for clinical laboratory assessments will be collected at the time points specified in the schedule of events (Table 10-1 and Table 10-2). To determine eligibility, retesting will be allowed once during Screening period based on the investigator's discretion. Samples should be collected prior to study drug administration. Blood samples do not need to be collected in a fasting state unless in the opinion of the investigator fasting blood samples are required.

Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples except erythrocyte sedimentation rate (ESR) will be analyzed at the central laboratory. The ESR samples will be analyzed locally using kits supplied. A standard ESR kit using Westergren method of assessment will be supplied to study centers for use where the normal level will be considered to be no more than 20 mm/h for women and no more than 15 mm/h for men.

The following laboratory analyses will be performed.

Clinical chemistry	Total protein, serum bilirubin (total, direct), ALT, AST, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-MB, troponin I, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and CRP
Hematology	Red blood cells, ESR, total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination

Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity to determine serum sickness (Section 6.4.3.1). Serum samples for C3, C4, and total hemolytic complement will be assessed if delayed hypersensitivity occurs to determine serum sickness. Analysis will be performed at the central laboratory.

6.4.19 Drug-Induced Liver Injury Monitoring

The abnormal elevation in ALT and/or AST accompanying increased serum total bilirubin in the absence of other causes of hepatocellular injury are considered a signal of the potential drug-induced liver injury (DILI) case. Therefore, a close monitoring on the liver enzyme elevations upon starting the administration of the study drug is necessary [Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009].

For the patients presenting the following laboratory abnormalities, a close monitoring for possible DILI will be initiated:

- Patients with normal value of AST and/or ALT at baseline: any single AST and/or ALT elevation > 3×ULN.
- Patients with abnormal value of AST and/or ALT above the ULN at baseline: any single AST and/or ALT elevation > 2×baseline values and > 3×ULN.

The following process of close monitoring is recommended and the process will be specified in the relevant study document (e.g., center guidance document).

The medical monitors of CELLTRION, Inc. or designee and the investigator will be notified when the above laboratory abnormalities are detected. The investigator will also contact the patients who have the above laboratory abnormalities as soon as possible, preferably within the recommended time frame of 48 to 72 hours from awareness of the abnormal results, to conduct an unscheduled laboratory testing including AST, ALT, alkaline phosphatase, and total bilirubin. These patients will be evaluated for an underlying etiology of increased AST and/or ALT levels by performing the following assessments:

- A more detailed history of concomitant medications and recreational drugs (including non-prescription drugs, alcohol, supplement consumption, and drugs that are known to cause liver toxicity, such as acetaminophen)
- More details about signs and symptoms of possible liver toxicity and concurrent disease, if any.
- Family history, sexual history, travel history, occupational exposure, history of liver disease, occupational/work or environmental exposure, or any relevant history that are considered to impact on the increased liver function tests.
- Additional laboratory test for creatine kinase, γ-glutamyltransferase, and international normalized ratio (INR) may be required.
- Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g., biliary tract), if it is required.

Abnormal laboratory values will be followed up until the results are back to normal or baseline level, or the etiology of elevated laboratory values is determined and abnormal values are considered stable, at the investigator's discretion.

A patient who meets the following criteria will be discontinued from the study irrespective of the investigation results of etiology of the increased laboratory abnormalities.

- ALT and/or AST > 8×ULN
- ALT and/or AST > 5×ULN for more than 2 weeks
- ALT and/or AST > 3×ULN and (total bilirubin > 2×ULN or INR > 1.5) and alkaline phosphatase < 2×ULN
- ALT and/or AST > 3×ULN with signs or symptoms consistent with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or higher than 5% of eosinophilia value.

6.4.20 Patient's Assessment of Local Site Pain

All patients will assess local site pain using a 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 15 minutes) after the end of administration of study drug at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Patient's assessment of pain is measured by the patient indicating the extent of their pain in the local site where study drug was administered by marking a line (|) through the 100 mm line (Appendix 10.7).

6.4.21 Prior and Concomitant Medications

Use of all prior and concomitant medications for the treatment of UC, latent TB, and/or hepatitis C (if applicable), from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF and used as analysis of safety.

Use of all medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) or from when the ICF is signed, whichever is earlier, will be recorded until the EOS visit. All concomitant medications will also be recorded when any ADR is ongoing at the EOS visit. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in both the 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. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in both the source documents and the eCRF. Prior and concomitant medications will be coded to drug class and

preferred term (PT) according to the World Health Organization (WHO) Drug Dictionary Sep 2019 or later.

6.5 Sample Collections

The total volume of blood collected for each assessment is discussed in each specific laboratory manual.

The total volume of stool sample is discussed in the specific laboratory manual.

The sample collection tube may be changed during the study, and details will be provided in the laboratory manual.

The total number for biopsy sample is discussed in the specific laboratory manual or relevant documents.

6.5.1 Pharmacokinetic Blood Sampling

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

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.2 Pharmacodynamic Sampling (CRP, Fecal Calprotectin)

Samples for PD (CRP, fecal calprotectin) will be obtained in accordance with the laboratory manual from each patient at the time points specified in the schedule of events (Table 10-1 and Table 10-2). During the treatment period, samples should be collected before study drug administration. All samples should be collected as close as possible to the scheduled time point, and the actual sampling date must be recorded in both the source documents and the eCRF.

Blood samples for CRP are the same samples as those for routine safety (clinical laboratory testing) assessments. Serum samples for CRP assessment will be stored and shipped to the central laboratory as detailed in Section 6.6.2.

Stool samples for fecal calprotectin will be handled and shipped to the central laboratory according to the laboratory manual.

6.5.3 Safety Sampling

Blood samples for routine safety (clinical laboratory testing [including CRP]), serum pregnancy testing, complement (C3, C4), anti-ds DNA, and total hemolytic complement testing will be collected for analysis throughout the study at the time points specified in the schedule of events (Table 10-1 and Table 10-2). All samples should be collected as close as

possible to the scheduled time point, and the actual sampling date must be recorded in both the source documents and the eCRF.

Additional blood samples for hepatitis B, hepatitis C, HBV DNA, HCV RNA, HIV-1 and -2, and stool samples for stool microbiology will also be required at Screening.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.4 Immunogenicity Blood Sampling

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

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.5 Interferon-γ Release Assay Blood Sampling

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

Samples should be stored and shipped as detailed in Section 6.6.2.

6.5.6 Biopsy sampling for histologic assessment

Biopsy samples for histologic assessment will be obtained in accordance with the laboratory manual or relevant documents from each patient at the time points specified in the schedule of events (Table 10-1 and Table 10-2). During the treatment period, samples should be collected before study drug administration. All samples should be collected as close as possible to the scheduled time point, and the actual sampling date must be recorded in both the source documents and the eCRF.

Samples should be stored and shipped as detailed in Section 6.6.2.

6.6 Labeling, Storage, and Transportation of Samples

6.6.1 Sample Labeling

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

6.6.2 Sample Storage and Shipment

During the study, biopsy samples for histologic assessment, stool samples for fecal calprotectin and stool microbiology and blood samples for PK, PD, immunogenicity, and other safety analyses will be collected.

Where appropriate, the serum should be transferred into a sufficient number of transfer vials for transport to assigned testing facilities. Primary and back-up samples will be shipped to the central laboratory according to the laboratory manual, and primary samples should be shipped separately from the back-up samples. Additionally, back-up samples for PK, and immunogenicity should be retained at the central laboratory as a back-up for up to 5 years after the end of the study in case additional analysis is required. If additional analysis for PK and immunogenicity is not required, the sample will be stored in CELLTRION, Inc. or a designated biobank for an additional 5 years (from the date the sample is transferred to the biobank) unless a specific authorization is given by CELLTRION, Inc. to destroy the sample. Additional tests for PK and immunogenicity can be conducted if it is required from a regulatory or medical perspective.

Details on sample storage and shipment will be followed according to the laboratory manual or relevant documents.

6.7 Overdose Management

An overdose is defined as any dose that is 10% or more than the dose prescribed. Overdose may be symptomatic or asymptomatic. Symptoms associated with an overdose must be recorded as an AE and the details provided according to Section 6.4.16.3. An overdose without signs or symptoms must be documented in the study medication section of the eCRF.

Although not strictly due to an overdose, infusion-related reactions/systemic injection reaction or localized injection site reactions are possible and hypersensitivity must be monitored according to the details in Section 6.4.3.

7 Statistical Analysis Plan

Statistical analysis will be performed using [redacted] The statistical methods for this study will be described in a detailed statistical analysis plan (SAP), which will be finalized prior to locking of the database. Changes from analyses planned in this protocol will be documented in the SAP. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report. The randomization will be stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by modified Mayo score).

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

Final determination of the major protocol deviations that can affect the data analysis will be made at the blinded data review meeting held in accordance with ICH Technical Requirements for Registration of Pharmaceuticals for Human Use harmonised tripartite guideline E9.

7.1 Efficacy Analysis

7.1.1 Primary Efficacy Analysis

The primary endpoint for the study is as follows:

- Clinical remission at Week 54, defined as the following modified Mayo score:

  (1) Stool frequency subscore of 0 or 1 point, and

  (2) Rectal bleeding subscore of 0 point, and

  (3) Endoscopic subscore of 0 or 1 point

The primary endpoint will be tested at the 1-sided significance level of 2.5% on the all randomized population using the p-value from Fisher's exact test. If the p-value is ≤ 0.025, the statistical significance of the primary endpoint will be concluded. If the primary endpoint is significant, the fixed sequence procedure will be used for key secondary endpoints in order to preserve the Type I error. The supportive analysis for the primary endpoint will be performed in the PP population.

The primary endpoint, sensitivity analyses, will be performed using the logistic regression model and Cochran-Mantel-Haenszel test stratified by randomization factors on the all-randomized population. To evaluate the effect of missing data on the primary endpoint, tipping point analyses will be conducted on the all-randomized population. Statistical test for the primary endpoint will be conducted using the endoscopic subscore of the Mayo score that is

determined at central level. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter at Week 54 in the analysis of the primary endpoint.

7.1.2 Secondary Efficacy Analysis

The following list of secondary endpoints are the key secondary endpoints for analysis, and the ranking of these analyses will be detailed in the study SAP:

- Clinical response at Week 54, defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Mucosal healing at Week 54, defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute RHI score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point
- Corticosteroid-free remission at Week 54, defined as being in clinical remission by modified Mayo score in addition to not requiring any treatment with corticosteroid for at least 8 weeks at Week 54, among the patients who used oral corticosteroids at baseline.

The key secondary endpoints will be tested at the 1-sided significance level of 2.5% on the all-randomized population using the p-value from Fisher's exact test. The first key secondary endpoint will be tested only if the primary endpoint is statistically significant, and the next key secondary endpoint will be tested only if the previous key secondary endpoint is statistically significant. The supportive analysis for the key secondary endpoints will be performed in the PP population. Statistical test for the key secondary endpoints will be conducted using the endoscopic subscore of the Mayo score and RHI score that are determined at central level. The patients whose dose was adjusted to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter or non-responder at Week 54 in the analysis of key secondary endpoints.

The following secondary efficacy endpoints will be assessed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). The secondary endpoints will be summarized using descriptive statistics or frequency tables.

- Clinical remission assessed at Weeks other than Week 54, defined as the following modified Mayo score:

  (1) Stool frequency subscore of 0 or 1 point, and

  (2) Rectal bleeding subscore of 0 point, and

(3) Endoscopic subscore of 0 or 1 point

- Maintenance of clinical remission at Week 54, defined as being in clinical remission by modified Mayo score, among the patients in clinical remission by modified Mayo score at Week 10
- Sustained remission at both Week 22 and Week 54, defined as a stool frequency subscore of 0 or 1, and rectal bleeding subscore of 0
- Clinical response assessed at Weeks other than Week 54, defined as a decrease in modified Mayo score from baseline of at least 2 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Mucosal healing assessed at Weeks other than Week 54, defined as an absolute endoscopic subscore of 0 or 1 point from modified Mayo score and an absolute RHI score of 3 points or less with an accompanying laminal propria neutrophils and neutrophils in epithelium subscore of 0 point
- The scores and change from baseline in SIBDQ

7.1.3 Exploratory Efficacy Analysis

The following exploratory efficacy endpoints will be assessed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). The exploratory endpoints will be summarized using descriptive statistics or frequency tables.

- Clinical remission, with normalization of stool frequency at Week 54, defined as the following modified Mayo score:

  (1) Stool frequency subscore of 0 point, and

  (2) Rectal bleeding subscore of 0 point, and

  (3) Endoscopic subscore of 0 or 1 point
- Total clinical remission, defined as a total Mayo score (stool frequency, rectal bleeding, endoscopic, and PGA subscores) of 2 points or lower with no individual subscore exceeding 1 point
- Total clinical response, defined as a decrease in total Mayo score from baseline of at least 3 points and at least 30%, with an accompanying decrease in rectal bleeding subscore of at least 1 point or an absolute rectal bleeding subscore of 0 or 1 point
- Partial clinical remission, defined as a partial Mayo score (stool frequency, rectal bleeding, and PGA subscores) of 1 point or lower

- Partial clinical response, defined as a decrease in partial Mayo score from baseline of at least 2 points, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point, or an absolute subscore for rectal bleeding of 0 or 1 point

7.2 Pharmacokinetic Analysis

Serum concentrations of study drug will be summarized by treatment at each scheduled collection time. In addition to the standard summary statistics, the geometric mean and coefficient of variation (CV) will also be presented at each time point. Individual concentrations and scheduled and actual sample times will be presented in data listings by treatment.

Pharmacokinetic parameters will be computed by noncompartmental methods using appropriate validated software [redacted]

As secondary PK endpoints, C_{trough} will be assessed up to Week 100 and C_{max} will be assessed at Week 6.

- C_{trough} trough concentration (concentration before the next dosing of study drug)
- C_{max} observed maximum serum concentration after study drug infusion

Pharmacokinetics variables will be presented in listings and summarized in tables. For PK parameters, the summary tables will display the following descriptive statistics: n, mean, median, standard deviation, minimum, maximum, geometric mean, and CV. The PK parameters and concentrations will be summarized in the PK population.

7.3 Pharmacodynamic Analysis

The secondary PD endpoints (CRP, fecal calprotectin) will be assessed at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

The PD endpoints will be summarized by treatment at each scheduled collection time. In addition to the standard summary statistics, the geometric mean and CV will also be presented at each time point. The PD endpoints will be analyzed in the PD population.

7.4 Safety Analysis

The secondary safety endpoints will be assessed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Further details will be presented in the SAP, as appropriate. The following safety parameters will be determined as safety assessments:

- Immunogenicity
- Hypersensitivity monitoring (including delayed hypersensitivity monitoring)

- Vital sign measurements (including blood pressure, heart and respiratory rates, and body temperature) and weight
- 12-lead ECGs
- Monitoring of TB signs and symptoms
- Chest X-ray
- IGRA
- Diabetes mellitus assessment
- Monitoring of cardiovascular disease related signs and symptoms
- NYHA functional classification assessment
- Hepatitis B and C and HIV-1 and -2 status
- Stool microbiology
- Anti-ds DNA assessment
- Physical examination findings
- AEs (including SAEs)
- AEs of special interest (infusion-related reaction/systemic injection reaction [hypersensitivity/anaphylactic reaction], delayed hypersensitivity, localized injection site reaction, infection, malignancy)
- Pregnancy testing
- Clinical laboratory analyses
- Monitoring of DILI
- Local site pain using 100 mm VAS
- Prior and concomitant medications

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

- Immunogenicity
- Clinical laboratory analyses
- Complement (C3, C4) and total hemolytic complement

7.4.1 Demographics, Baseline, and Background Characteristics

Demographics (age, gender, 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.

7.4.2 Adverse Events

Adverse events will be coded to system organ class (SOC) and PT according to MedDRA v22.1 or the most recent version. Adverse events will be graded for severity according to the CTCAE v5.0.

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

- Number and percentage of patients reporting at least 1 (treatment-emergent) AE
- 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 AEs of special interest (infusion-related reaction/systemic injection reaction [hypersensitivity/anaphylactic reaction], delayed hypersensitivity, localized injection site reaction, infection, malignancy)

If more than 1 AE is recorded for a patient within any SOC or PT, the patient will be counted only once using the most severe assessment. All safety data will be listed and summarized by treatment group as appropriate in the safety population.

7.4.3 Clinical Laboratory Analyses

Clinical laboratory tests (clinical chemistry, hematology, and urinalysis), IGRA, anti-ds DNA, and pregnancy testing will be summarized by treatment at each scheduled collection time. For continuous parameters, change from baseline will also be summarized for all scheduled collection times after the first infusion.

All laboratory results will be listed.

7.4.4 Immunogenicity

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

7.4.5 Stool Microbiology

All data will be listed where appropriate.

7.4.6 Electrocardiograms, Hypersensitivity Monitoring, Physical Examination, Vital Signs, and Weight

Electrocardiograms, hypersensitivity monitoring, physical examinations, vital signs (systolic and diastolic blood pressure, heart and respiratory rates, and body temperature), and weight will be summarized by treatment at each scheduled collection time. Change from baseline will also be summarized for all scheduled collection times after the first infusion.

7.4.7 Patient's Assessment of Local Site Pain

Local site pain measurements by VAS will only be assessed immediately (not exceeding 15 minutes) after the end of administration of study drug at each scheduled collection time and will be summarized by treatment group.

7.4.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded to drug class and PT according to the WHO Drug Dictionary and will be summarized by treatment.

7.4.9 Other Safety Analyses

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

7.5 Sample Size Calculations

The sample size of 417 patients (278 in CT-P13 SC group and 139 in Placebo SC group) was estimated to provide 80% statistical power to detect a statistically significant clinical effectiveness of CT-P13 SC in comparison with Placebo SC in the following primary endpoint at the 1-sided significance level of 2.5%.

- Clinical remission at Week 54 assuming a treatment difference of 15% and placebo rate of 45%

Considering a 32% non-responder rate of clinical response at Week 10 before randomization, a total of approximately 615 patients will be enrolled at Week 0. The number of enrolled patients may be adjusted based on the actual number of randomized at Week 10.

A total sample size of 417 patients provides at least 90% statistical power for clinical response at Week 54, one of the key secondary endpoints, under the assumption of a treatment difference of 20% and placebo rate of 50% at the 1-sided significance level of 2.5%. Key secondary endpoints other than clinical response at Week 54 are not applicable for power calculation due to lack of relevant references.

7.6 Analysis Sets

The intent-to-treat (ITT) population is defined as all enrolled patients.

The all-randomized population is defined as all randomly assigned patients at Week 10. The all-randomized population will be used for analysis of primary and key secondary endpoints.

The PP population is defined as all randomly assigned patients who receive all doses (full) of study drug prior to Week 54 and who have at least 1 efficacy evaluation after Week 10 treatment and who do not have any major protocol deviation that is relevant to efficacy analysis. The PP population will also be used to provide supportive results of primary and key secondary endpoints.

The PK population is defined as all randomly assigned patients who receive at least 1 dose (full) of study drug at Week 10 or thereafter and who have at least 1 PK result after Week 10 treatment.

The PD population is defined as all randomly assigned patients who receive at least 1 dose (full) of study drug at Week 10 or thereafter and who have at least 1 PD result after Week 10 treatment.

The safety population is defined as all randomly assigned patients who receive at least 1 dose (full or partial) of study drug at Week 10 or thereafter.

7.6.1 Description of Subgroups to be Analyzed

Additional subgroup analyses could be implemented to reflect medical, regulatory, regional, or ethnic considerations.

7.7 Interim Analyses

No interim analyses are planned for this study.

7.8 Data Quality Assurance

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

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

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

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

8 Investigator's Obligations

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

8.1 Confidentiality and Data Protection

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

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

8.2 Institutional Review

Regulations and the ICH guidelines require that approval be obtained from an IRB/IEC before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R2): Good Clinical Practice and the Declaration of Helsinki (WMA 2013) will be maintained by the study center and will be available for review by CELLTRION, Inc. or its designee.

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

The investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must supply CELLTRION, Inc. or its designee with written documentation of continued review of the clinical research.

8.3 Informed Consent

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

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

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

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

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

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

8.4 Study Reporting Requirements

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in Section 6.4.16.3. In addition, the investigator agrees to submit annual reports to his or her IRB/IEC as appropriate. The investigator also agrees to provide CELLTRION, Inc. with an adequate report shortly after completion of the investigator's participation in the study.

8.5 Financial Disclosure and Obligations

The investigators are required to provide financial disclosure information to allow CELLTRION, Inc. to submit the complete and accurate certification or disclosure statements required under US Title 21 Code of Federal Regulations (CFR) Part 54. In addition, the investigator must provide to CELLTRION, Inc. a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

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

8.6 Investigator Documentation

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

- IRB/IEC approval.
- Original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572 or equivalent, fully executed, and all updates on a new fully executed Form FDA 1572 or equivalent.
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572 or equivalent. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow CELLTRION, Inc. to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to CELLTRION, Inc. a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian.
- Laboratory certifications and normal ranges for any local laboratories used by the center, in accordance with 42 CFR 493.

8.7 Study Conduct

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

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

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

The investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must supply CELLTRION, Inc. or its designee with written documentation of continued review of the clinical research.

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

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

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

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

8.9 Coding Dictionaries

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

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

8.10 Adherence to Protocol

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

8.11 Adverse Events and Study Report Requirements

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs to CELLTRION, Inc. and/or IRB/IEC according to the timeline and method outlined in Section 6.4.16.3. In addition, the principal investigator or subinvestigator agrees to submit annual reports to the relevant IRB/IEC as appropriate. The principal investigator or subinvestigator also agrees to provide CELLTRION, Inc. with an adequate report shortly after completion of the investigator's participation in the study.

8.12 Investigator's Final Report

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

8.13 Records Retention

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

Essential documents will be retained until at least 15 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 15 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with CELLTRION, Inc. It is the responsibility of CELLTRION, Inc. to inform the

principal investigator or subinvestigator/institution as to when these documents no longer need to be retained.

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

8.14 Patient Identification Register

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

8.15 Publications

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

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

9 Study Management

9.1 Sponsor

CELLTRION, Inc.

[redacted]

Sponsor representative

[redacted]

9.2 Vendor Contact

Contract Research Organization:

[redacted]

SAE Reporting

[redacted]

[redacted]

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

9.3 Analytical Facilities

Any analytical facilities and procedures utilized for this study must be Good Laboratory Practice compliant.

Details of analytical facilities are presented in the ICF.

9.4 Data Safety Monitoring Board

This study will be monitored by an independent data safety monitoring board. The data safety monitoring board will meet every 6 to 8 months with the exception of 1 additional meeting, which will be held after all patients have reached Week 10. During each meeting, the data safety monitoring board will review and evaluate accumulating safety data such as any new and serious unexpected safety signals, deaths, SAEs, AEs of special interest, and AEs leading to discontinuation to ensure the safety of study patients. The data safety monitoring board will also provide recommendations regarding the acceptability of continuing the study based on the safety monitoring.

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

9.5 Monitoring

9.5.1 Monitoring of the Study

The clinical monitor, as a representative of CELLTRION, Inc., has the obligation to follow the study closely. In doing so, the clinical monitor may visit the investigator and study facility at periodic intervals, in addition to maintaining necessary telephone and letter contact. The clinical monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

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

9.5.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In

the event of an audit, the investigator agrees to allow CELLTRION, Inc., representatives of CELLTRION, Inc., or other regulatory agencies access to all study records.

The investigator should promptly notify CELLTRION, Inc. and its designee of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to CELLTRION, Inc.

9.6 Management of Protocol Amendments and Deviations

9.6.1 Modification of the Protocol

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

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

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

9.6.2 Protocol Violations and Deviations

The 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 will be submitted to the IRB/IEC for review and approval, to CELLTRION, Inc. 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 CELLTRION, Inc. and the IRB/IEC and agreed to by the investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion, exclusion, or primary endpoint criteria. A protocol violation occurs when there is nonadherence to the protocol by the patient and investigator that results in a significant and additional risk to the patient. Protocol violations can include nonadherence to inclusion or

exclusion criteria, enrollment of the patient without prior approval by CELLTRION, Inc., or nonadherence to regulatory regulations or ICH E6(R2) guidelines.

Protocol violations and deviations will be documented by the clinical monitor throughout the course of monitoring visits. Investigators will be notified in writing by the monitor of violations and deviations. The IRB/IEC should be notified of all protocol violations and deviations in accordance with local regulation.

9.7 Study Termination

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

The end of the study is defined as the date on which the last patient completes the last visit (including EOS visit and ADR follow-up) if the study is not discontinued by CELLTRION, Inc. decision before this date.

9.8 Final Report

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

CELLTRION, Inc. plans to prepare 2 CSRs, but additional CSRs will be generated upon requirements for regulatory or academic purposes, including but not limited to:

- Data for each patient up to Week 54
- Data for each patient after completion of all visits

10 Appendices

10.1 Schedule of Events

Table 10-1 Schedule of Events for Induction and Maintenance Phase

	Screening	Induction Phase				Maintenance Phase									EOS[1]
Study Week		**0**	**2**	**6**	**8[2]**	**10[3]**	**12[3]**	**14**	**22[4]**	**24[4]**	**30**	**38**	**46**	**54**	
Study Day	**–42 ~ 0**	**0**	**14**	**42**	**56**	**70**	**84**	**98**	**154**	**168**	**210**	**266**	**322**	**378**	
Dosing Window[5]		**N/A**	**± 3 days**			**± 3 days**									
Treatment group 1 [6]		**CT-P13 IV**				**CT-P13 SC**			**CT-P13 SC[7]**						
Treatment group 2 [8]						**Placebo SC**			**Placebo SC[7]**						
Informed consent	X														
Demography	X														
Medical history	X														
Hepatitis B and HBV DNA test[9]	X							(X[10])			(X[10])		(X[10])		(X)
Hepatitis C and HCV RNA test[11]	X							(X[10])			(X[10])		(X[10])		(X)
HIV -1 & -2 test	X														
Stool microbiology[12]	X														
Serum pregnancy test[13]	X														X
Anti-ds DNA test[14]	X														X
Chest X-ray[15]	X														
IGRA[16]	X	X[10]		X[10]				X[10]			X[10]			X[10]	X
Inclusion and exclusion criteria	X	X[10]													
Randomization						X[10]									
Efficacy assessments															
Total & Modified Mayo score assessment[17]	X[18]					X[10]			X[10]					X[10]	X
Partial Mayo score assessment[17]	X[18]		X[10]	X[10]		X[10]		X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
Flexible proctosigmoidoscopy (Endoscopic subscore of the Mayo score)[19]	X[20]				X				X[10]					X[10, 20]	X
Histologic assessment (RHI score)[21]	X					X			X					X	X
Biopsy for histologic assessment[22]	X				X				X[10]					X[10]	X
SIBDQ		X[10]	X[10]	X[10]		X[10]		X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
Safety and other assessments															
Urine pregnancy test[23]		X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	

	Screening	Induction Phase				Maintenance Phase									EOS[1]
Study Week		**0**	**2**	**6**	**8[2]**	**10[3]**	**12[3]**	**14**	**22[4]**	**24[4]**	**30**	**38**	**46**	**54**	
Study Day	**−42 ~ 0**	**0**	**14**	**42**	**56**	**70**	**84**	**98**	**154**	**168**	**210**	**266**	**322**	**378**	
Dosing Window[5]		**N/A**	**± 3 days**			**± 3 days**									
Clinical laboratory tests[24]	X	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
Physical examinations	X	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
Vital signs and weight[25]	X	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
NYHA class assessment	X	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
12-lead ECG[26]	X			X		X		X			X			X	X
Hypersensitivity monitoring[27]		X	X	X		X	X	X	X		X	X	X	X	
Immunogenicity[28]		X[10]				X[10]		X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
C3, C4 and total hemolytic complement[29]		X[10]													
PK blood samples[30]		X[10]	X[10]	X[10,30]		X[10]		X[10]	X[10, 30]	X[10, 30]	X[10]	X[10]	X[10]	X[10]	
PD blood samples (CRP)[31]	X	X[10]	X[10]	X[10]		X[10]		X[10]	X[10]		X[10]	X[10]	X[10]	X[10]	X
Fecal calprotectin[32]	X					X[10]			X[10]					X[10]	X
VAS local site pain[33]						X	X	X	X		X	X	X	X	
Prior, concomitant medications[34]	X														
TB clinical monitoring[35]	X														
Cardiovascular disease monitoring[36]	X														
AE monitoring[37]	X														

Abbreviations: AE, adverse event; Anti-ds DNA, anti-double stranded DNA; CRP, C-reactive protein; ECG, electrocardiogram; EOS, End-of-Study; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IGRA, interferon-γ release assay; IV, intravenous; N/A, not applicable; NYHA, New York Heart Association; PD, pharmacodynamic; PK, pharmacokinetic; RHI, Robarts histopathology index; SC, subcutaneous; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TB, tuberculosis; VAS, Visual Analogue Scale.

1. All EOS assessments will be completed after 4 weeks (±3 days) after the last dose of CT-P13 SC or Placebo SC is received, if a patient withdraws prior to Week 102 treatment. For patients who early discontinue the study drug before administration of CT-P13 SC or Placebo SC at Week 10, the EOS visit will be completed after 8 weeks (±3 days) from the last dose of CT-P13 IV is received.
2. At Week 8, only endoscopy and biopsy will be performed for the evaluation of Mayo score and histologic assessments at Week 10. The endoscopy result at Week 8 will be used for randomization at Week 10. Endoscopy and biopsy at Week 8 will be completed within 14 days prior to Mayo score and histologic assessments at Week 10.
3. At Weeks 10 and 12, initial training for self-injection of CT-P13 SC or Placebo SC via PFS will be conducted. If needed, the patient or caregiver will be retrained during the study on how to perform the injection of the study drug.

4. Between Week 22 and Week 24, additional PK sampling visits will be conducted only on patients who agreed to collect further blood samples for Population PK analysis.
5. A dosing window of ±3 days is allowed, including self-injection. The minimal dose interval of 11 days is allowed from Week 10.
6. For Treatment group 1, CT-P13 IV (5 mg/kg) will be administered at Weeks 0, 2, and 6. From Week 10 onwards, CT-P13 SC (120 mg) will be administered during Maintenance Phase. Further doses of study drug with CT-P13 SC will be given every 2 weeks via PFS through Week 54.
7. From Week 22, dose adjustment will be allowed. The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria. The patients who received Placebo SC may receive CT-P13 SC 240 mg every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
8. For Treatment group 2, CT-P13 IV (5 mg/kg) will be administered at Weeks 0, 2, and 6. From Week 10 onwards, Placebo SC (matching volume to CT-P13 SC 120 mg) will be administered during Maintenance Phase. Further doses of study drug with Placebo SC will be given every 2 weeks via PFS through Week 54.
9. At Screening, HBsAg, HBsAb, and HBcAb must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient cannot be enrolled. If a patient has results of HBsAg (negative), HBsAb (negative or positive), and HBcAb (positive), a HBV-DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient cannot be enrolled. If the HBV DNA test result is negative and the patient does not have any evidence of liver cirrhosis, the patient can be enrolled. For patients enrolled based on the HBV DNA test, tests for HBsAg, HBsAb, HBV DNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94, and EOS visits. In patients who develop hepatitis B reactivation, study drug should be stopped and the patient must be withdrawn from the study. Hepatitis B analysis will be performed at the central laboratory.
10. Assessed prior to study drug administration.
11. At Screening, hepatitis C antibody and HCV RNA must be assessed in all patients (mandatory). If the HCV RNA test result is positive, the patient cannot be enrolled. If the hepatitis C antibody and HCV RNA test results are both negative, the patient can be enrolled. If the hepatitis C antibody result is positive and HCV RNA test result is negative, the patient can be enrolled as long as the patient does not have liver cirrhosis and achieved a SVR for at least 12 weeks after the completing the hepatitis C infection treatment. For enrolled patients who have a result of hepatitis C antibody (positive), the tests for HCV RNA, AST, ALT, and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94, and EOS visits. In patients who develop hepatitis C activation, study drug should be stopped, and the patient must be withdrawn from the study. Hepatitis C analysis will be performed at the central laboratory.
12. Stool microbiology (enteric pathogens, ova and parasites, and *Clostridium difficile* toxin test) will be performed at Screening and at any point in the study when a patient becomes symptomatic, including worsening or return of disease activity, at the investigator's discretion. Analysis will be performed at the central laboratory.
13. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS visit. Patients who are of childbearing potential with only negative results from a serum pregnancy test can be enrolled.
14. An anti-ds DNA test will be performed at Screening and at the EOS visit. If during the course of the study, a patient develops the signs or symptoms of systemic lupus erythematosus or lupus-like disease, the investigator may obtain unscheduled anti-ds DNA and other tests to aid in the evaluation. Analysis will be performed at the central laboratory.
15. A chest X-ray (both posterior-anterior and lateral views) is not required at Screening if a chest X-ray result from within the 42 days prior to the first administration of the study drug (Day 0) is available.
16. The IGRA analysis will be performed at the central laboratory.
17. With the exception of Screening, the Mayo score diary will be collected by patients for 7 days immediately prior to the Mayo score assessment and the most recent 3 days (not necessarily consecutive days) within the 7 days will be used to calculate the Mayo score. If the Mayo score assessment is performed at the same date as the flexible proctosigmoidoscopy or full colonoscopy procedure, the 3 days overlapping with endoscopy procedure (i.e., from the day before and up to the next day of the endoscopy procedure) will not be used to calculate the Mayo score.

18. To determine eligibility, the Mayo score diary will be completed within 3 days immediately prior to the first administration of the study drug (Day 0), and the Mayo score will be calculated at Day 0.
19. Full colonoscopy may also be performed based on investigator's discretion. If full colonoscopy has been performed, it can replace flexible proctosigmoidoscopy. Flexible proctosigmoidoscopy (or full colonoscopy) for endoscopic subscore assessment will be performed within 14 days prior to the Mayo score assessment. Flexible proctosigmoidoscopy (or full colonoscopy) can be performed whenever needed based on investigator's discretion including determination of loss of response. Endoscopic subscore by flexible proctosigmoidoscopy (or full colonoscopy) will be evaluated at the central level by an independent reviewer blinded to treatment allocation to confirm eligibility, determine loss of response and for reporting purposes. The local endoscopic subscore will be considered during evaluation of the endoscopic subscore at the central level.
20. The Screening flexible proctosigmoidoscopy (or full colonoscopy) will be performed within 14 days prior to the first administration of the study drug (Day 0). At Screening, full colonoscopy will be performed, instead of flexible proctosigmoidoscopy, for the patients who had an increased risk of colorectal cancer according to the exclusion criteria 8 or who require full colonoscopy at the investigator's discretion for the reasons including suspected extensive colitis or pancolitis. For the patients who had been performed full colonoscopy at Screening, full colonoscopy will be performed at Week 54.
21. Histologic assessment by RHI score will be evaluated at the central level by an independent reviewer blinded to treatment allocation for reporting purposes.
22. Biopsy will be performed within 14 days prior to the histologic assessment.
23. A urine pregnancy test for women of childbearing potential will be used to confirm that patients are not pregnant before study drug administration on each visit day of scheduled time point or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.
24. To determine eligibility, retesting will be allowed once during Screening period based on the investigator's discretion. Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples except ESR will be analyzed at the central laboratory. The ESR samples will be analyzed locally using kits supplied. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity to determine serum sickness.

Clinical chemistry	Total protein, serum bilirubin (total, direct), ALT, AST, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-MB, troponin I, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and CRP
Hematology	Red blood cells, ESR, total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination

25. Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented once at Screening.
26. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the investigator's discretion.
27. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of study drug administration, within 15 minutes after the end of study drug administration, and 1 hour [+10 minutes] after the end of study drug administration) will be monitored for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any type of ECG can be performed. Delayed hypersensitivity will be monitored, which includes serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption, or edema).

28. Serum samples for immunogenicity testing will be drawn at the same time as the clinical laboratory tests before dosing, where applicable. On the day of initiation of dose adjustment, serum samples for immunogenicity analysis will be collected before study drug administration. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity to determine serum sickness. Analysis will be performed at the central laboratory.
29. Additional serum samples for complement (C3, C4), and total hemolytic complement will be assessed if delayed hypersensitivity occurs to determine serum sickness. Analysis will be performed at the central laboratory.
30. Blood samples for PK analysis will be collected at pre-dose (prior to the beginning of study drug administration) of Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102, and within 15 minutes after the end of the study drug infusion of Week 6. On the day of initiation of dose adjustment, blood samples for PK analysis will be collected at pre-dose. For patients who agreed to collect further blood samples, additional blood samples for further Population PK analysis will be collected at the following time points: any time between 48 hours and 72 hours after study drug administration of Week 22, any time between 120 hours and 168 hours after study drug administration of Week 22, and pre-dose of Week 24.
31. C-reactive protein samples will be drawn at the same time as the clinical laboratory blood samples.
32. Fecal calprotectin analysis will be performed at the central laboratory.
33. All patients will assess local site pain using 100 mm VAS immediately (not exceeding 15 minutes) after the end of administration of study drug.
34. Use of all prior and concomitant medications for the treatment of UC, latent TB, and/or hepatitis C (if applicable) from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) or from when the ICF is signed, whichever is earlier, will be recorded until the EOS visit. All concomitant medications will also be recorded when any ADR is ongoing at the EOS visit.
35. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
36. Throughout the study, patients will be monitored for cardiovascular disease related signs and symptoms such as, but not limited to, shortness of breath, palpitations, chest pain, chest discomfort and/or fainting.
37. Adverse events will be assessed from the date the patient signs the ICF until the last assessment date or EOS visit. Where an ADR (i.e., related to study drug) is ongoing at the EOS visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure. AEs of special interest (i.e., infusion-related reaction/systemic injection reaction, infection, delayed hypersensitivity, localized injection site reaction, and malignancy) should be closely monitored.

Table 10-2 Schedule of Events for Extension Phase

	Extension Phase						EOS[1]
Study Week	**62**	**70**	**78**	**86**	**94**	**102**	
Study Day	**434**	**490**	**546**	**602**	**658**	**714**	
Dosing Window[2]	**± 3 days**						
Study Treatment[3]	**CT-P13 SC**						
Hepatitis B and HBV DNA test[4]	(X[5])		(X[5])		(X[5])		(X)
Hepatitis C and HCV RNA test[6]	(X[5])		(X[5])		(X[5])		(X)
Serum pregnancy test[7]							X
Stool microbiology[8]							
Anti-ds DNA test[9]							X[10]
IGRA[11]		X[5]		X[5]		X[5]	X[10]
Efficacy assessments							
Total & Modified Mayo score assessment[12]						X[5]	X[10]
Partial Mayo score assessment[12]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[10]
Flexible proctosigmoidoscopy (Endoscopic subscore of the Mayo score)[13]						X[5]	X[10]
Histologic assessment (RHI score)[14]						X	X[10]
Biopsy for histologic assessment[15]						X[5]	X[10]
SIBDQ		X[5]		X[5]		X[5]	X[10]
Safety and other assessments							
Urine pregnancy test[16]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	
Clinical laboratory tests[17]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Physical examinations	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Vital signs and weight[18]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
NYHA class assessment	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X

	Extension Phase						EOS[1]
Study Week	**62**	**70**	**78**	**86**	**94**	**102**	
Study Day	**434**	**490**	**546**	**602**	**658**	**714**	
Dosing Window[2]	**± 3 days**						
12-lead ECG[19]		X		X		X	X
Hypersensitivity monitoring[20]	X	X	X	X	X	X	
Immunogenicity[21]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
C3, C4 and total hemolytic complement[22]							
PK blood samples[23]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	
PD blood samples (CRP)[24]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Fecal calprotectin[25]		X[5]		X[5]		X[5]	X[10]
VAS local site pain[26]	X	X	X	X	X	X	
Prior, Concomitant medications[27]	X						
TB clinical monitoring[28]	X						
Cardiovascular disease monitoring[29]	X						
AE monitoring[30]	X						

Abbreviations: AE, adverse event; Anti-ds DNA, anti-double stranded DNA; CRP, C-reactive protein; ECG, electrocardiogram; EOS, End-of-Study; HBV, hepatitis B virus; HCV, hepatitis C virus; IGRA, interferon-γ release assay; NYHA, New York heart association; PD, pharmacodynamics; PK, pharmacokinetics; RHI, Robarts histopathology index; SC, subcutaneous; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TB, tuberculosis; VAS, Visual Analogue Scale.

1. All EOS assessments will be completed 4 weeks (±3 days) after the last dose of CT-P13 SC is received.
2. A dosing window of ±3 days is allowed, including self-injection. The minimal dose interval of 11 days is allowed.
3. All patients will receive active treatment with CT-P13 SC 120 mg via PFS from Week 56. The patients who received CT- P13 SC 240 mg in the Maintenance Phase will continue receiving the same doses of CT-P13 SC for the study treatment in the Extension Phase. During the Extension Phase, dose adjustment will be allowed. The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
4. For patients enrolled based on the HBV DNA test, the tests for HBsAg, HBsAb, HBV DNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94, and EOS visits. In patients who develop hepatitis B reactivation, study drug should be stopped, and the patient must be withdrawn from the study. Hepatitis B analysis will be performed at the central laboratory.
5. Assessed prior to study drug administration.

6. For enrolled patients who have a result of hepatitis C antibody (positive), tests for HCV RNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94 and EOS visits. In patients who develop hepatitis C activation, study drug should be stopped and the patient must be withdrawn from the study. Hepatitis C analysis will be performed at the central laboratory.
7. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS visit.
8. Stool microbiology (enteric pathogens, ova and parasites, and *Clostridium difficile* toxin test) will be performed at Screening and at any point in the study when a patient becomes symptomatic, including worsening or return of disease activity, at the investigator's discretion. Analysis will be performed at the central laboratory.
9. An anti-ds DNA test will be performed at Screening and at the EOS visit. If during the course of the study, a patient develops the signs or symptoms of systemic lupus erythematosus or lupus-like disease, the investigator may obtain unscheduled anti-ds DNA and other tests to aid in the evaluation. Analysis will be performed at the central laboratory.
10. End-of-Study assessments will only be performed if the assessments were not done at Week 102, or for patients with discontinuation before Week 102.
11. The IGRA analysis will be performed at the central laboratory.
12. With the exception of Screening, the Mayo score diary will be collected by patients for 7 days immediately prior to the Mayo score assessment and the most recent 3 days (not necessarily consecutive days) within the 7 days will be used to calculate the Mayo score. If the Mayo score assessment is performed at the same date as the flexible proctosigmoidoscopy or full colonoscopy procedure, the 3 days overlapping with endoscopy procedure (i.e., from the day before and up to the next day of the endoscopy procedure) will not be used to calculate the Mayo score.
13. Full colonoscopy may also be performed based on investigator's discretion. If full colonoscopy has been performed, it can replace flexible proctosigmoidoscopy. Flexible proctosigmoidoscopy (or full colonoscopy) for endoscopic subscore assessment will be performed within 14 days prior to the Mayo score assessment. Flexible proctosigmoidoscopy (or full colonoscopy) can be performed whenever needed based on investigator's discretion including determination of loss of response. Endoscopic subscore by flexible proctosigmoidoscopy (or full colonoscopy) will be evaluated at the central level by an independent reviewer blinded to treatment allocation to confirm eligibility, determine loss of response and for reporting purposes. The local endoscopic subscore will be considered during evaluation of the endoscopic subscore at the central level.
14. Histologic assessment by RHI score will be evaluated at the central level by an independent reviewer blinded to treatment allocation for reporting purposes.
15. Biopsy will be performed within 14 days prior to the histologic assessment.
16. A urine pregnancy test for women of childbearing potential will be used to confirm that patients are not pregnant before study drug administration on each visit day of scheduled time point or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.
17. Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples except ESR will be analyzed at the central laboratory. The ESR samples will be analyzed locally using kits supplied. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity to determine serum sickness.

Clinical chemistry	Total protein, serum bilirubin (total, direct), ALT, AST, alkaline phosphatase, γ-glutamyltransferase, blood urea nitrogen, creatinine, creatine kinase, creatine kinase-MB, troponin I, albumin, sodium, potassium, calcium, chloride, inorganic phosphorus, glucose, lactate dehydrogenase, total cholesterol, triglyceride, high-density lipoprotein cholesterol, and CRP
Hematology	Red blood cells, ESR, total and differential white blood cell count, absolute neutrophil count, lymphocyte count, platelet count, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and hematocrit
Urinalysis	Bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity, urobilinogen, and microscopic examination

18. Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting).
19. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the investigator's discretion.
20. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of study drug administration, within 15 minutes after the end of study drug administration, and 1 hour [+10 minutes] after the end of study drug administration) will be monitored for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any type of ECG can be performed. Delayed hypersensitivity will be monitored, which includes serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption, or edema).
21. Serum samples for immunogenicity testing will be drawn at the same time as the clinical laboratory tests before dosing, where applicable. On the day of initiation of dose adjustment, serum samples for immunogenicity analysis will be collected before study drug administration. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity to determine serum sickness, as well. Analysis will be performed at the central laboratory
22. Additional serum samples for complement (C3, C4), total hemolytic complement will be assessed if delayed hypersensitivity occurs to determine serum sickness. Analysis will be performed at the central laboratory.
23. Blood samples for PK analysis will be collected at pre-dose (prior to the beginning of study drug administration) of Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102, and within 15 minutes after the end of the study drug infusion of Week 6. On the day of initiation of dose adjustment, blood samples for PK analysis will be collected at pre-dose.
24. C-reactive protein samples will be drawn at the same time as the clinical laboratory blood samples.
25. Fecal calprotectin analysis will be performed at the central laboratory.
26. All patients will assess local site pain using 100 mm VAS immediately (not exceeding 15 minutes) after the end of administration of study drug.
27. Use of all prior and concomitant medications for the treatment of UC, latent TB, and/or hepatitis C (if applicable) from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) or from when the ICF is signed, whichever is earlier, will be recorded until the EOS visit. All concomitant medications will also be recorded when any ADR is ongoing at the EOS visit.
28. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
29. Throughout the study, patients will be monitored for cardiovascular disease related signs and symptoms such as, but not limited to shortness of breath, palpitations, chest pain, chest discomfort, and/or fainting.
30. Adverse events will be assessed from the date the patient signs the ICF until the last assessment date or EOS visit. Where an ADR (i.e., related to study drug) is ongoing at the EOS visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure. AEs of special interest (i.e., infusion-related reaction/systemic injection reaction, infection, delayed hypersensitivity, localized injection site reaction, and malignancy) should be closely monitored.

10.2 Diabetes Mellitus Assessment

Diabetes mellitus is defined by the criteria for the diagnosis of diabetes mellitus according to the American Diabetes Association. Patients are to be excluded from the study if they have uncontrolled diabetes mellitus even after insulin treatment at Screening. Details of the American Diabetes Association criteria for the diagnosis of diabetes mellitus are provided in Table 10-3.

Table 10-3 Criteria for the Diagnosis of Diabetes Mellitus

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

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

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

Reference: American Diabetes Association, 2006.

10.3 New York Heart Association Functional Classification

As defined in Zhang et al. 2018, the New York Heart Association (NYHA) classification is used in patients with heart failure.

Class	Symptoms
I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II (Mild)	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III (Moderate)	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea.
IV (Severe)	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

10.4 Short Inflammatory Bowel Disease Questionnaire

SIBDQ

Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease the way you have been feeling in general, and how your mood has been.

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from
(Systemic)

   1 All of the time
   2 Most of the time
   3 A good bit of the time
   4 Some of the time
   5 A little of the time
   6 Hardly any of the time
   7 None of the time

2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from
(Social)

   1 All of the time
   2 Most of the time
   3 A good bit of the time
   4 Some of the time
   5 A little of the time
   6 Hardly any of the time
   7 None of the time

SIBDQ

3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from
(Social)

1 A great deal of difficulty; activities made impossible
2 A lot of difficulty
3 A fair bit of difficulty
4 Some difficulty
5 A little difficulty
6 Hardly any difficulty
7 No difficulty; the bowel problems did not limit sports or leisure activities

4. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from
(Bowel)

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

5. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from
(Emotional)

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

SIBDQ

6. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from
(Bowel)

1 A major problem
2 A big problem
3 A significant problem
4 Some trouble
5 A little trouble
6 Hardly any trouble
7 No trouble

7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from
(Systemic)

1 A major problem
2 A big problem
3 A significant problem
4 Some trouble
5 A little trouble
6 Hardly any trouble
7 No trouble

8. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option form
(Emotional)

1 None of the time
2 A little of the time
3 some of the time
4 A good bit of the time
5 Most of the time
6 Almost all of the time
7 All of the time

SIBDQ

9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from
(Bowel)

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from
(Emotional)

1 All of the time
2 Most of the time
3 A good bit of the time
4 Some of the time
5 A little of the time
6 Hardly any of the time
7 None of the time

10.5 Mayo Scoring System

No.	Items	Score
1	**Stool frequency**[1]	
	Normal no. of stools for this patient	0
	1 to 2 stools more than normal	1
	3 to 4 stools more than normal	2
	5 or more stools more than normal	3
2	**Rectal bleeding**[2]	
	No blood seen	0
	Streaks of blood with stool less than half the time	1
	Obvious blood (more than just streaks) or streaks of blood with stool most of the time	2
	Blood alone passes	3
3	**Findings of flexible proctosigmoidoscopy**[3]	
	Normal or inactive disease	0
	Mild disease (erythema, decreased vascular pattern)	1
	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)	2
	Severe disease (spontaneous bleeding, ulceration)	3
4	**Physician's global assessment**[4]	
	Normal	0
	Mild disease	1
	Moderate disease	2
	Severe disease	3

Total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease.
Modified Mayo score ranges from 0 to 9, excluding PGA, with higher scores indicating more severe disease.

1. Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.
2. The daily bleeding score represents the most severe bleeding of the day. Rectal bleeding subscore of the Mayo Score is modified in accordance with FDA guidance so that a value of 2 is consisted of obvious blood (more than just streaks) and streaks of blood with stool most of the time.
3. Endoscopic subscore of the Mayo Score is modified in accordance with FDA guidance so that a value of 1 does not include friability.
4. The physician's global assessment acknowledged the 3 other criteria; the patient's recollection of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient's performance status.

Source: Schroeder et al. 1987

10.6 Robarts Histopathology Index

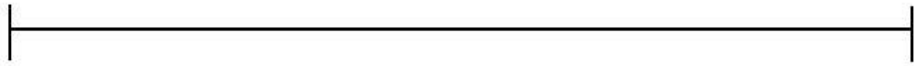
Component	Features	Score
Chronic inflammatory infiltrate	No increase	0
	Mild but unequivocal increase	1
	Moderate increase	2
	Marked increase	3
Lamina propria neutrophils	None	0
	Mild but unequivocal increase	1
	Moderate increase	2
	Marked increase	3
Neutrophils in epithelium	None	0
	<5% crypts involved	1
	<50% crypts involved	2
	>50% crypts involved	3
Erosion or ulceration	No erosion, ulceration or granulation tissue	0
	Recovering epithelium + adjacent inflammation	1
	Probable erosion-focally stripped	1
	Unequivocal erosion	2
	Ulcer or granulation tissue	3

Robarts histopathology index = 1×chronic inflammatory infiltrate level + 2×lamina propria neutrophils + 3×neutrophils in epithelium + 5×erosion or ulceration

Source: Mosli et al. 2017

10.7 Visual Analog Scale: Local Site Pain

Patient assessment of local site pain is measured by the patient indicating the extent of their pain in the local site where study drug was administered by marking a line (|) through the 100 mm line (0 mm equals no pain and 100 mm equals extreme pain). The length of the line is measured from the left (in mm) and the value (in mm) is recorded in the patient's eCRF.



0 mm **100 mm**

No pain Extreme pain

10.8 Guideline for Individual Patient Withdrawal Criteria

Patients who meet any of the following criteria will be withdrawn from the study.

- Two sequential absolute neutrophil count $< 0.5 \times 10^3$ cells/μL (SI units: $< 0.5 \times 10^9$ cells/L)
- Two sequential hemoglobin < 8.0 g/dL (SI units: $< 8.0 \times 10^9$ cells/L)
- Two sequential platelet count $< 25 \times 10^3$ cells/μL (SI units: $< 25 \times 10^9$ cells/L)
- Two sequential CK elevations > 10×ULN
- ALT and/or AST > 8×ULN
- ALT and/or AST > 5×ULN for more than 2 weeks
- ALT or AST > 3×ULN and (total bilirubin > 2×ULN or INR > 1.5) and alkaline phosphatase < 2×ULN
- ALT and/or AST > 3×ULN with signs and symptoms consistent with the appearance of fatigue, nausea, vomiting right upper quadrant pain or tenderness, fever, rash, and/or higher than 5% of eosinophilia value

For the clinical laboratory results that require 2 sequential tests, the investigator will contact the patients, preferably within the recommended time frame of 3 to 5 days from awareness of the abnormal results, to conduct the unscheduled laboratory testing.

- Development of signs of disease progression in the investigator's judgement
- Any AE that would compromise patient's safety if he or she continues to participate in the study, including but not limited to the following:
  - New serious and life-threatening infections leading to hospitalization including bacterial sepsis, invasive fungal infections (such as histoplasmosis)
  - Active TB
  - Life-threatening treatment-related anaphylactic reactions
  - Hepatitis B reactivation (HBV DNA or HBsAg test positive)
  - Hepatitis C activation (HCV RNA test positive)
  - New onset of lymphoma and other malignancies confirmed by imaging and/or pathology test
  - New onset of demyelinating disease
  - New onset of lupus-like syndrome

  - Heart failure of NYHA class III or IV
  - DILI
  - Systemic lupus erythematosus or lupus-like disease (anti-ds DNA test positive)
- A significant protocol deviation(s)
- Pregnancy
- Investigator's decision
- Withdrawal of consent or refusal to continue treatment and/or procedures/observations
- Lost to follow-up
- Death
- Study termination by the sponsor
- Non-responder at Week 10

11 Reference List

American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2006;29(Suppl 1):S43-8.

Bazzoni F, Beutler B. The tumor necrosis factor ligand and receptor families. N Engl J Med. 1996;334(26):1717-25.

CELLTRION, Inc. CT-P13. Investigator's Brochure, 15th ed. Incheon, South Korea; 2019. 211 p.

Cohen RB, Dittrich KA. Anti-TNF therapy and malignancy - a critical review. Can J Gastroenterol. 2001;15(6):376-84.

Faubion WA Jr, Loftus EV Jr, Harmsen WS, et al. The natural history of corticosteroid therapy for inflammatory bowel disease: a population-based study. Gastroenterology. 2001;121(2):255-60.

Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet. 2002;359(9317):1541-9.

Hsia EC, Ruley KM, Rahman MU. Infliximab (Remicade®): from bench to clinical practice. A paradigm shift in rheumatology practice. APLAR J Rheumatol. 2006(2);9:107-18.

Inflectra (infliximab) [prescribing information]. Celltrion Inc. Incheon (Republic of Korea); 2019. [cited 2019 October]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=37eaca10-d812-48bc-8b8e-b836bfa9968f

Jackisch C, Müller V, Maintz C, et al. Subcutaneous administration of monoclonal antibodies in oncology. Geburtshilfe Frauenheilkd. 2014; 74(4): 343–9.

Mosli MH, Feagan BG, Zou G, et al. Development and validation of a histological index for UC. Gut. 2017 Jan 1;66(1):50-8.

Ordás I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet. 2012;380(9853):1606-19.

Park JH, Seo GY, Lee JS, et al. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. J Rheumatol. 2009;36(10);2158-63.

Peschon JJ, Torrance DS, Stocking KL, et al. TNF receptor-deficient mice reveal divergent roles for p55 and p75 in several models of inflammation. J Immunol. 1998;160(2):943-52.

Remsima (infliximab): [summary of product characteristics]. Celltrion Inc. Incheon (Republic of Korea); EMEA/H/C/002576- IB/0061; 2019. [cited 2019 March 03]. Available from:

https://www.ema.europa.eu/en/documents/product-information/remsima-epar-product-information_en.pdf

Rutgeerts P, Sandborn W.J., Feagan B.G, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2005;353(23):2462-76.

Schroeder KW, Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. N Engl J Med. 1987; 317(26): 1625-29.

Tartaglia LA, Goeddel DV, Reynolds C, et al. Stimulation of human T-cell proliferation by specific activation of the 75-kDa tumor necrosis factor receptor. J Immunol. 1993;151(9):4637-41.

US Food and Drug Administration. Center for Drug Evaluation and Research. Center for Biologics Evaluation and Research. (2009). Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. Maryland: Drug Safety. Available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

Zhang R, Ma S, Shanahan L, et al. Discovering and identifying New York heart association classification from electronic health records. BMC Med Inform Decis Mak, 2018; 18(Suppl 2): 48.