CLINICAL STUDY PROTOCOL

An Open-label, Randomized, Parallel-Group, Phase I Study to Evaluate Pharmacokinetics, Efficacy and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients With Active Crohn's Disease and Active Ulcerative Colitis

PROTOCOL NUMBER CT-P13 1.6

Protocol Number: CT-P13 1.6

EudraCT Number: 2016-002124-89

Test Formulation: CT-P13 SC administered subcutaneously

Sponsor: [redacted]

Sponsor Contact: [redacted]

SAE Reporting: [redacted]

Version and Date of Protocol: Protocol Version 3.0, 09 January 2018

CONFIDENTIAL

Protocol Approval – Sponsor Signatory

Study Title	An Open-label, Randomized, Parallel Group, Phase I Study to evaluate Pharmacokinetics, Efficacy and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients With Active Crohn's disease and Active Ulcerative Colitis
Protocol Number	CT-P13 1.6
Protocol Date	Protocol Version 3.0, 09 January 2018

Protocol accepted and approved by:

[redacted]

[redacted]

Declaration of Investigator

I have read and understand all sections of the protocol entitled "An Open-label, Randomized, Parallel Group, Phase I Study to evaluate Pharmacokinetics, Efficacy and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients With Active Crohn's disease and Active Ulcerative Colitis" and the accompanying current investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Protocol Version 3.0, 09 January 2018, the International Conference on Harmonisation harmonised tripartite guideline E6(R2): Good Clinical Practice and the Declaration of Helsinki (WMA2013), and all applicable government regulations. I will not make changes to the protocol before consulting with CELLTRION, Inc. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study drug only to patients under my personal supervision or the supervision of a subinvestigator.

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

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

Signature of Principal Investigator	Date

Printed Name of Principal Investigator

Table of Contents

List of Figures

List of Tables

Protocol Synopsis

Protocol Number: CT-P13 1.6

Title: An Open-label, Randomized, Parallel Group, Phase I Study to evaluate Pharmacokinetics, Efficacy and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients With Active Crohn's disease and Active Ulcerative Colitis

Clinical Phase: Phase I

Planned Number of Study Centers/Countries:

Part 1:

It is expected that up to approximately 50 study centers will enrol patients in approximately 10 countries.

Part 2:

It is expected that up to approximately 120 study centers will enrol patients in approximately 17 countries.

Test Product Formulation, Dose, and Regimen:

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

Part 1:

Following cohorts will be administered CT-P13 SC:

- CT-P13, 120 mg by SC injection via pre-filled syringe (PFS) every other week
- CT-P13, 180 mg by SC injection via PFS every other week
- CT-P13, 240 mg by SC injection via PFS every other week

Part 2:

- Patients less than 80 kg weight (body weight <80 kg): CT-P13 120 mg by SC injection via PFS every other week
- Patients at or above 80 kg weight (body weight ≥80 kg): CT-P13 240 mg by SC injection via PFS every other week

Reference Drug, Dose, and Regimen:

Part 1 & Part 2:

CT-P13 (5 mg/kg) by IV infusion administered as a 2-hour infusion per dose.

Objectives:

Part 1:

Primary objective:

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

Secondary objectives:

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

Part 2:

Primary objective:

- To demonstrate that CT-P13 SC is noninferior to CT-P13 IV in terms of PK, as determined by the C_{trough} (trough concentration, pre-dose level) at Week 22.

Secondary objectives:

- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks)
- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54

Tertiary objectives:

- To evaluate genotypes as biomarkers (optional)
- To evaluate amino acids as biomarkers
- To evaluate patient overall satisfaction of CT-P13 IV and CT-P13 SC

Sample Size:

Part 1:

Approximately 40 (at least 24) male or female patients with active Crohn's disease (CD) will be randomly assigned at Week 6 in a 1:1:1:1 ratio into four study cohorts as follows:

Cohort Number	Dosage	Investigational Product	Method of Administration
Cohort 1	5 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Cohort 2	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection
Cohort 3	180 mg	CT-P13 SC 90 mg/PFS	Double SC injection
Cohort 4	240 mg	CT-P13 SC 120 mg/PFS	Double SC injection

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

Part 2:

Minimum 130 male or female patients with active CD or Ulcerative Colitis (UC) will be randomly assigned at Week 6 in a 1:1 ratio to the CT-P13 SC or CT-P13 IV (approximately 65 patients per treatment group) treatment groups as follows:

Arm Number	Dosage	Investigational Product	Method of Administration
Arm 1[1]	5 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Arm 2[2]	120 mg (<80 kg)	CT-P13 SC 120 mg/PFS	Single SC injection
	240 mg (≥80 kg)	CT-P13 SC 120 mg/PFS	Double SC injection

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

[1]CT-P13 IV will be switched to CT-P13 SC at Week 30. The dosage of CT-P13 SC will be determined based on the patient's body weight at Week 30.

[2]The dosage of CT-P13 SC will be determined based on the patient's body weight at Week 6.

Main Selection Criteria:

Part 1:

Male or female patients with active CD who has CDAI score between 220 and 450 points will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Part 2:

Male or female patients with active CD who has CDAI score between 220 and 450 points or with active UC who has total Mayo scores of 6 to 12 points will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Inclusion Criteria:

The inclusion criteria are divided into 3 categories: general inclusion criteria, active Crohn's disease inclusion criteria and active Ulcerative colitis inclusion criteria. Patients must meet all of the general inclusion criteria and disease-specific inclusion criteria according to their indication to be enrolled in this study:

General Inclusion Criteria

1. Patient who is a male or female aged 18 to 75 years old, inclusive.
2. 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

3. Patient who has the following hematology laboratory test results at Screening:
   - Hemoglobin ≥8.5 g/dL (SI [Système International d'Unités] units: ≥85 g/L or 5.28 mmol/L)
   - White blood cell count ≥3.5 × 10^3 cells/μL (SI units: ≥3.5 × 10^9 cells/L)
   - Neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
   - Platelet count ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L)
4. Patient who has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
5. Patient (or legal guardian, if applicable) who is informed of the full nature and purpose of the study, including possible risks and side effects, is given ample time and opportunity to read or understand this information, and has signed and dated the written informed consent before inclusion in the study.
6. 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.

Active Crohn's Disease Inclusion Criteria

1. Patient who has Crohn's disease with a score on the CDAI of 220 to 450 points.
2. **For Part 2**, patient who meets at least one of following at Screening;
   - C-reactive protein (CRP) concentration >0.5 mg/dL
   - Fecal calprotectin >100 μg/g
   - Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) of ≥6 points for ileal-colonic CD or ≥4 points including ulcer score from at least one segment for ileal CD or colonic CD
3. Patient who has Crohn's disease of at least 3 months' disease duration prior to the first administration of the study drug (Day 0).
4. Patient who has been treated for active Crohn's disease but has not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who is intolerant to or has medical contraindications for such therapies.
5. Stable doses of following Crohn's disease treatments or currently not receiving during specified time frame:
   - Azathioprine (AZA) or 6-mercaptopurine (6-MP) at least for 8 weeks prior to the first administration of the study drug (Day 0)
   - Methotrexate (MTX) at least for 6 weeks prior to the first administration of the study drug (Day 0)
   - Oral corticosteroids at the equivalent dose of 20 mg/day of prednisone or less at least for 2 weeks prior

to the first administration of the study drug (Day 0)

- Oral budesonide at the dose of 6 mg/day or less at least for 4 weeks prior to the first administration of the study drug (Day 0)
- 5-aminosalicylates (5-ASA) at least for 4 weeks prior to the first administration of the study drug (Day 0)

Active Ulcerative Colitis Inclusion Criteria (Part 2 only)

1. Patient who has active Ulcerative colitis as defined by a total Mayo score between 6 and 12 points with endoscopic evidence of active Ulcerative colitis as indicated by endoscopic subscore of ≥2 at Screening.
2. Patient who has Ulcerative colitis of at least 3 months' disease duration prior to the first administration of the study drug (Day 0).
3. Patient who has been treated for active Ulcerative colitis but not responded despite conventional therapy including corticosteroids alone or in combination with 6-MP or AZA and medications containing 5-ASA, or who is intolerant to or has medical contraindications for such therapies.
4. Stable doses of following Ulcerative colitis treatments or currently not receiving during specified time frame:
   - AZA or 6-MP at least for 8 weeks prior to the first administration of the study drug (Day 0)
   - MTX at least for 6 weeks prior to the first administration of the study drug (Day 0)
   - Oral corticosteroids at the equivalent dose of 20 mg/day of prednisone or less at least for 2 weeks prior to the first administration of the study drug (Day 0)
   - Oral budesonide at the dose of 6 mg/day or less at least for 4 weeks prior to the first administration of the study drug (Day 0)
   - Oral 5-ASA at least for 4 weeks prior to the first administration of the study drug (Day 0)
5. Patient who has more than 8 years of disease duration of Ulcerative colitis must have documented evidence for absence of colorectal cancer or dysplasia by full colonoscopy examination performed within a year prior to the first administration of the study drug (Day 0).

Exclusion Criteria:

The exclusion criteria are divided into 4 categories: general exclusion criteria, tuberculosis exclusion criteria, active Crohn's disease exclusion criteria and active Ulcerative colitis exclusion criteria. Patients meeting any of the following criteria will be excluded from the study:

General Exclusion Criteria

1. Patient who has previously received a biological agent for the treatment of Crohn's disease or Ulcerative colitis and/or a TNFα inhibitor for the treatment of other disease.
2. Patient who has allergies to any of the excipients of infliximab or any other murine and/or human proteins, or patient with a hypersensitivity to immunoglobulin product.
3. Patient who has a current or past history of following infection:
   - **For Part 1**, current or past history of chronic infection with hepatitis C or human immunodeficiency virus (HIV)-1 or -2 or current infection with hepatitis B

     For Part 2, a known infection with HIV, hepatitis B, or hepatitis C (carriers of hepatitis B and hepatitis C are not permitted to enrol into the study, but past hepatitis B resolved 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 within 6 months prior to the first administration of the study drug (Day 0)
   - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 0)
   - Past or current granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis). A patient who has a past diagnosis of those infections with sufficient documentation of complete resolution can be enrolled.

4. Patient who has received or has plan to receive any of following prohibited medications or treatment:
   - Any biological agents for the treatment of Crohn's disease or Ulcerative colitis
   - Parenteral corticosteroids for the treatment of Crohn's disease or Ulcerative colitis within 2 weeks prior to Screening
   - Antibiotics for the treatment of Crohn's disease or Ulcerative colitis within 2 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)
   - Thalidomide, tacrolimus, or cyclosporine within 3 months prior to the first administration of the study drug (Day 0)
   - Live or live-attenuated vaccine within 4 weeks of the first administration of the study drug (Day 0)
   - Abdominal surgery, including but not limited to, for 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)
   - Subtotal and total colectomy prior to the first administration of the study drug (Day 0)
   - Use of 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)
5. Patient who has a medical condition including one or more of the following:
   - Diagnosed obstruction by imaging or clinical symptoms (e.g., abdominal distention or vomiting) highly suggestive of small bowel obstruction
   - Diagnosed Short bowel syndrome
   - Stoma (e.g., ileostomy or colostomy) within 6 months prior to the first administration of the study drug (Day 0)
   - Classified as obese (body mass index $\geq$35 kg/m^2)
   - Uncontrolled diabetes mellitus, even after insulin treatment
   - Uncontrolled hypertension (as defined by systolic blood pressure $\geq$160 mmHg or diastolic blood pressure $\geq$100 mmHg)
   - History of any malignancy within 5 years prior to the first administration of the study drug (Day 0) except completely excised and cured squamous carcinoma of the uterine cervix in situ, cutaneous basal cell carcinoma, or cutaneous squamous cell carcinoma
   - History of lymphoma or lymphoproliferative disease or bone marrow hyperplasia
   - New York Heart Association 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 opinion of the investigator), including but not limited to chronic obstructive pulmonary disease, asthma, bronchiectasis, or pleural effusion
   - Previous diagnosis or symptoms suggestive of demyelinating disorders, including multiple sclerosis and Guillain Barré syndrome
   - Any conditions significantly affecting the nervous system (i.e., neuropathic conditions or nervous system damage)
   - Any other serious acute or chronic medical or psychiatric condition that may increase the risk associated with study participation or investigational product administration or that may interfere with the interpretation of study results
6. Patient who has a current or past history of drug or alcohol abuse.
7. Patient who has had treatment with any other investigational device or medical product within 4 weeks prior

to the first administration of the study drug (Day 0) or 5 half-lives, whichever is longer.

8. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.
9. Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.

Tuberculosis Exclusion Criteria

1. **For Part 1**, a patient who has a history of tuberculosis (TB) or a current diagnosis of TB. A patient who has a past diagnosis of active TB with sufficient documentation of complete resolution can be enrolled.

   For Part 2, a patient who has a history of TB or a current diagnosis of TB. A patient who has a past diagnosis of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.
2. Patient who has had exposure to person with active TB such as first degree family members or co-workers
3. **For Part 1**, a patient who has an indeterminate result for interferon-γ release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at Screening. A patient who has a past diagnosis of latent TB with sufficient documentation of prophylaxis can be enrolled.

   For Part 2, a patient who has an indeterminate result for IGRA or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at Screening. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the repeated IGRA result is again indeterminate, the patient must be excluded from the study. If the repeated IGRA result is negative, the patient can be included in the study. A patient who has a past diagnosis of latent TB cannot be enrolled despite sufficient documentation of prophylaxis.

Active Crohn's Disease Exclusion Criteria

1. Patient who has active entero-vesical, entero-retroperitoneal, entero-cutaneous, and entero-vaginal fistulae within 6 months prior to the first administration of the study drug (Day 0). Entero-enteral fistulae without clinical significant symptoms upon investigator's opinion and anal fistulae without draining problems are allowed.
2. Patient who has taken more than 3 small-bowel resection procedures prior to the first administration of the study drug (Day 0).

Active Ulcerative Colitis Exclusion Criteria (Part 2 only)

1. Patient who is taking rectally administered medications containing corticosteroids or 5-ASA for the treatment of ulcerative colitis within 2 weeks prior to Screening.

Study Design:

This study is an open-label, randomized, multicenter, parallel-group, Phase I study designed to evaluate pharmacokinetics, efficacy and safety between CT-P13 SC and CT-P13 IV in patients with active CD or active UC up to Week 54. The study consists of two parts:

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

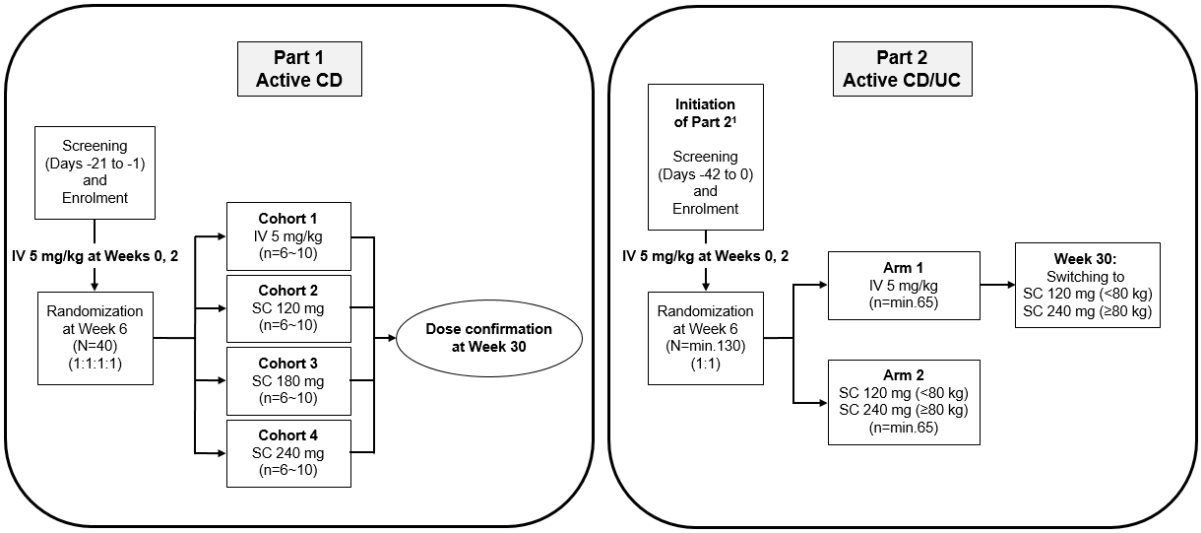
The duration of the study will be up to 65 weeks for Part 1, which includes Screening (up to 3 weeks) and the last dose at 54 weeks plus the following 8 weeks off-dose period, prior to the End-of-Study Visit.

- **Part 2**, designed to demonstrate noninferiority in PK between CT-P13 SC and CT-P13 IV, includes:
  - Screening (Days -42 to 0)
  - Treatment Period (Week 0 dosing through Week 54)
  - End-of-Study (2 weeks after the last dose is received)

The duration of the study will be up to 62 weeks for Part 2, which includes Screening (up to 6 weeks) and the last dose at 54 weeks plus the following 2 weeks off-dose period, prior to the End-of-Study Visit.

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

Figure S1 Overview of Study Design



IV, intravenous; SC, subcutaneous; CD, Crohn's Disease; UC, Ulcerative Colitis.

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

Study Schedule:

Part 1:

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

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

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

The randomization to treatment assignment will be stratified by:

- Region (European or non-European)
- Current use of treatment with AZA or 6-MP or MTX (used or not used)
- Clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease)
- Body weight at Week 6 (≤70 kg or >70 kg)

Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

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

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

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

Dose escalation up to 10 mg/kg will be allowed for patients from Cohort 1 since Week 30 if the patient initially responded but then lost response at each visit. Loss of response is defined as any of following: (1) an increase in CDAI of at least 70 points from the lowest CDAI score with a total score over 220, or (2) need of the initiation of a new treatment for active Crohn's disease. Dose escalation by dose interval shortening will not be allowed.

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

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

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

Figure S2 Patient Assessment Overview for Part 1

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

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

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

Part 2:

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

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

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

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

The randomization to treatment assignment will be stratified by:

- Current use of treatment with AZA or 6-MP or MTX (used or not used)
- Disease (Crohn's disease or Ulcerative colitis)
- Clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease or partial Mayo score for Ulcerative colitis)

- Body weight at Week 6 (<80 kg or ≥80 kg)

Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments.

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

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

- **Arm 1:** further 3 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22). CT-P13 IV will be then switched to CT-P13 SC at Week 30 with CT-P13 SC dose based on body weight at Week 30. Further doses of CT-P13 SC will be given every 2 weeks up to Week 54.
- **Arm 2:** CT-P13 SC dose based on body weight at Week 6 will be administered by PFS at Week 6 and then every 2 weeks up to Week 54.

For patients receiving CT-P13 SC 120 mg every 2 weeks, dose escalation to CT-P13 SC 240 mg every 2 weeks will be allowed since Week 30 if the patient initially responded but then lost response at Week 30, 38, 46 or 54 visit. Dose escalation will not be allowed for patients receiving CT-P13 SC 240 mg every 2 weeks. Loss of response is defined as need of the initiation of a new treatment for active CD or UC, or as following:

- For Crohn's disease, if patient has an increase in CDAI ≥70 points from the lowest CDAI score with a total score ≥220
- For Ulcerative colitis, if patient meets (1) and either of (2) or (3);
  - (1) an increase in rectal bleeding subscore ≥1 point from the lowest score with actual value of >1 point
  - (2) an increase in partial Mayo score ≥2 points from the lowest score with actual value of ≥4 points
  - (3) an increase in endoscopic subscore ≥1 point from the lowest score with actual value of >1 point

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

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

Figure S3 Patient Assessment Overview for Part 2

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

1. Additional visits will only be made by patients who need extra training for CT-P13 SC injection

2. A visit window of ±3 days is allowed throughout the study period, including the End-of-Study Visit.
3. Only patients from Arm 2 will make visits for additional pharmacokinetic assessment.

End-of-Study Visit: The End-of-Study Visit will occur 2 weeks after the last dose of CT-P13 SC is received. For patients with early discontinuation before switching to CT-P13 SC at Week 30 in Arm 1 or before randomization at Week 6 in Arm 2, the End-of-Study Visit will occur 8 weeks after the last dose of CT-P13 IV is received.

Pharmacokinetic Assessments:

Primary Endpoint for Part 1:

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

Secondary Endpoints for Part 1:

The following PK parameters will be determined as secondary PK endpoints between Week 22 and Week 30:

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

The following PK parameter will be determined as secondary PK endpoint up to Week 54:

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

Primary Endpoint for Part 2:

- C_{trough} Trough concentration (pre-dose level) at Week 22

Secondary Endpoints for Part 2:

The following PK parameters will be determined as secondary PK endpoints between Week 22 and Week 30:

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

The following PK parameter will be determined as secondary PK endpoint up to Week 54:

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

Efficacy Assessments:

Secondary Endpoints for Part 1:

- CDAI-70 response, defined as a decrease in CDAI score of 70 points or more from the baseline value

- CDAI-100 response, defined as a decrease in CDAI score of 100 points or more from the baseline value
- Clinical remission, defined as an absolute CDAI score of less than 150 points
- Endoscopic response, defined as a decrease in 50% or more of SES-CD score
- Endoscopic remission, defined as an absolute SES-CD score of 2 points or less
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Secondary Endpoints for Part 2:

For active CD;

- CDAI-70 response, defined as a decrease in CDAI score of 70 points or more from the baseline value
- CDAI-100 response, defined as a decrease in CDAI score of 100 points or more from the baseline value
- Clinical remission, defined as an absolute CDAI score of less than 150 points
- Endoscopic response, defined as a decrease in 50% or more of SES-CD score
- Endoscopic remission, defined as an absolute SES-CD score of 2 points or less
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

For active UC;

- Clinical response, defined as a decrease in total Mayo score from baseline at least 3 points and at least 30%, 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
- Clinical response, defined as a decrease in partial Mayo score from baseline 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
- Clinical remission, defined as a total Mayo score of 2 points or lower with no individual subscore exceeding 1 point, or partial Mayo score of 1 point or lower
- Mucosal healing, defined as an absolute endoscopic subscore of 0 or 1 from Mayo Scoring System (MSS)
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Pharmacodynamic Assessments:

Secondary Endpoints for both Part 1 and Part 2:

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

- Fecal Calprotectin
- C-reactive protein (CRP)

Biomarker Assessment:

Tertiary Endpoints for Part 2:

The following parameters will be assessed as biomarkers:

- Genotypes (including, but not limited to FcRn)
- Amino acids (including, but not limited to Tryptophan)

For genotype assessments, blood samples of patients who sign a separate informed consent form will be collected.

Safety Assessments:

Secondary Endpoints for both Part 1 and Part 2:

Safety assessments will be performed on immunogenicity, hypersensitivity monitoring (including delayed hypersensitivity monitoring), vital sign measurements (including blood pressure, heart and respiratory rates, and body temperature), weight, interferon-γ release assay, chest X-ray, hepatitis B and C and HIV-1 and -2 status, physical examination findings, 12-lead ECGs, AEs (including serious AEs), adverse event of special interest (infections, infusion-related reactions/hypersensitivity/ anaphylactic reactions [administration-related reactions],

delayed hypersensitivity, injection site reactions, malignancies), signs and symptoms of TB, clinical laboratory analyses, pregnancy testing, prior and concomitant medications, and local site pain using 100 mm Visual Analogue Scale (VAS).

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

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

Patient Overall Satisfaction Assessment:

Tertiary endpoint for Part 2:

Patient overall satisfaction of CT-P13 IV and CT-P13 SC will be assessed by using 100 mm VAS.

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.

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

Pharmacokinetic Analysis:

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

Part 1 Primary: No formal sample size estimation was performed because no confirmatory analyses are planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) are considered to be sufficient to investigate the primary objective of this study. The observed AUC_{τ} between patients treated with CT-P13 IV or CT-P13 SC at steady state between Week 22 and Week 30 will be presented in listing and summarized in table. The table will display the following descriptive statistics; n, mean, SD, median, minimum, maximum, geometric mean, and coefficient of variation (CV).

Part 2 Primary: The primary endpoint is the C_{trough} (pre-dose level) at Week 22. A sample size of 104 subjects (52 patients each in the CT-P13 SC and CT-P13 IV treatment groups) provide 90% power to demonstrate noninferiority of CT-P13 SC to CT-P13 IV based on the 95% one-sided confidence interval for the geometric mean ratio of CT-P13 SC to CT-P13 IV in C_{trough}. In the sample size calculation, noninferiority margin of 80%, one-sided alpha level 5%, expected ratio of 1.3 and CV of 100% were assumed. Considering 20% drop-out rate, total 130 patients (65 patients each in the CT-P13 SC and CT-P13 IV treatment groups) will be required.

A reassessment of sample size accounting for the actual ratio of geometric means and CV will be made using the result from Part 1. The sample size will not be decreased from the initial 130 total sample size but could be increased up to 200 patients in case that actual ratio of geometric means decreases to 1.18 or actual CV increases up to 140%. Sample size will be determined considering DSMB's recommendation based upon the review of PK, efficacy, PD and safety data found over the first 30 weeks from Part 1 of the study.

The primary endpoint will be assessed by statistical comparison of C_{trough} for CT-P13 SC and for CT-P13 IV. The observed C_{trough} between patients treated with CT-P13 IV or CT-P13 SC at Week 22 will be analyzed using an analysis of covariance model (ANCOVA).

Point estimates (geometric least square means and ratio of geometric least square means) will be calculated from back transforming the least squares means of the log-transformed values of C_{trough} and difference in the least squares means. 90% confidence interval (CI) for the ratio of the geometric least square means will also be

produced. The noninferiority of CT-P13 SC to CT-P13 IV will be concluded if the lower bound 90% CI for the ratio of the geometric least square means is higher than 0.8.

Part 1 & Part 2 Secondary: Pharmacokinetic parameters will be presented in listings and summarized in tables. The tables will display the following descriptive statistics: n, mean, median, SD, minimum, maximum, the geometric mean and CV.

Efficacy Analysis:

Part 1 & Part 2 Secondary: The following secondary efficacy endpoints will be summarized using descriptive statistics:

- For active CD, clinical response (CDAI-70, CDAI-100), clinical remission by CDAI score, endoscopic response and remission, and SIBDQ.
- For active UC, clinical response (by total or partial Mayo Score), clinical remission (by total or partial Mayo Score), mucosal healing, and SIBDQ

Pharmacodynamic Analysis:

Part 1 & Part 2 Secondary: The secondary pharmacodynamic endpoints (CRP, Fecal calprotectin) will be summarized using descriptive statistics (including geometric mean and CV).

Safety Analysis:

Part 1 & Part 2 Secondary: Adverse events will be coded to system organ class and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events v4.03. Prior and concomitant medications will be coded to drug class and preferred term according to World Health Organization Drug Dictionary. All safety data will be listed and summarized by treatment group as appropriate.

Biomarker Analysis:

Part 2 Tertiary: Descriptive analyses will be performed on genotypes (including, but not limited to FcRn) and amino acids (including, but not limited to Tryptophan) by treatment groups.

Patient Overall Satisfaction Analysis:

Part 2 Tertiary: Descriptive analyses will be performed on patient overall satisfaction of CT-P13 IV and CT-P13 SC by treatment groups.

List of Abbreviations

Abbreviation	Definition
5-ASA	5-aminosalicylates
6-MP	6-mercaptopurine
AE	adverse event
AS	ankylosing spondylitis
AUC_{ss8W}	total exposure over the 8 weeks interval from Week 22 to Week 30
AUC_{τ}	area under the concentration-time curve
AUC_{τ}/DN	dose normalized total exposure over dosing interval
AZA	Azathioprine
BA	Bioavailability
cA2	anti-TNF chimeric monoclonal antibody
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	confidence interval
CL	Clearance after CT-P13 Intravenous dosing
CL/F	Apparent clearance after CT-P13 Subcutaneous dosing
C_{max}	Observed maximum serum concentration
C_{max}/DN	dose normalized peak exposure
CRP	C-reactive protein
CT-P13	infliximab (CELLTRION, Inc.)
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentration
CV	Coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
ESR	erythrocyte sedimentation rate
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus

ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IGRA	Interferon- γ release assay
IRB	institutional review board
IV	Intravenous
IVRS	interactive voice response system
IWRS	interactive Web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
MSS	Mayo Scoring System
MTX	Methotrexate
NYHA	New York Heart Association
PD	Pharmacodynamic
PFS	Pre-filled syringe
PK	Pharmacokinetic
PT	preferred term
PVG	Pharmacovigilance
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SD	standard deviation
SES-CD	Simplified Endoscopic Activity Score for Crohn's Disease
SI	Système International d'Unités
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	system organ class
$T_{1/2}$	terminal half life
TEAE	Treatment-emergent adverse event
TB	Tuberculosis
T_{max}	time of observed maximum serum concentration
TNFα	tumor necrosis factor-alpha

τ_{obs}	observed tau
UC	Ulcerative colitis
ULN	upper limit of normal
VAS	Visual Analogue Scale

1 Introduction

1.1 Background

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

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

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

Inflammatory bowel disease is a collective term referring to a group of chronic inflammatory conditions of the colon and small intestine, of which CD and UC are the main types [Baumgart and Carding 2007]. CD is characterized by relapsing and remitting episodes, with complications of stricture, fistulas, or abscesses over time [Colombel et al. 2010; Peyrin-Biroulet et al. 2010; Cosnes et al. 2011]. UC is characterized by mucosal ulceration, rectal bleeding, diarrhea, and abdominal pain [Rutgeerts et al. 2005].

1.2 CT-P13

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

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

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

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

1.3 Preclinical Studies

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

1.4 Clinical Study

The safety, clinical response and pharmacokinetics of an experimental infliximab formulation for subcutaneous or intramuscular administration in RA was assessed in an open-label, randomized, Phase I study [Westhovens et al. 2006]. The study was conducted in 3 stages. In Stage I, 15 subjects were randomly assigned to receive a single SC injection of infliximab 0.5 mg/kg, 1.5 mg/kg or 3.0 mg/kg. In Stage II, 21 subjects received one of the following 3 infliximab treatment regimens, with 7 subjects randomized to each treatment group: 100 mg

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

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

1.5 Study Rationale

Infliximab has initially been developed for intravenous infusion. A new subcutaneous infliximab formulation is being developed by Celltrion, Inc. as an alternative to the intravenous regimen where subcutaneous infliximab injection typically takes less than 2 minutes. Potential benefits of such administration include improved patient convenience, better compliance, reduced pharmacy preparation times, and optimisation of medical resources. The availability of a subcutaneous formulation of infliximab would increase the treatment options available to patients, particularly those wishing to self-administer their therapy [Jackisch et al. 2014]. This Phase 1 randomized, open-label, multicenter, parallel-group study is designed to evaluate efficacy, pharmacokinetics, pharmacodynamics, biomarkers and safety between CT-P13 SC and CT-P13 IV in patients with active CD or active UC.

2 Study Objectives

2.1 Primary Objective for Part 1

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

2.2 Secondary Objectives for Part 1

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

2.3 Primary Objective for Part 2

- To demonstrate that CT-P13 SC is noninferior to CT-P13 IV in terms of PK, as determined by the C_{trough} (trough concentration, pre-dose level) at Week 22

2.4 Secondary Objectives for Part 2

- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV (over the first 30 weeks)
- To evaluate efficacy, PK, PD and overall safety of CT-P13 SC up to Week 54

2.5 Tertiary Objectives for Part 2

- To evaluate genotypes as biomarkers (optional)
- To evaluate amino acids as biomarkers
- To evaluate patient overall satisfaction of CT-P13 IV and CT-P13 SC

3 Investigational Plan

3.1 Study Design

This study is an open-label, randomized, multicenter, parallel-group, Phase I study designed to evaluate pharmacokinetics, efficacy and safety between CT-P13 SC and CT-P13 IV in patients with active CD or active UC up to Week 54.

This study consists of two parts:

- **Part 1**, designed to find the optimal dose of CT-P13 SC, includes (described in Section 3.2.1):
    - Screening (Days -21 to -1)
    - Treatment Period (Week 0 dosing through Week 54)
    - End-of-Study (8 weeks after the last dose is received)
- **Part 2**, designed to demonstrate noninferiority in PK between CT-P13 SC and CT-P13 IV, includes (described in Section 3.2.2):
    - Screening (Days -42 to 0)
    - Treatment Period (Week 0 dosing through Week 54)
    - End-of-Study (2 weeks after the last dose is received)

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

Table 3-1 Study Drug Randomization for Part 1

Cohort Number	Dosage	Investigational Product	Method of Administration
Cohort 1	5 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Cohort 2	120 mg	CT-P13 SC 120 mg/PFS	Single SC injection
Cohort 3	180 mg	CT-P13 SC 90 mg/PFS	Double SC injection
Cohort 4	240 mg	CT-P13 SC 120 mg/PFS	Double SC injection

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

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

In Part 2, minimum 130 male or female patients with active CD or active UC will be randomly assigned at Week 6 in a 1:1 ratio to 1 of 2 treatment groups, CT-P13 SC and CT-P13 IV (approximately 65 patients per treatment group) as presented in Table 3-2.

Table 3-2 Study Drug Randomization for Part 2

Arm Number	Dosage	Investigational Product	Method of Administration
Arm 1[1]	5 mg/kg	CT-P13 IV 100 mg/vial	2-hour IV infusion
Arm 2[2]	120 mg (<80 kg)	CT-P13 SC 120 mg/PFS	Single SC injection
	240 mg (≥80 kg)	CT-P13 SC 120 mg/PFS	Double SC injection

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

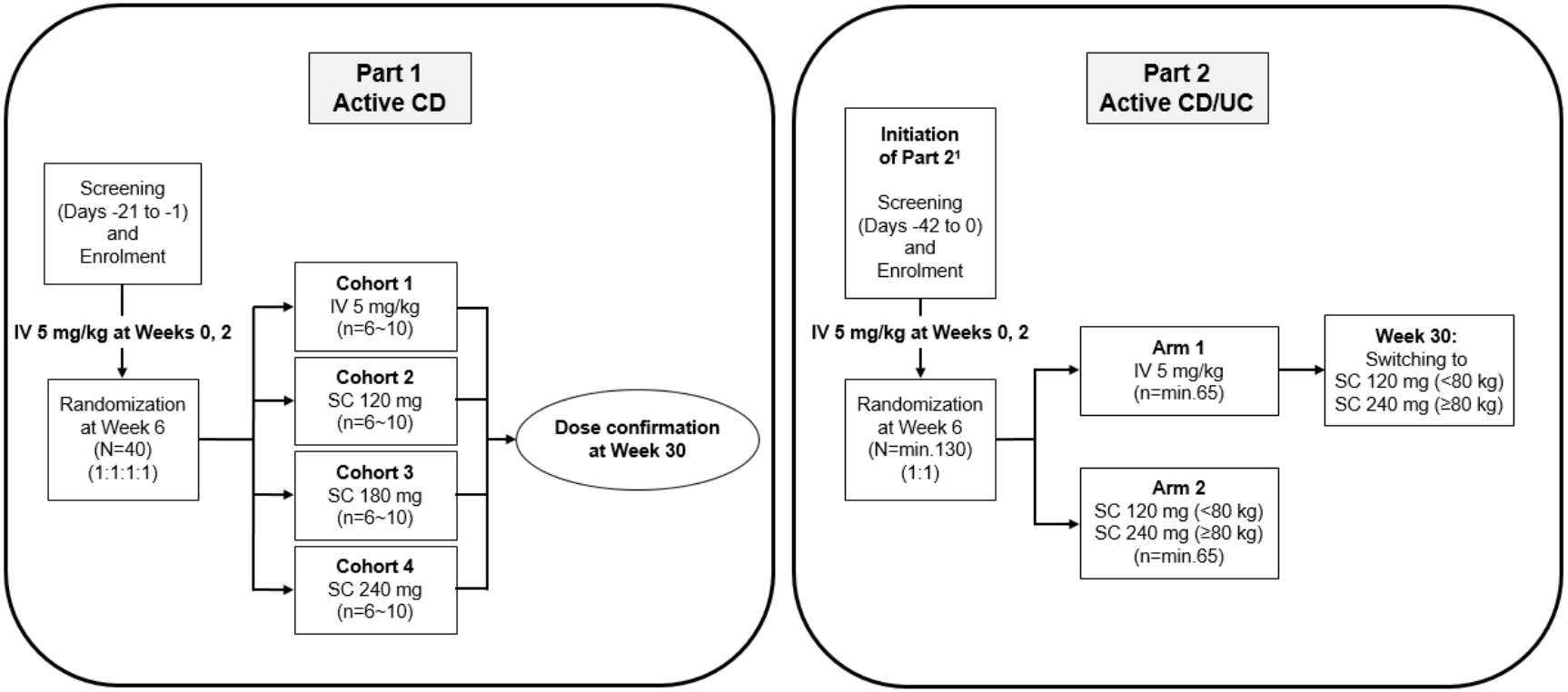
[1]CT-P13 IV will be switched to CT-P13 SC at Week 30. The dosage of CT-P13 SC will be determined based on the patient's body weight at Week 30.

[2]The dosage of CT-P13 SC will be determined based on the patient's body weight at Week 6.

The duration of the study will be up to 62 weeks for Part 2, which includes Screening (up to 6 weeks) and the last dose at 54 weeks plus the following 2 weeks off-dose period, prior to the End-of-Study Visit.

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

Figure 3-1 Overview of Study Design



IV, intravenous; SC, subcutaneous; CD, Crohn's Disease; UC, Ulcerative Colitis.

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

3.2 Study Overview

3.2.1 Part 1

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

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

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

The randomization to treatment assignment will be stratified by:

- Region (European or non-European)
- Current use of treatment with azathioprine (AZA) or 6-mercaptopurine (6-MP) or methotrexate (MTX) (used or not used)
- Clinical response at Week 6 (responder or non-responder by Crohn's Disease Activity Index (CDAI)-70 for Crohn's disease [see Section 7.2.1.1])
- Body weight at Week 6 (≤70 kg or >70 kg)

Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments (see Section 6.6).

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

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

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

Dose escalation up to 10 mg/kg will be allowed for patients from Cohort 1 since Week 30 if the patient initially responded but then lost response at each visit. Loss of response is defined as any of following: (1) an increase in CDAI of at least 70 points from the lowest CDAI score with a total score over 220, or (2) need of the initiation of a new treatment for active Crohn's disease. Dose escalation by dose interval shortening will not be allowed.

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

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

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

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

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

Figure 3-2 Patient Assessment Overview for Part 1

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

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

CT-P13 SC will be injected by a healthcare professional at each site visit (Weeks 6, 8, 10, 14, 22, 24, 26, 28, 30, 38, 46 and 54). After proper training in injection technique, patients may self-inject with CT-P13 SC if their investigator determines that it is appropriate at any other weeks (Weeks 12, 16, 18, 20, 32, 34, 36, 40, 42, 44, 48, 50 and 52) (see Section 6.2 and 6.6).

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

3.2.2 Part 2

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

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

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

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

The randomization to treatment assignment will be stratified by:

- Current use of treatment with AZA or 6-MP or MTX (used or not used)
- Disease (Crohn's disease or Ulcerative colitis)
- Clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease or partial Mayo score for Ulcerative colitis [see Section 7.2.1.1 and 7.2.2.1])
- Body weight at Week 6 (<80 kg or ≥80 kg)

Patients may also be premedicated 30 to 60 minutes prior to the start of study treatment administration and any premedications such as but not limited to antihistamine (at equivalent dose of 2 to 4 mg of chlorpheniramine), hydrocortisone, paracetamol, and/or nonsedating antihistamine (at equivalent dose of 10 mg of cetirizine) can be given at the investigator's discretion. Patients will comply with all appropriate visits and assessments (see Section 6.6).

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

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

- **Arm 1:** further 3 doses of CT-P13 IV will be administered at Week 6 and every 8 weeks thereafter up to Week 22 (Weeks 14 and 22). CT-P13 IV will be then switched to CT-P13 SC at Week 30 with CT-P13 SC dose based on body weight at Week 30. Further doses of study treatment with CT-P13 SC will be given every 2 weeks up to Week 54.
- **Arm 2:** CT-P13 SC dose based on body weight at Week 6 will be administered by PFS at Week 6 and then every 2 weeks up to Week 54.

For patients receiving CT-P13 SC 120 mg every 2 weeks, dose escalation to CT-P13 SC 240 mg every 2 weeks will be allowed since Week 30 if the patient initially responded but then lost

response at Week 30, 38, 46 or 54 visit. Dose escalation will not be allowed for patients receiving CT-P13 SC 240 mg every 2 weeks. Loss of response is defined as need of the initiation of a new treatment for active CD or UC, or as following:

- For Crohn's disease, if patient has an increase in CDAI ≥70 points from the lowest CDAI score with a total score ≥220
- For Ulcerative colitis, if patient meets (1) and either of (2) or (3);
  - (1) an increase in rectal bleeding subscore ≥1 point from the lowest score with actual value of >1 point
  - (2) an increase in partial Mayo score ≥2 points from the lowest score with actual value of ≥4 points
  - (3) an increase in endoscopic subscore ≥1 point from the lowest score with actual value of >1 point

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

The primary pharmacokinetic endpoint evaluation will be conducted during the Maintenance Phase at Week 22, and secondary pharmacokinetic endpoint evaluations will be conducted during the Treatment Period up to Week 54, with blood samples for analysis obtained at the time points specified in the schedule of events (Table 10-2).

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

The patient assessment Overview for Part 2 is illustrated in Figure 3-3.

Figure 3-3 Patient Assessment Overview for Part 2

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

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

CT-P13 SC will be injected by a healthcare professional at each site visit (Weeks 6, 14, 22, 30, 38, 46, 54 and Weeks 24, 26, 28 for patients who will make PK sampling visits). After proper training in injection technique, patients may self-inject with CT-P13 SC if their investigator determines that it is appropriate at any other scheduled administration weeks.

End-of-Study Visit: The End-of-Study Visit will occur 2 weeks after the last dose is received.For patients with early discontinuation before switching to CT-P13 SC at Week 30 in Arm 1 or before randomization at Week 6 in Arm 2, the End-of-Study Visit will occur 8 weeks after the last dose of CT-P13 IV is received.

4 Study Population

4.1 Selection of Study Population

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

In **Part 2**, it is expected that approximately 120 study centers will enrol patients in approximately 17 countries. It is planned to enrol appropriate number of patients to randomize minimum 130 male and female patients with active CD or active UC. Patients will be randomized at Week 6 in a 1:1 ratio (approximately 65 patients per treatment group) into the CT-P13 IV or CT-P13 SC treatment groups as presented in Table 3-2.

For **Part 1**, male or female patients with active CD who has CDAI score between 220 and 450 points will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

For **Part 2**, male or female patients with active CD who has CDAI score between 220 and 450 points or with active UC who has total Mayo scores of 6 to 12 points will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

4.2 Inclusion Criteria

The inclusion criteria are divided into 3 categories: general inclusion criteria, active Crohn's disease inclusion criteria and active Ulcerative colitis inclusion criteria. Patients must meet all of the general inclusion criteria and disease-specific inclusion criteria according to their indication to be enrolled in this study:

4.2.1 General Inclusion Criteria

1. Patient who is a male or female aged 18 to 75 years old, inclusive.
2. 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

3. Patient who has the following hematology laboratory test results at Screening:
   - Hemoglobin ≥8.5 g/dL (SI [Système International d'Unités] units: ≥85 g/L or 5.28 mmol/L)
   - White blood cell count ≥3.5 × 10^3 cells/μL (SI units: ≥3.5 × 10^9 cells/L)
   - Neutrophil count ≥1.5 × 10^3 cells/μL (SI units: ≥1.5 × 10^9 cells/L)
   - Platelet count ≥100 × 10^3 cells/μL (SI units: ≥100 × 10^9 cells/L)
4. Patient who has the ability to comprehend the full nature and purpose of the study, including possible risks and side effects, to cooperate with the investigator, to understand verbal and/or written instructions, and to comply with the requirements of the entire study.
5. Patient (or legal guardian, if applicable) who is informed of the full nature and purpose of the study, including possible risks and side effects, is given ample time and opportunity to read or understand this information, and has signed and dated the written informed consent before inclusion in the study.
6. 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.

4.2.2 Active Crohn's Disease Inclusion Criteria

1. Patient who has Crohn's disease with a score on the CDAI of 220 to 450 points.
2. **For Part 2**, patient who meets at least one of following at Screening;
   - C-reactive protein (CRP) concentration >0.5 mg/dL
   - Fecal calprotectin >100 μg/g
   - Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) of ≥6 points for ileal-colonic CD or ≥4 points including ulcer score from at least one segment for ileal CD or colonic CD
3. Patient who has Crohn's disease of at least 3 months' disease duration prior to the first administration of the study drug (Day 0).
4. Patient who has been treated for active Crohn's disease but has not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who is intolerant to or has medical contraindications for such therapies.
5. Stable doses of following Crohn's disease treatments or currently not receiving during specified time frame:
   - Azathioprine (AZA) or 6-mercaptopurine (6-MP) at least for 8 weeks prior to the first administration of the study drug (Day 0)
   - Methotrexate (MTX) at least for 6 weeks prior to the first administration of the study drug (Day 0)
   - Oral corticosteroids at the equivalent dose of 20 mg/day of prednisone or less at least for 2 weeks prior to the first administration of the study drug (Day 0)
   - Oral budesonide at the dose of 6 mg/day or less at least for 4 weeks prior to the first administration of the study drug (Day 0)

- 5-aminosalicylates (5-ASA) at least for 4 weeks prior to the first administration of the study drug (Day 0)

4.2.3 Active Ulcerative Colitis Inclusion Criteria (Part 2 only)

1. Patient who has active Ulcerative colitis as defined by a total Mayo score between 6 and 12 points with endoscopic evidence of active colitis as indicated by endoscopic subscore of ≥2 at Screening.
2. Patient who has Ulcerative colitis of at least 3 months' disease duration prior to the first administration of the study drug (Day 0).
3. Patient who has been treated for active Ulcerative colitis but not responded despite conventional therapy including corticosteroids alone or in combination with 6-MP or AZA and medications containing 5-ASA, or who is intolerant to or has medical contraindications for such therapies.
4. Stable doses of following Ulcerative colitis treatments or currently not receiving during specified time frame:
   - AZA or 6-MP at least for 8 weeks prior to the first administration of the study drug (Day 0)
   - MTX at least for 6 weeks prior to the first administration of the study drug (Day 0)
   - Oral corticosteroids at the equivalent dose of 20 mg/day of prednisone or less at least for 2 weeks prior to the first administration of the study drug (Day 0)
   - Oral budesonide at the dose of 6 mg/day or less at least for 4 weeks prior to the first administration of the study drug (Day 0)
   - Oral 5-ASA at least for 4 weeks prior to the first administration of the study drug (Day 0)
5. Patient who has more than 8 years of disease duration of Ulcerative colitis must have documented evidence for absence of colorectal cancer or dysplasia by full colonoscopy examination performed within a year prior to the first administration of the study drug (Day 0).

4.3 Exclusion Criteria

The exclusion criteria are divided into 4 categories: general exclusion criteria, tuberculosis exclusion criteria, active Crohn's disease exclusion criteria and active Ulcerative colitis 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 a biological agent for the treatment of Crohn's disease or Ulcerative colitis and/or a TNFα (tumor necrosis factor-alpha) inhibitor for the treatment of other disease.
2. Patient who has allergies to any of the excipients of infliximab or any other murine and/or human proteins, or patient with a hypersensitivity to immunoglobulin product.
3. Patient who has a current or past history of following infection:
   - **For Part 1**, current or past history of chronic infection with hepatitis C or human immunodeficiency virus (HIV)-1 or -2 or current infection with hepatitis B

     For Part 2, a known infection with HIV, hepatitis B, or hepatitis C (carriers of hepatitis B and hepatitis C are not permitted to enrol into the study, but past hepatitis B resolved 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 within 6 months prior to the first administration of the study drug (Day 0)
   - Recurrent herpes zoster or other chronic or recurrent infection within 6 weeks prior to the first administration of the study drug (Day 0)
   - Past or current granulomatous infections or other severe or chronic infection (such as sepsis, abscess or opportunistic infections, or invasive fungal infection such as histoplasmosis). A patient who has a past diagnosis of those infections with sufficient documentation of complete resolution can be enrolled.
4. Patient who has received or has plan to receive any of following prohibited medications or treatment:

- Any biological agents for the treatment of Crohn's disease or Ulcerative colitis
- Parenteral corticosteroids for the treatment of Crohn's disease or Ulcerative colitis within 2 weeks prior to Screening
- Antibiotics for the treatment of Crohn's disease or Ulcerative colitis within 2 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)
- Thalidomide, tacrolimus, or cyclosporine within 3 months prior to the first administration of the study drug (Day 0)
- Live or live-attenuated vaccine within 4 weeks of the first administration of the study drug (Day 0)
- Abdominal surgery, including but not limited to, for 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)
- Subtotal and total colectomy prior to the first administration of the study drug (Day 0)
- Use of 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)

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

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

6. Patient who has a current or past history of drug or alcohol abuse.
7. Patient who has had treatment with any other investigational device or medical product within 4 weeks prior to the first administration of the study drug (Day 0) or 5 half-lives, whichever is longer.
8. Female patient who is currently pregnant, breastfeeding, or planning to become pregnant or breastfeed within 6 months of the last dose of study drug.

9. Patient who, in the opinion of his or her general practitioner or the investigator, should not participate in the study.

4.3.2 Tuberculosis Exclusion Criteria

1. **For Part 1**, a patient who has a history of tuberculosis (TB) or a current diagnosis of TB. A patient who has a past diagnosis of active TB with sufficient documentation of complete resolution can be enrolled.

   For Part 2, a patient who has a history of TB or a current diagnosis of TB. A patient who has a past diagnosis of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.

2. Patient who has had exposure to person with active TB such as first degree family members or co-workers.

3. **For Part 1**, a patient who has an indeterminate result for interferon-γ release assay (IGRA) or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at Screening. A patient who has a past diagnosis of latent TB with sufficient documentation of prophylaxis can be enrolled.

   For Part 2, a patient who has an indeterminate result for IGRA or latent TB (defined as a positive result of IGRA with a negative examination of chest x-ray) at Screening. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the repeated IGRA result is again indeterminate, the patient must be excluded from the study. If the repeated IGRA result is negative, the patient can be included in the study. A patient who has a past diagnosis of latent TB cannot be enrolled despite sufficient documentation of prophylaxis.

4.3.3 Active Crohn's Disease Exclusion Criteria

1. Patient who has active entero-vesical, entero-retroperitoneal, entero-cutaneous, and entero-vaginal fistulae within 6 months prior to the first administration of the study drug (Day 0). Entero-enteral fistulae without clinical significant symptoms upon investigator's opinion and anal fistulae without draining problems are allowed.

2. Patient who has taken more than 3 small-bowel resection procedures prior to the first administration of the study drug (Day 0).

4.3.4 Active Ulcerative Colitis Exclusion Criteria (Part 2 only)

1. Patient who is taking rectally administered medications containing corticosteroids or 5-ASA for the treatment of ulcerative colitis within 2 weeks prior to Screening.

4.4 Withdrawal of Patients from the Study

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

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

Reasons for withdrawal include the following:

- Patient develops signs of disease progression in the judgment of the investigator
- Patient withdraws consent or refuses to continue treatment and/or procedures/observations
- Patient has any AE that would compromise his or her safety if he or she continues to participate in the study
- Patient has a significant protocol violation
- Patient is lost to follow-up
- Patient dies
- Study terminated by the sponsor
- Pregnancy

- Investigator's decision

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

4.4.1 Recruitment of Additional Patients

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

4.5 Premature Discontinuation of the Study

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

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

5 Study Procedures

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

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

5.1 Efficacy Assessments

Efficacy assessment will be performed according to the indications in Part 1 and Part 2.

- Part 1: active Crohn's disease
- Part 2: active Crohn's disease or active Ulcerative colitis

5.1.1 Active Crohn's Disease (CD)

Efficacy will be assessed by the evaluation of CDAI score, Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) score in patients who had confirmed mucosal abnormalities from previous assessment, 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).

5.1.1.1 Crohn's Disease Activity Index (CDAI) Assessment

Clinical response and remission will be assessed by evaluation of the CDAI score. CDAI score will be calculated at CDAI assessment date prior to dosing (Table 10-1 and Table 10-2), once all components of the CDAI are available. CDAI score is comprised of patient's CDAI diary entries, hematocrit results, and assessments performed by site investigator including but not limited to physical examination, vital signs and weight (Appendix 10.5). For CDAI assessment at Screening and during the study period, hematocrit results from local laboratory within the 7 days prior to the CDAI assessment date will be used. To ensure quality of data and consistency, it is recommended that the CDAI assessments are performed by the same physician at each site throughout the entire study period if applicable. Source data related to CDAI score should be recorded in relevant eCRF pages.

Patients will complete CDAI diary according to patient diary instruction. To determine eligibility, the components of the CDAI must be completed within 7 days prior to the first administration of the study drug (Day 0) and CDAI score will be calculated at Day 0. The CDAI diary should be completed by patients for 7 consecutive days immediately prior to CDAI assessment date, except when CDAI assessment is performed at the same date of colonoscopy procedure. If patient is planned to have bowel preparation for colonoscopy procedure, patient should complete CDAI diary for 7 consecutive days not to overlap with three days over colonoscopy procedure (i.e., from the day before and up to the next day of colonoscopy procedure).

5.1.1.2 Endoscopic Response and Remission

Endoscopic response or remission will be assessed by evaluation of mucosal abnormalities. The degree of mucosal abnormalities will be assessed by colonoscopy (endoscopic examination of luminal surface of gastrointestinal tract which may include the rectum, colon and terminal ileum) using the SES-CD (see Appendix 10.6). Colonoscopy 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). For colonoscopy after Screening, assessment window of -14 days is allowed. For **Part 2**, colonoscopy will be evaluated centrally by independent reviewer blinded to treatment allocation for reporting purposes, and evaluated at local level to confirm eligibility and for treatment practice.

Colonoscopy will be performed in all patients at Screening. However, for patients with Crohn's disease only, colonoscopy at Screening would not be required if there is documented colonoscopy report of no colonic involvement within 3 years or endoscopic evidence of inflammation consistent with Crohn's disease within 3 months prior to the first administration of the study drug (Day 0).

In patients who have any mucosal abnormalities (defined as SES-CD score of more than 0) or SES-CD score of 0 with inaccessible component or with missing component at Screening, colonoscopy will be repeated at Week 22 (for Part 2) or Week 30 (for Part 1) to assess endoscopic response or remission. Colonoscopy at Week 54 will be repeated in patients who have any mucosal abnormalities or SES-CD score of 0 with inaccessible component or with missing component at Week 22 (for Part 2) or Week 30 (for Part 1). However, colonoscopy can be performed whenever if needed based on investigator's discretion even if patient has no mucosal abnormalities confirmed from previous colonoscopy.

5.1.1.3 Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Short Inflammatory Bowel Disease Questionnaire 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).

5.1.2 Active Ulcerative Colitis (UC)

Efficacy will be assessed by the evaluation of the Mayo Scoring System (MSS), mucosal healing by endoscopic subscore from MSS, and SIBDQ. All patients will have efficacy assessments performed at the time points specified in the schedule of events (Table 10-2).

5.1.2.1 Mayo Scoring System (MSS) Assessment

Clinical response and remission will be assessed by evaluation of the MSS (Appendix 10.7). The MSS will be calculated at MSS assessment date prior to dosing (Table 10-2). Total Mayo score is comprised of all components of MSS (stool frequency, rectal bleeding, endoscopic subscore and physician's global assessment) and partial Mayo score is comprised of 3 components excluding endoscopic subscore. To ensure quality of data and consistency, it is recommended that MSS assessments including flexible proctosigmoidoscopy are performed by the same physician at each site throughout the entire study period if applicable. Source data related to MSS should be recorded in relevant eCRF pages.

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 MSS. Flexible proctosigmoidoscopy will be performed in all patients at Screening and at the time points specified in the schedule of events (Table 10-2). Flexible proctosigmoidoscopy for endoscopic subscore assessment after Screening, assessment window of -14 days is allowed. Flexible proctosigmoidoscopy can be performed whenever needed based on investigator's discretion and if colonoscopy has been performed, it can replace flexible proctosigmoidoscopy for evaluation of endoscopic subscore. Endoscopic subscore by flexible proctosigmoidoscopy (or colonoscopy) will be evaluated centrally by independent reviewer blinded to treatment allocation for reporting purposes, and evaluated at local level to confirm eligibility or loss of response for treatment practice.

Patients will complete MSS diary according to patient diary instruction. To determine eligibility, total Mayo score will be calculated at Day 0 using endoscopic subscore during Screening period and other 3 components completed within 3 days prior to the first administration of the study drug (Day 0).

The MSS diary should be completed by patients for 3 consecutive days immediately prior to MSS assessment date, except when MSS assessment is performed at the same date of flexible proctosigmoidoscopy (or colonoscopy) procedure. If patient is planned to have bowel preparation for flexible proctosigmoidoscopy (or colonoscopy) procedure, patient should complete MSS diary for 3 consecutive days not to overlap with 3 days over procedure (i.e., from the day before and up to the next day of procedure).

5.1.2.2 Mucosal Healing

Mucosal healing will be assessed by endoscopic subscore of the MSS according to Section 5.1.2.1. The endoscopic subscore of the MSS evaluate the degree of endoscopic rectal inflammation based on a 4-point scale according to flexible proctosigmoidoscopy findings; 0 point for normal, 1 point for Mild, 2 points for Moderate, and 3 points for Severe disease (Appendix 10.7).

5.1.2.3 Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

Short Inflammatory Bowel Disease Questionnaire 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).

5.2 Pharmacokinetic Assessments

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

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

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

Table 5-1 Steady-state Pharmacokinetic Sampling Time Points – Part 1

Visit (Day)	Cohort 1	Cohort 2, 3 and 4	
		Group A	Group B
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 3, 8 and 24 hr (±15 min) after SOI • 48 hr (±2 hr) after SOI • 96 hr (±4 hr) after SOI • 168 ±6 hr after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 26 (Day 182)	• 28±1 days after SOI at Week 22	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	• Pre-dose* • 168 ±6 hr after injection
Week 28 (Day 196)	• 42±1 days after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 30 (Day 210)	• Pre-dose* (or 56 days after SOI at Week 22**)	• Pre-dose* (or 14 days after the Week 28 injection**)	

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

As primary pharmacokinetic endpoint, AUC_{τ} (area under the concentration time curve at steady state between Week 22 and Week 30) will be assessed.

As secondary pharmacokinetic endpoints, following parameters will be assessed between Week 22 and Week 30:

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

In addition, C_{trough} up to Week 54 will be assessed as secondary PK endpoint.

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

- **Group A:** frequent sampling at Weeks 22 (Arm 2A)
- **Group B:** frequent sampling at Weeks 24 (Arm 2B)
- **Group C:** frequent sampling at Weeks 26 (Arm 2C)
- **Group D:** frequent sampling at Weeks 28 (Arm 2D)

Table 5-2 Steady-state Pharmacokinetic Sampling Time Points – Part 2

Visit (Day)	Arm 1	Arm 2			
		Group A	Group B	Group C	Group D
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 1 hr (±15 min) after EOI • 8 hr (±15 min) after SOI • 24 hr (±15 min) after SOI • 48±2 hr after SOI • 168±6 hr after SOI	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection	• Pre-dose**	• Pre-dose**	• Pre-dose**
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose**	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection	• N/A	• N/A
Week 26 (Day 182)	• 28±1 days after SOI at Week 22	• N/A	• Pre-dose**	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection	• N/A

Visit (Day)	Arm 1	Arm 2			
		Group A	Group B	Group C	Group D
Week 28 (Day 196)	• 42±1 days after SOI at Week 22	• N/A	• N/A	• Pre-dose**	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection
Week 30 (Day 210)	• Pre-dose*	• Pre-dose**	• Pre-dose**	• Pre-dose**	• Pre-dose**

EOI, End of the infusion; hr, hours; min; minutes; N/A, not applicable; SOI, Start of the infusion.
*prior to the beginning of study treatment administration on dosing day (or 56 days after previous dosing day only if patient has not received study treatment on each relevant dosing day)
**prior to the beginning of study treatment administration on dosing day (or 14 days after previous dosing day only if patient has not received study treatment on each relevant dosing day)
Note: If a patient in Arm 2 is not able to attend any of the sampling visits, it should be discussed with the Sponsor in advance.

As primary pharmacokinetic endpoint, C_{trough} at Week 22 (pre-dose level at Week 22) will be assessed. As secondary pharmacokinetic endpoints, following parameters will be assessed between Week 22 and Week 30:

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

In addition, C_{trough} up to Week 54 will be assessed as secondary PK endpoint.

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

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

5.3 Pharmacodynamic Assessments

Samples for pharmacodynamic assessments (CRP and Fecal calprotectin) will be collected prior to beginning of study treatment administration at the time points specified in the schedule of events (Table 10-1 and Table 10-2).

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

5.4 Biomarker Assessments for Part 2

The following parameters will be assessed as biomarkers:

- Genotypes (including, but not limited to FcRn)
- Amino acids (including, but not limited to Tryptophan)

For amino acids assessments, blood samples and consumption time of foods or drinks containing protein will be collected at the time points specified in the schedule of events (Table 10-2). For genotype assessments, blood samples of patients who sign a separate informed consent form will be collected at the time points specified in the schedule of events (Table 10-2). These samples will be used for research purposes to identify dynamic biomarkers that maybe predictive of response to CT-P13 treatment (in terms of dose, efficacy, safety and tolerability).

5.5 Safety Assessments

5.5.1 Patient's Self-reporting of Adverse Events

Patient diary will be distributed to all patients 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 is any signs and symptoms after study treatment administration, patient will record them in patient diary and site personnel will review diary at each visit throughout the study up to and including End-of-Study Visit. However, patients will contact the principal investigator or subinvestigator at any time after the first administration of the study drug (Day 0) if any severe symptoms develop and investigator will determine whether patient to be referred to investigator or to continue the next dose administration. Details will be recorded in both the source documents and the eCRF.

5.5.2 Immunogenicity Testing

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

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

5.5.3 Hypersensitivity Monitoring

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

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

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

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

5.5.3.1 Delayed Hypersensitivity Monitoring

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

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

- Immunogenicity
- Clinical Laboratory Analyses

- Complement (C3, C4) and Total Hemolytic Complement

5.5.4 Vital Signs and Weight

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

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

5.5.5 Electrocardiogram

All scheduled 12-lead ECGs (performed locally) must be performed after the patient has rested quietly for at least 5 minutes in the supine position. A 12-lead ECG will be performed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). If, following the ECG review by the investigator, there are any ECG findings that would indicate cardiac insufficiency or QT prolongation, the patient will be referred to a cardiologist to confirm the abnormality, then after investigator will report the event in the source documents and the eCRF. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion. In case of hypersensitivity, any types of ECG can be performed (Section 5.5.3).

5.5.6 Tuberculosis Assessment

For Part 1, a patient who has a history of TB or a current diagnosis of TB at Screening will be excluded from the study. A patient who has a past diagnosis of active TB with sufficient documentation of complete resolution can be enrolled.

For Part 2, a patient who has a history of TB or a current diagnosis of TB at Screening will be excluded from the study. A patient who has a past diagnosis of active TB cannot be enrolled despite sufficient documentation of complete resolution of active TB.

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

Latent TB is defined as the presence of a positive IGRA (Section 5.5.6.2) with a negative examination of chest x-ray (Section 5.5.6.1).

For Part 1, a patient who has an indeterminate result for IGRA or latent TB at Screening will not be included in the Study. A patient who has a past diagnosis of latent TB with sufficient documentation of prophylaxis can be enrolled.

For Part 2, a patient who has an indeterminate result for IGRA or latent TB at Screening will not be included in the Study. If the result of the IGRA is indeterminate at Screening, 1 retest will be possible during the Screening period. If the IGRA result is again indeterminate or positive, the patient should be excluded from the study. If the repeated IGRA result is negative, the patients may be included in the study. A patient with confirmed latent TB during Screening cannot be enrolled. A patient who has a past diagnosis of latent TB cannot be enrolled despite sufficient documentation of prophylaxis.

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

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

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

For Part 1, no further IGRA test is required during Treatment Period for the following patients:

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

5.5.6.1 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.

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.

5.5.6.2 Interferon-γ Release Assay (IGRA)

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 Screening, Weeks 30 and 54, and at the End-of-Study Visit.

5.5.7 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.

5.5.8 Congestive Heart Failure Assessment

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

5.5.9 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 must be excluded from the study.

For Part 1, if a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), this patient can be enrolled by the investigator's discretion based on clinical laboratory results and the infection history of hepatitis.

For Part 2, if a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), a Hepatitis B virus (HBV)-DNA test will be further assessed at Screening. If the HBV-DNA test result is positive, the patient should be excluded from the study and if the HBV-DNA test result is negative, the patient can be included. For the patients enrolled based on the HBV-DNA test, the test of HBsAg, HBsAb and HBV-DNA will be additionally performed at Weeks 22, 46 and End-of-Study visits. Aspartate aminotransferase, alanine aminotransferase and total bilirubin results will be monitored as well. In patients who develop hepatitis B reactivation, study treatment should be stopped and the patient must be withdrawn from the study.

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

5.5.10 Physical Examinations

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

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

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

5.5.11 Adverse Events

5.5.11.1 Definitions

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

Adverse Event

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the principal investigator or subinvestigator at any time after the ICF is signed if any symptoms develop (see Section 5.5.1). Adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or worsening of the underlying disease or of other pre-existing conditions will be reported. In addition, changes in vital signs,

physical examination and laboratory tests will be recorded as (S)AE(s) in the eCRF if they are judged clinically relevant by the investigator.

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

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

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

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

Abnormal Laboratory Value

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

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

Adverse Events of Special Interest

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

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

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

- Delayed hypersensitivity

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

- Injection site reaction

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

- Infection

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

- Malignancy

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

Serious Adverse Event

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

Unlisted (Unexpected) Adverse Event

An unlisted or unexpected AE is defined as an event of which the nature or severity is not consistent with the applicable product information (e.g., investigator's brochure) for an

unapproved investigational product or the label (e.g., package insert or summary of product characteristics/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 Charactristics.

5.5.11.2 Eliciting and Documenting Adverse Events

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

For **Part 2**, serious adverse drug reactions (SADRs) occurring up to 8 weeks after last dose of study drug will be reported and followed up until 8 weeks after last dose of study drug. In addition, if it is ongoing until 8 weeks after last dose of study drug, it should be followed up for a further 30 days (Section 5.5.11.6).

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

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

In addition to patient observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings) or other documents relevant to patient safety.

5.5.11.3 Reporting Adverse Events

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

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

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

The severity and the relationship or association of the study drug in causing or contributing to the AE will be characterized as defined in Sections 5.5.11.4 and 5.5.11.5.

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

For Part 1 and 2, after the End-of-Study Visit, SADRs will be reported to CELLTRION, Inc. or its designee.

Serious Adverse Events

Any AE considered serious by the investigator or subinvestigator or that meets SAE criteria (Section 5.5.11.1) must be reported to the [redacted] Pharmacovigilance (PVG) Department within 24 hours from the time study center personnel first learn about the event and during normal business hours. The following contact information is to be used for SAE reporting:

[redacted]

Data entry should be completed in the remote data capture system by the investigator within 24 hours of awareness of an SAE. In the event that this is not possible (e.g., system failure or access problems), the study center should complete an SAE report form and fax to [redacted] PVG within 24 hours of awareness of the event. The remote data capture system should be updated

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

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

CELLTRION, Inc. or its designee is responsible for reporting unexpected fatal or life-threatening 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.

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

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

- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., subject has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);

- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

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

5.5.11.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE will be graded based on the CTCAE v4.03, based on the following general guidelines (a semicolon indicates "or" within each description):

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

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

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

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

Grade 5: Death related to AE

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. If an AE upgrades in intensity or, changes from non-serious to serious, a new AE needs to be reported. If an AE downgrades in

intensity, it should not be reported as a new AE. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

5.5.11.5 Assessment of Causality

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

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

Unrelated:	This relationship suggests that there is no association between the study drug and the reported event.
Possible:	This relationship suggests that treatment with the study drug caused or contributed to the AE, i.e., the event follows a reasonable temporal sequence from the time of study drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.
Probable:	This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the study drug, known or previously reported adverse reactions to the study drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.
Definite:	This relationship suggests that a definite causal relationship exists between study drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

5.5.11.6 Follow-Up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF. The related AEs will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure (see also Section 5.5.11.2).

5.5.12 Pregnancy

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

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

5.5.13 Clinical Laboratory Analyses

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

A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the End-of-Study Visit. Patients with only negative results from serum pregnancy test can be enrolled. A urine pregnancy test for women of childbearing potential should be used to confirm patients are not pregnant prior to study drug administration on each visit day or more frequently if required by country-specific legislation.

The following laboratory analyses will be performed:

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

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

5.5.14 Patient's Assessment of Local Site Pain

All patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Patient's assessment of pain is measured by the patient indicating the extent of their pain by marking a line (|) through the 100 mm line (Appendix 10.8).

5.6 Patient Overall Satisfaction Assessment for Part 2

All patients in Part 2 will assess their overall satisfaction of CT-P13 IV and CT-P13 SC by using 100 mm VAS after the end of administration of study drug at the time points specified in the schedule of events (Table 10-2). Patient's assessment of overall satisfaction about procedure and duration of the study drug administration on that visit day, regardless of other external conditions (e.g., interaction with doctor/nurse, distance from home to hospital,

transportation, etc.) is measured by the patient indicating his or her overall satisfaction of the study drug administration by marking a line (|) through the 100 mm line (Appendix 10.9).

5.7 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 specific laboratory manual.

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

5.7.1 Pharmacokinetic Blood Sampling

Blood samples for PK assessments will be collected at the time points specified in Section 5.2. 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 5.8.2.

5.7.2 Pharmacodynamic Sampling (CRP, Fecal calprotectin)

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

Blood samples for CRP 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 5.8.2.

Sampling and handling for calprotectin testing will be conducted only at the qualified or feasible sites.

Fecal samples will be handled and shipped to the central laboratory according to the laboratory manual.

5.7.3 Biomarker Blood Sampling for Part 2

The following parameters will be assessed as biomarkers:

- Genotypes (including, but not limited to FcRn)
- Amino acids (including, but not limited to Tryptophan)

For amino acids assessments, blood samples and consumption time of foods or drinks containing protein will be collected at the time points specified in the schedule of events (Table 10-2). For genotype assessments, blood samples of patients who sign a separate informed consent form will be collected. These samples will be used for research purposes to identify dynamic biomarkers that maybe predictive of response to CT-P13 treatment (in terms of dose, efficacy, safety and tolerability).

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

5.7.4 Routine Safety Blood Sampling

Blood samples for routine safety (clinical laboratory testing [including CRP and ESR], hepatitis B and C testing, HBV-DNA and HIV-1 and -2 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).

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

5.7.5 Immunogenicity Blood Sampling

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

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

5.7.6 Interferon-γ Release Assay (IGRA) Blood Sampling

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

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

5.8 Labeling, Storage, and Transportation of Samples

5.8.1 Sample Labeling

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

5.8.2 Sample Storage and Shipment

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

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

5.9 Overdose Management

An overdose is defined as any dose that is 10% or more than the dose prescribed. Overdose may be symptomatic or asymptomatic. Symptoms associated with an overdose must be recorded as an AE and the detail provided according to the details in Section 5.5.11.3 and an overdose without signs or symptoms must be documented in the study medication section of the eCRF.

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

6 Study Treatments

6.1 Method of Assigning Patients to Treatment Groups

An interactive voice recognition system (IVRS) or interactive Web response system (IWRS) will be used for the randomization. Biostatistics will generate the randomization schedule for IVRS or IWRS, which will link sequential patient randomization numbers to treatment codes. For **Part 1**, the randomization will be stratified by region (European or non-European), current use of treatment with AZA or 6-MP or MTX (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease) and body weight at Week 6 (≤70 kg or >70 kg). For **Part 2**, the randomization will be stratified by current use of treatment with AZA or 6-MP or MTX (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease or partial Mayo score for Ulcerative colitis), body weight at Week 6 (<80 kg or ≥80 kg) and disease (Crohn's disease or Ulcerative colitis). The randomization numbers will be blocked, and within each block the same number of patients will be allocated to each treatment group. The block size will not be revealed.

6.2 Treatments Administered

CT-P13 IV will be administered as a 2-hour (+15 minutes) IV infusion. Patients will be dosed at specific time points as detailed in the schedule of events (see Section 6.6, Table 10-1 and Table 10-2).

CT-P13 SC will be injected by a healthcare professional at each site visit at the time points specified in the schedule of events (see Section 6.6, Table 10-1 and Table 10-2). CT-P13 SC will be injected at a slow, steady rate at any of following site;

(1) the front of the middle thighs, or

(2) the abdomen, except for the 5 cm area right around the navel, or

(3) the outer area of the upper arms (except for self-injection).

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

After proper training in injection technique, patients may self-inject with CT-P13 SC if their investigator determines that it is appropriate. CT-P13 SC can be administered by another person, such as a family member or friend who is instructed properly by investigator or designee.

For each new 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, following 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 new injection should be given at least 3 cm away from the most recent area injected.

For Part 1, only patients in Cohort 1 will be allowed for dose escalation up to 10 mg/kg since Week 30 if the patient initially responded but then lost response at each visit. Loss of response is defined as any of following: (1) an increase in CDAI of at least 70 points from the lowest CDAI score with a total score over 220, or (2) need of the initiation of a new treatment for active Crohn's disease. Dose escalation by dose interval shortening will not be allowed.

For Part 2, for patients receiving CT-P13 SC 120 mg every 2 weeks, dose escalation to CT-P13 SC 240 mg every 2 weeks will be allowed since Week 30 if the patient initially responded but then lost response at Week 30, 38, 46 or 54 visit. Dose escalation will not be allowed for patients receiving CT-P13 SC 240 mg every 2 weeks. Loss of response is defined as need of the initiation of a new treatment for active CD or UC, or as following:

- For Crohn's disease, if patient has an increase in CDAI ≥70 points from the lowest CDAI score with a total score ≥220
- For Ulcerative colitis, if patient meets (1) and either of (2) or (3);
  - (1) an increase in rectal bleeding subscore ≥1 point from the lowest score with actual value of >1 point
  - (2) an increase in partial Mayo score ≥2 points from the lowest score with actual value of ≥4 points
  - (3) an increase in endoscopic subscore ≥1 point from the lowest score with actual value of >1 point

6.2.1 Premedication

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

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

6.3 Identity of Investigational Product

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

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

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

CT-P13 IV will be prepared as detailed in the Remsima summary of product characteristics [Remsima Product Information, 2016].

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

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

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

As CT-P13 (infliximab) vials do not contain preservatives, the solution for infusion should be used as soon as possible and within 3 hours of reconstitution and dilution (a maximum of 1-hour interruption is permitted during administration [see Section 6.6]). Including the maximum interruption allowed, the solution for infusion must be used within 4 hours of reconstitution and dilution. Any unused portion should be discarded. An infusion pump or gravity method will be used to administer the investigational product.

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

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

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

The following drug supplies will be used in the study:

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

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

6.4 Management of Clinical Supplies

6.4.1 Study Drug Packaging and Storage

The clinical supplies group will provide prepacked supplies for each patient. Kits will be assigned at randomization using the IWRS or IVRS.

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

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

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

6.4.2 Study Drug Accountability

It is the responsibility of the clinical investigator to ensure that all study drug received at the study center will be inventoried and accounted for throughout the study and the result recorded in the drug accountability form maintained at the study center. The drug accountability will be

verified by the monitor during on-site monitoring visits. Study drug will be stored in a limited-access area or in a locked cabinet under appropriate environmental conditions.

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

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

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

6.5 Blinding and Breaking the Blind

This is an open-label study.

6.6 Treatment Compliance

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

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

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

At each time of CT-P13 SC self-injection, patients should record details of injection in patient's diary including the date and time of injection, kit number of each syringe, 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 unused syringes to judge patient's dosing compliance and the source data will be recorded in eCRF.

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

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

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

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

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

6.7 Prior, Concomitant, and Subsequent Medications

Patients will be excluded from the study if patients have any of prohibited medications and/or treatment (Section 6.8). Killed vaccinations are acceptable during the study.

Concomitant medications for the treatment of Crohn's disease or Ulcerative colitis will be allowed following inclusion criteria (Section 4.2).

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

Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) patient enrolment until the last assessment date or End-of-Study Visit, will be recorded in the patient's eCRF. All concomitant medications will also be recorded when any serious adverse drug reactions occur after the End-of-Study Visit. This will include all prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

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

6.7.1 Prior, Concomitant, and Subsequent Medications for Part 1

6.7.1.1 Azathioprine (AZA) or 6-mercaptopurine (6-MP), MTX, 5-aminosalicylates (5-ASA)

Immunomodulators (such as AZA, 6-MP, MTX) or 5-ASA will be allowed if patients maintained stable doses for the specified timeframe according to the inclusion criteria (Section 4.2) and stable dose should be maintained throughout the study.

Any change of doses for immunomodulator should be discussed with the medical monitors of CELLTRION, Inc. or its designee in advance.

6.7.1.2 Corticosteroids

Oral corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent dose of 30 mg/day of prednisone 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 corticosteroids at the first administration of the study drug (Day 0), following tapering regimen will be recommended if the patient's condition has been improved at the investigator's discretion: for patients receiving corticosteroids >20 mg/day equivalent

dose of prednisone, tapering regimen at the maximum rate of 5 mg/week is recommended. In case of corticosteroids dose of ≤20 mg/day equivalent dose of prednisone, the maximum tapering rate of 2.5 mg/week is recommended.

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

6.7.1.3 Antibiotics

Antibiotic for the treatment of Crohn's disease or Ulcerative colitis will be allowed if patients maintained stable dose for at least 4 weeks prior to the first administration of the study drug (Day 0) (Section 4.2).

6.7.2 Prior, Concomitant, and Subsequent Medications for Part 2

6.7.2.1 Azathioprine (AZA) or 6-mercaptopurine (6-MP), MTX

Immunomodulators (such as AZA, 6-MP, MTX) will be allowed if patients maintained stable doses for the specified timeframe according to the inclusion criteria (Section 4.2) and stable dose should be maintained throughout the study.

Any change of doses for immunomodulator should be discussed with the medical monitors of CELLTRION, Inc. or its designee in advance.

6.7.2.2 Corticosteroids

Oral corticosteroids at the equivalent dose of 20 mg/day of prednisone 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 corticosteroids at the first administration of the study drug (Day 0), corticosteroid treatment should be kept up to Week 6 as the same dose level. After Week 6 the following tapering regimen can be followed if the patient's condition has been improved at the investigator's discretion: 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 the dose of 6 mg/day or less will be allowed if the patient has received 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 budesonide at the first administration of the study drug (Day 0), budesonide treatment should be kept up to Week 6 as the same dose level. After Week 6 the following tapering regimen can be followed if the patient's condition has been improved at the investigator's discretion: tapering rate of 3 mg every 2 weeks is recommended.

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

6.7.2.3 5-aminosalicylates (5-ASA)

For Crohn's disease, 5-ASA will be allowed if patients maintained stable doses for the specified timeframe according to the inclusion criteria (Section 4.2) and stable dose should be maintained throughout the study.

For Ulcerative colitis, only oral 5-ASA will be allowed if patients maintained stable doses for the specified timeframe according to the inclusion criteria (Section 4.2) and stable dose should be maintained throughout the study.

6.8 Prohibited Therapy

The following medications and treatments are prohibited during the study;

- Any biological agents for the treatment of Crohn's disease or Ulcerative colitis
- Parenteral corticosteroids for the treatment of Crohn's disease or Ulcerative colitis
- Any TNFα (tumor necrosis factor alpha) inhibitor, except for study treatment
- Alkylating agents
- Thalidomide, tacrolimus, or cyclosporine
- Live or live-attenuated vaccine
- Abdominal surgery, including but not limited to, for active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection or intra-abdominal or pancreatic abscess requiring surgical drainage

- Any other investigational device or medical product
- Use of exclusive enteral or parenteral nutrition

Following medications and treatments are prohibited only for **Part 2** of the study;

- Antibiotics for the treatment of Crohn's disease or Ulcerative colitis
- For **Ulcerative colitis**, rectally administered medications containing corticosteroids or 5-ASA for the treatment of Ulcerative colitis

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. For **Part 1**, the randomization will be stratified by region (European or non-European), current use of treatment with AZA or 6-MP or MTX (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease) and body weight at Week 6 (≤70 kg or >70 kg). For **Part 2**, the randomization will be stratified by current use of treatment with AZA or 6-MP or MTX (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease or partial Mayo score for Ulcerative colitis), body weight at Week 6 (<80 kg or ≥80 kg) and disease (Crohn's disease or Ulcerative colitis).

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

7.1 Pharmacokinetic Analyses

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

Mean serum concentration time profiles of study drug will be plotted by treatment on linear and semilogarithmic scales based on scheduled sample times. Individual concentrations and scheduled and actual sample times will be presented in data listings by treatment.

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

7.1.1 Primary Pharmacokinetic Endpoint for Part 1

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

7.1.2 Primary Pharmacokinetic Endpoint for Part 2

For the primary pharmacokinetic endpoint, the observed C_{trough} (pre-dose level) between patients treated with CT-P13 IV and CT-P13 SC at Week 22 will be analyzed using an analysis of covariance model (ANCOVA).

Point estimates (geometric least square means and ratio of geometric least square means) will be calculated from back transforming the least squares means of the log-transformed values of C_{trough} and difference in the least squares means. 90% confidence interval (CI) for the ratio of the geometric least square means will also be produced. The noninferiority of CT-P13 SC to CT-P13 IV will be concluded if the lower bound 90% CI for the ratio of the geometric least square means is higher than 0.8.

7.1.3 Secondary Pharmacokinetic Endpoints for Part 1

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

- AUC_{ss8W} Total exposure over 8 weeks interval from Week 22 to Week 30
- C_{max} Observed maximum serum concentration after study drug administration
- T_{max} Time of observed maximum serum concentration
- $T_{1/2}$ Terminal half life
- C_{trough} Trough concentration (concentration before the next study drug administration)
- MRT Mean residence time
- CL Clearance after IV dosing

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

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

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

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

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

7.1.4 Secondary Pharmacokinetic Endpoints for Part 2

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

- AUC_{τ} Area under the concentration-time curve at steady state between Week 22 and Week 30
- AUC_{ss8W} Total exposure over the 8 weeks interval from Week 22 to Week 30
- C_{max} Observed maximum serum concentration after study drug administration
- T_{max} Time of observed maximum serum concentration
- $T_{1/2}$ Terminal half life
- MRT Mean residence time
- CL Clearance after IV dosing

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

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

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

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

Population PK modelling will be performed using AUC_{τ} and C_{trough} and these PK variables, including C_{max}, will be presented in listings and summarized in tables. For PK parameters, the summary tables will display the following descriptive statistics: n, mean, median, SD, minimum, maximum, geometric mean and CV.

7.2 Efficacy Analyses

Efficacy population will be used for efficacy analyses.

7.2.1 Secondary Efficacy Endpoints for Part 1

Secondary efficacy endpoints will be assessed at the time points specified in the schedule of events (Table 10-1). Efficacy population will be used for efficacy analyses.

The following efficacy parameters will be determined as secondary endpoints:

- CDAI-70 response
- CDAI-100 response
- Clinical remission

- Endoscopic response and remission
- SIBDQ

7.2.1.1 CDAI-70 and CDAI-100

The number and percentage of patients achieving clinical response according to CDAI criteria (CDAI-70 or CDAI-100) will be summarized by treatment group. A patient is defined as having a CDAI-70 (or CDAI-100) response if there is a decrease in CDAI score of 70 points or more (100 points or more for CDAI-100 response) from the baseline value.

Descriptive statistics for actual and change from baseline will be calculated by treatment at each study visit.

7.2.1.2 Clinical Remission by CDAI

The number and percentage of patients achieving clinical remission will be summarized by treatment group. Clinical remission is defined as an absolute CDAI score of less than 150 points.

7.2.1.3 Endoscopic Response and Remission

The number and percentage of patients achieving endoscopic response or remission will be summarized by treatment group. Endoscopic response in patients with active CD is defined as a decrease in 50% or more of SES-CD score and endoscopic remission defined as an absolute SES-CD score of 2 points or less in patients who have confirmed mucosal abnormalities at baseline. The degree of mucosal abnormalities will be assessed using by using the SES-CD [Daperno et al. 2004].

7.2.1.4 Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The SIBDQ data will be listed and summarized by treatment group. The SIBDQ is a quality-of-life questionnaire for patients with inflammatory bowel disease. 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) (Appendix 10.4).

7.2.2 Secondary Efficacy Endpoints for Part 2

Secondary efficacy endpoints will be assessed at the time points specified in the schedule of events (Table 10-2). Efficacy population will be used for efficacy analyses.

The following efficacy parameters for patients with active CD will be determined as secondary endpoints as specified in Section 7.2.1:

- CDAI-70 response (Section 7.2.1.1)
- CDAI-100 response (Section 7.2.1.1)
- Clinical remission (Section 7.2.1.2)
- Endoscopic response and remission (Section 7.2.1.3)
- SIBDQ (Section 7.2.1.4)

The following efficacy parameters for patients with active UC will be determined as secondary endpoints:

- Clinical response (total/partial Mayo score)
- Clinical remission (total/partial Mayo score)
- Mucosal healing
- SIBDQ (Section 7.2.1.4)

7.2.2.1 Clinical Response by Mayo Scoring System

The number and percentage of patients achieving clinical response according to total Mayo score will be summarized by treatment group at Week 22, Week 54 (or End-of-Study Visit, if not obtained at Week 54), and any other visits when all components are available. A patient is defined as having a clinical response if there is a decrease in total Mayo score from baseline at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute subscore for rectal bleeding of 0 or 1.

Likewise, the proportion of patients achieving clinical response according to partial Mayo score will be summarized by treatment group. Partial Mayo score will be summarized when 3 components of stool frequency, rectal bleeding and physician’s global assessment are available. A patient is defined as having a clinical response if there is a decrease in partial Mayo score

from baseline 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.

Descriptive statistics for actual and change of total or partial Mayo score from baseline will be calculated by treatment and study visit.

7.2.2.2 Clinical Remission by Mayo Scoring System

The number and percentage of patients achieving clinical remission will be summarized for total Mayo score and partial Mayo score respectively by treatment group. Clinical remission is defined as a total Mayo score of 2 points or lower with no individual subscore exceeding 1 point, or partial Mayo score of 1 point or lower.

7.2.2.3 Mucosal Healing

The number and percentage of patients achieving mucosal healing will be summarized by treatment group. Mucosal healing in patients with active UC is defined as absolute endoscopic subscore of 0 or 1 from MSS.

7.3 Pharmacodynamic Analyses for Part 1 and 2

Secondary pharmacodynamic endpoints will be assessed at the time points specified in the schedule of events (Table 10-1 and Table 10-2). Pharmacodynamic population will be used for pharmacodynamic analyses. The following PD parameters will be determined as secondary endpoints:

- CRP
- Fecal calprotectin

Pharmacodynamic data will be summarized by treatment at each scheduled collection time. In additional to the standard summary statistics, the geometric mean and CV will also be presented at each time point.

7.4 Biomarker Analyses for Part 2

Biomarkers as tertiary endpoints will be assessed at the time points specified in the schedule of events (Table 10-2). Descriptive analyses will be performed on genotypes (including, but not limited to FcRn) and amino acids (including, but not limited to Tryptophan) by treatment groups.

7.5 Safety Analyses for Part 1 and 2

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 secondary endpoints:

- Immunogenicity testing
- Hypersensitivity monitoring (including delayed hypersensitivity monitoring)
- Vital sign measurements (including blood pressure, heart and respiratory rates, and body temperature) and weight
- TB monitoring of signs and symptoms
- IGRA and chest X-ray
- Hepatitis B and C, HIV-1 and -2 status and diabetes mellitus assessment
- Congestive heart failure assessment
- Physical examination findings
- 12-lead ECGs
- AEs including SAEs
- AEs of Special Interest (including infections, infusion-related reactions/hypersensitivity/anaphylactic reactions [administration-related reactions], delayed hypersensitivity, injection site reactions, malignancies)
- Clinical laboratory analyses
- Patient's assessment of local site pain (VAS)
- Pregnancy testing
- Prior and Concomitant medications
- Complement (C3, C4) and total hemolytic complement

7.5.1 Demographic, Baseline, and Background Characteristics

Demographics (age, gender, race, and etc.) and baseline and background characteristics will be presented in summary tables. Qualitative data (e.g., medical history) will be summarized in

contingency tables, and quantitative data (e.g., age) will be summarized using quantitative descriptive statistics.

7.5.2 Adverse Events

Adverse events will be coded to system organ class (SOC) and preferred term (PT) according to MedDRA. Adverse events will be graded for severity according to the CTCAE v4.03.

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

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

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.

7.5.3 Clinical Laboratory Analyses

Clinical laboratory tests (hematology, clinical chemistry, and urinalysis), IGRA 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.

7.5.4 Immunogenicity (Anti-CT-P13 Antibodies)

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

7.5.5 Electrocardiograms, Physical Examination, Vital Signs and Weight

Electrocardiograms, Physical examination, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, 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.

7.5.6 Patient's assessment of Local Site Pain

Local site pain measurements by VAS will only be assessed immediately (not exceeding 1 hour) after the end of administration of study drug at each scheduled collection time and will be summarized by treatment group.

7.5.7 Prior and Concomitant Medications

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

7.6 Patient Overall Satisfaction Analysis for Part 2

Patient overall satisfaction of CT-P13 IV and CT-P13 SC as tertiary endpoint will be assessed at the time points specified in the schedule of events (Table 10-2). Descriptive analyses will be performed by treatment groups.

7.7 Sample Size Calculations

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

For **Part 2**, the primary endpoint is the C_{trough} (pre-dose level) at Week 22. A sample size of 104 subjects (52 patients each in the CT-P13 SC and CT-P13 IV treatment groups) provide 90% power to demonstrate noninferiority of CT-P13 SC to CT-P13 IV based on the 95% one-sided confidence interval for the geometric mean ratio of CT-P13 SC to CT-P13 IV in C_{trough}. In the sample size calculation, noninferiority margin of 80%, one-sided alpha level 5% expected ratio of 1.3 and CV of 100% were assumed. Considering 20% drop-out rate, total 130 patients (65 patients each in the CT-P13 SC and CT-P13 IV treatment groups) will be required.

A reassessment of sample size accounting for the actual ratio of geometric means and CV will be made using the result from Part 1. The sample size will not be decreased from the initial 130 total sample size but could be increased up to 200 patients in case that actual ratio of geometric means decreases to 1.18 or actual CV increases up to 140%. Sample size will be determined considering DSMB's recommendation based upon the review of PK, efficacy, PD and safety data found over the first 30 weeks from Part 1 of the study.

7.8 Analysis Sets

Intended-to-Treated (ITT) population is defined as all enrolled patients. The following analysis sets will be used in the statistical analyses. Five patient populations are defined: all-randomized, pharmacokinetic (PK), pharmacodynamic (PD), efficacy and safety population in each Part 1 and Part 2. In addition, for each analysis population the number of patients will be presented.

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

PK Population: The PK population is defined as all randomly assigned patients who receive at least one full dose of study drug at Week 6 or thereafter and who have at least one PK concentration result after Week 6 treatment in all-randomized population. The primary PK endpoints of AUC_{τ} between Week 22 and Week 30 for Part 1 will be analysed in patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in PK population. The primary PK endpoints of C_{trough} at Week 22 (pre-dose level at Week 22) for Part 2 will be analysed in patients who received all doses (full) of study drug up to Week 22 (prior to Week 22) in PK population.

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

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

Safety Population: The safety population is defined as all randomly assigned patients who receive at least 1 dose (partial or full) of study drug at Week 6 or thereafter.

A major protocol deviation that may affect the interpretation of study results of efficacy will be excluded from efficacy population. A major protocol deviation that may affect the interpretation of study results of PK will be excluded from PK population. Final determinations of the efficacy and PK population will be made at the data review meeting held in accordance with ICH harmonised tripartite guideline E9.

7.8.1 Description of Subgroups to be Analyzed

For Part 2, all data analysis including PK primary endpoint will be analysed in all patients including CD and UC patients. Subgroup analysis by each disease (CD and UC) will be done in PK secondary endpoints, PD, efficacy and safety analysis.

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

7.9 Interim Analyses

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

7.10 Data Quality Assurance

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

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

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

8 Investigator's Obligations

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

8.1 Confidentiality and Data Protection

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

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

8.2 Institutional Review

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

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

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

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

8.3 Informed Consent

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

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

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

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

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

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

8.4 Study Reporting Requirements

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the time line and method outlined in Section 5.5.11.3. In addition, the principal investigator or subinvestigator agrees to submit annual reports to his or her IRB/IEC as appropriate. The principal investigator or subinvestigator also agrees to provide the sponsor with an adequate report shortly after completion of the principal investigator's or subinvestigator's participation in the study.

8.5 Financial Disclosure and Obligations

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

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

8.6 Investigator Documentation

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

- IRB/IEC approval.
- An original investigator-signed investigator agreement page of the protocol.
- Curriculum vitae for the principal investigator and each subinvestigator. Current licensure must be noted on the curriculum vitae. They will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.

- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An IRB/IEC-approved informed consent, samples of study center advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians.
- Laboratory certifications and normal ranges for any local laboratories used by the study center, in accordance with 42 CFR 493.

8.7 Study Conduct

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

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

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

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

8.8 Data Collection

8.8.1 Electronic Case Report Forms and Source Documents

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

The eCRFs are accessed through the system which allows for on-site data entry and data management. Study center users can read from and write to the sponsor's database where the clinical data are collected. This provides immediate 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. Previous and concomitant medications will be coded using the WHO Drug Dictionary.

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

8.10 Adherence to Protocol

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

8.11 Reporting Adverse Events

By participating in this study, the principal investigator or subinvestigator agrees to submit reports of SAEs according to the time line and method outlined in Section 5.5.11.3. In addition, the principal investigator or subinvestigator agrees to submit annual reports to the relevant

IRB/IEC as appropriate. The principal investigator or subinvestigator also agrees to provide the sponsor with an adequate report shortly after completion of the principal investigator's or subinvestigator's participation in the study.

8.12 Investigator's Final Report

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

8.13 Records Retention

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

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

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

8.14 Patient Identification Register

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

8.15 Publications

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

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

9 Study Management

9.1 Sponsor

[redacted]

Sponsor Representative

[redacted]

9.2 Vendor Contact

[redacted]

SAE Reporting

[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. The following analytical facilities will be used:

[redacted]

[redacted]

9.4 Data Safety Monitoring Board

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

During **Part 1** of the trial, DSMB will review the PK modelling report containing PK, efficacy, PD and safety data over the first 30 weeks from Part 1 and recommend the optimal dose (dose level and dosing interval) for CT-P13 SC. **Part 2** will be initiated after determination on sample size for Part 2 considering DSMB's recommendation.

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

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

9.5 Monitoring

9.5.1 Monitoring of the Study

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

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

9.5.2 Inspection of Records

Principal investigators or subinvestigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the principal investigator or subinvestigator agrees to allow the sponsor, representatives of the sponsor, or other regulatory agencies access to all study records.

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

9.6 Management of Protocol Amendments and Deviations

9.6.1 Modification of the Protocol

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

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

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

9.6.2 Protocol Violations and Deviations

The principal investigator or subinvestigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The principal investigator or subinvestigator may implement a deviation from, or a change of, the protocol

to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments will be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the principal investigator or subinvestigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion, exclusion, or primary endpoint criteria. A protocol violation occurs when there is nonadherence to the protocol by the patient, investigator, or subinvestigator that results in a significant and additional risk to the patient. Protocol violations can include nonadherence to inclusion or exclusion criteria, enrolment of the patient without prior sponsor approval, or nonadherence to regulatory regulations or ICH E6(R2) guidelines.

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

9.7 Study Termination

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

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

9.8 Final Report

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

The sponsor plans to prepare 3 clinical study reports, but additional clinical study reports will be generated upon requirements for regulatory or academic purposes, including but not limited to:

- reporting data for each patient after completion of all visits in Part 1,
- reporting data for each patient up to Week 30 in Part 2, and
- reporting data for each patient after completion of all visits in Part 2.

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

10 Appendices

10.1 Schedule of Events

Table 10-1 Schedule of Events for Part 1

	Screening	Treatment Period												EOS[2]
Study Week		**0**	**2**	**6**	**8[1]**	**10[1]**	**14**	**22**	**PK Monitoring Visit[24]**	**30**	**38**	**46**	**54**	
Study Day	**–21 to –1**	**0**	**14**	**42**	**56**	**70**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**							**± 3 days**	**± 5 days**			
Cohort 1 treatment		**IV**	**IV**	**IV**			**IV**	**IV**		**IV**	**IV**	**IV**	**IV**	
Cohort 2, 3 and 4[3] treatment				**SC**	**SC[1]**	**SC[1]**	**SC**							
Informed consent	X													
Demography[4]	X													
Medical history[5]	X													
Hepatitis B & C and HIV-1 & -2[6]	X													
Inclusion and exclusion criteria	X	X[7]												
Randomization				X[7]										
Serum pregnancy test	X													X
Urine pregnancy test[8]		X[7]	X[7]	X[7]			X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	
Clinical laboratory tests[9]	X	X[7]	X[7]	X[7]			X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X
ESR[10]	X	X[7]	X[7]	X[7]			X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X
Chest X-ray[11]	X													
Interferon-γ release assay[12]	X									X[7]			X[7]	X
Physical examinations	X	X[7]	X[7]	X[7]			X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X
Vital signs and Weight[13]	X	X[7]	X[7]	X[7]			X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X
12-lead ECG[14]	X			X			X			X			X	X
Colonoscopy (SES-CD)[15]	X[16]									X[7]			X[7]	X[18]
CDAI score[17]	X		X[7]	X[7]			X[7]	X[7]		X[7]			X[7]	X[18]
SIBDQ		X[7]	X[7]	X[7]			X[7]	X[7]		X[7]			X[7]	X[18]
VAS Local site pain[19]				X			X	X		X			X	
Fecal calprotectin[20]		X[7]	X[7]	X[7]			X[7]	X[7]		X[7]			X[7]	X[18]
Immunogenicity[21]		X[7]		X[7]			X[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X
Hypersensitivity monitoring[22]		X	X	X			X	X		X	X	X	X	
C3, C4 and Total Hemolytic Complement[23]		X[7]												
Pharmacokinetic blood sampling		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[24]	X[7]	X[7]	X[7]	X[7]	
Pharmacodynamic blood sampling (CRP)[25]	X	X[7]	X[7]	X[7]			X[7]	X[7]		X[7]			X[7]	X
Prior, Concomitant medications[26]	X													
TB clinical monitoring[27]	X													
AEs monitoring[28]	X													

Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ECG, Electrocardiogram; EOS, End-of-Study; ESR, Erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IV, intravenous; N/A, not applicable; SC, subcutaneous; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; SIBDQ, Simplified Inflammatory Bowel Disease Questionnaire; TB, tuberculosis; VAS, Visual Analogue Scale.

1. Visits 4 and 5 (Week 8 and Week 10) will only be made by patients from Cohorts 2, 3 and 4 for additional pharmacokinetic assessment.
2. All EOS assessments will be completed 8 weeks after the last study drug administration.
3. First CT-P13 SC will be administered by PFS at Week 6 and further SC injections will be given every 2 weeks up to Week 54. A dosing window of ±3 days up to and including Week 30 and of ±5 days after Week 30, including EOS is allowed.
4. Age, gender, ethnicity and race.
5. At Screening, patients will be assessed for the history of Crohn's disease or ulcerative colitis, respiratory disease, diabetes mellitus and congestive heart failure and etc.
6. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), this patient can be enrolled by the investigator's discretion based on clinical laboratory results and the infection history of hepatitis. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study. Hepatitis and HIV analysis will be performed at the central laboratory.
7. Assessed prior to study drug administration.
8. A urine pregnancy test for women of childbearing potential who have not been surgically sterilized will be used to confirm patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.
9. Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analyzed at the central laboratory. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness.
10. ESR samples will be analyzed at the local laboratory using kits supplied centrally.
11. A chest x-ray (both posterior-anterior and lateral views) is not required at Screening if a chest x-ray from within the 42 days prior to the first administration of the study drug (Day 0) is available.
12. The IGRA will be performed at the central laboratory. No further IGRA test is required during Treatment Period for the following patients:
    - Patient who has a history of active TB with sufficient documentation of complete resolution
    - Patient who has a history of latent TB with sufficient documentation of complete prophylaxis
13. Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented once at Screening.
14. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion.
15. Colonoscopy will be repeated in patients who have any confirmed mucosal abnormalities from previous assessment. For colonoscopy after Screening, assessment window of -14 days is allowed.
16. Colonoscopy for evaluation of mucosal abnormalities will be performed in all patients at Screening. However, colonoscopy at Screening would not be required if there is documented colonoscopy report of no colonic involvement within 3 years or endoscopic evidence of inflammation consistent with Crohn's disease within 3 months prior to the first administration of the study drug (Day 0).
17. CDAI score will be calculated once all components of the CDAI (patient's CDAI diary entries, hematocrit results, and assessments performed by site investigator) are available. For CDAI assessment at Screening and during the study period, hematocrit results from local laboratory within the 7 days prior to the CDAI assessment date will be used. Patients will complete CDAI diary at least 7 consecutive days prior to CDAI assessment date, except when CDAI assessment is performed at the same date of colonoscopy procedure. If patient is planned to have bowel preparation for colonoscopy procedure, patient should not complete CDAI diary during the day before and up to the next day of colonoscopy procedure.
18. End-of-Study assessments will only be performed if not done at Week 54.

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

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

Visit (Day)	Cohort 1	Cohort 2, 3 and 4	
		Group A	Group B
		• 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection	
Week 28 (Day 196)	• 42±1 days after SOI at Week 22	• Pre-dose* • 168 ±6 hr after injection	• Pre-dose* • 24±2 hr after injection • 48±2 hr after injection • 96 ±4 hr after injection • 168 ±6 hr after injection • 216 ±4 hr after injection • 264 ±4 hr after injection
Week 30 (Day 210)	• Pre-dose* (or 56 days after SOI at Week 22**)	• Pre-dose* (or 14 days after the Week 28 injection**)	

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

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

Table 10-2 Schedule of Events for Part 2

	Screening	Treatment Period										EOS[1]
Study Week		**0**	**2**	**6**	**14**	**22**	**PK Monitoring Visit[32]**	**30**	**38**	**46**	**54**	
Study Day	**–42~**	**0**	**14**	**42**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**									
Arm 1[2] treatment		**IV**	**IV**	**IV**	**IV**	**IV**		**SC[3]**	**SC[3]**			
Arm 2[4] treatment				**SC[4]**	**SC[4]**							
Informed consent	X											
Demography[5]	X											
Medical history[6]	X											
Hepatitis B and HBV-DNA[7]	X					(X[8])				(X[8])		(X)
Hepatitis C and HIV-1 & -2[9]	X											
Inclusion and exclusion criteria	X	X[8]										
Randomization				X[8]								
Serum pregnancy test[10]	X											X
Urine pregnancy test[11]		X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	
Clinical laboratory tests [12]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
ESR[13]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Chest X-ray[14]	X											
Interferon-γ release assay[15]	X							X[8]			X[8]	X[26]
Physical examinations	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Vital signs and Weight[16]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
12-lead ECG[17]	X			X	X			X			X	X
Fecal calprotectin[18]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X[26]
SIBDQ		X[8]	X[8]	X[8]	X[8]	X[8]		X[8]			X[8]	X[26]
Patients with Crohn's disease												
Colonoscopy (SES-CD)[19]	X[20]					X[8]					X[8]	X[26]
CDAI score[21]	X[22]		X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X[26]
Patients with Ulcerative Colitis												
Flexible proctosigmoidoscopy (Endoscopic subscore of MSS)[23]	X					X[8]					X[8]	X[26]
MSS assessment[24]	X[25]		X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X[26]
VAS Local site pain[27]		X	X	X	X	X		X	X	X	X	
VAS Patient overall satisfaction[28]		X	X	X	X	X		X	X	X	X	
Immunogenicity[29]		X[8]		X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Hypersensitivity monitoring[30]		X	X	X	X	X		X	X	X	X	

	Screening	Treatment Period										
Study Week		**0**	**2**	**6**	**14**	**22**	**PK Monitoring Visit[32]**	**30**	**38**	**46**	**54**	**EOS[1]**
Study Day	**–42~**	**0**	**14**	**42**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**									
C3, C4 and Total Hemolytic Complement[31]		X[8]										
Pharmacokinetic blood sampling		X[8]	X[8]	X[8]	X[8]	X[8]	X[32]	X[8]	X[8]	X[8]	X[8]	
Pharmacodynamic blood sampling (CRP)[33]	X	X[8]	X[8]	X[8]	X[8]	X[8]		X[8]	X[8]	X[8]	X[8]	X
Biomarkers (genotype, optional)[34]		X[8]										
Biomarkers (amino acids)[35]		X		X		X					X	
Prior, Concomitant medications[36]	X											
TB clinical monitoring[37]	X											
AEs monitoring[38]	X											

Abbreviations: AE, adverse event; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ECG, Electrocardiogram; EOS, End-of-Study; ESR, Erythrocyte sedimentation rate; HIV, human immunodeficiency virus; IV, intravenous; MSS, Mayo Scoring System; N/A, not applicable; SC, subcutaneous; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; SIBDQ, Simplified Inflammatory Bowel Disease Questionnaire; TB, tuberculosis; VAS, Visual Analogue Scale.

1. All EOS assessments will be completed 2 weeks after the last study drug administration. For patients with early discontinuation before switching to CT-P13 SC at Week 30 in Arm 1 or before randomization at Week 6 in Arm 2, the EOS Visit will occur 8 weeks after the last dose of CT-P13 IV is received.
2. CT-P13 IV will be administered at Weeks 0, 2, 6, 14 and 22. CT-P13 IV will be then switched to CT-P13 SC at Week 30 with CT-P13 SC dose based on body weight at Week 30. Further doses of study treatment with CT-P13 SC will be given every 2 weeks up to Week 54.
3. A dosing window of ±3 days is allowed, including self-injection.
4. CT-P13 SC dose based on body weight at Week 6 will be administered by PFS at Week 6 and further SC injections will be given every 2 weeks up to Week 54. A dosing window of ±3 days is allowed including self-injection.
5. Age, gender, ethnicity and race.
6. At Screening, patients will be assessed for the history of Crohn's disease or ulcerative colitis, respiratory disease, diabetes mellitus and congestive heart failure etc.
7. At Screening, hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient must be excluded from the study. If a patient has HBsAg (negative), HBsAb (negative or positive) and HBcAb (positive), a HBV-DNA test will be further assessed at Screening. If the HBV-DNA test result is positive, the patient should be excluded from the study and if the HBV-DNA test result is negative, the patient can be included. For patients enrolled based on the HBV-DNA test, the test of HBsAg, HBsAb and HBV-DNA will be additionally performed at Weeks 22, 46 and EOS visits. Aspartate aminotransferase, alanine aminotransferase and total bilirubin results will be monitored as well.
8. Assessed prior to study drug administration.
9. If hepatitis C antibody, HIV-1 or -2 test result is positive, the patient must be excluded from the study.
10. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS Visit.
11. A urine pregnancy test for women of childbearing potential will be used to confirm patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation. A urine pregnancy test will be performed locally. If a urine pregnancy test result is positive, a confirmatory serum pregnancy test will be performed at the central laboratory.
12. Clinical laboratory (clinical chemistry, hematology, and urinalysis [urine microscopy]) test samples will be analyzed at the central laboratory. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration to determine serum sickness. CRP samples for PD assessments should be drawn at the same time as the clinical laboratory blood samples.

13. ESR samples will be analyzed at the local laboratory using kits supplied centrally.
14. A chest x-ray (both posterior-anterior and lateral views) is not required at Screening if a chest x-ray from within the 42 days prior to the first administration of the study drug (Day 0) is available.
15. The IGRA will be performed at the central laboratory.
16. Vital signs (including blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented once at Screening.
17. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done by the investigator's discretion.
18. Sampling and handling for calprotectin testing will be conducted only at the qualified or feasible sites.
19. Colonoscopy will be repeated in patients who have any confirmed mucosal abnormalities from previous assessment. Colonoscopy will be evaluated centrally by independent reviewer blinded to treatment allocation for reporting purposes, and evaluated at local level to confirm eligibility and for treatment practice. For colonoscopy after Screening, assessment window of -14 days is allowed.
20. Colonoscopy will be performed in all patients at Screening. However, colonoscopy at Screening would not be required if there is documented colonoscopy report of no colonic involvement within 3 years or endoscopic evidence of inflammation consistent with Crohn's disease within 3 months prior to the first administration of the study drug (Day 0).
21. Patients will complete CDAI diary at least 7 consecutive days immediately prior to CDAI assessment date, except when CDAI assessment is performed at the same date of colonoscopy procedure. If patient is planned to have bowel preparation for colonoscopy procedure, patient should not complete CDAI diary during the day before and up to the next day of colonoscopy procedure.
22. To determine eligibility, the components of the CDAI must be completed within 7 days prior to the first administration of the study drug (Day 0) and CDAI score will be calculated at Day 0.
23. If colonoscopy has been performed, it can replace flexible proctosigmoidoscopy for evaluation of endoscopic subscore. Endoscopic subscore by flexible proctosigmoidoscopy (or colonoscopy) will be evaluated centrally by independent reviewer blinded to treatment allocation for reporting purposes, and evaluated at local level to confirm eligibility or loss of response for treatment practice. Flexible proctosigmoidoscopy for endoscopic subscore assessment after Screening, assessment window of -14 days is allowed.
24. Patients will complete MSS diary at least 3 consecutive days immediately prior to assessment date, except when MSS assessment is performed at the same date of flexible proctosigmoidoscopy (or colonoscopy) procedure. If patient is planned to have bowel preparation for flexible proctosigmoidoscopy (or colonoscopy) procedure, patient should not complete MSS diary during the day before and up to the next day of procedure.
25. To determine eligibility, total Mayo score will be calculated at Day 0 using endoscopic subscore during Screening period and other 3 components completed within 3 days prior to the first administration of the study drug (Day 0).
26. End-of-study assessment will only be performed if the assessment was not done at Week 54, or in patient with discontinuation before Week 54.
27. All patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug.
28. All patients will assess overall satisfaction of CT-P13 IV or CT-P13 SC by using 100 mm VAS immediately (not exceeding 1 hour) after the end of administration of study drug.
29. Serum samples for immunogenicity testing will be drawn at the same time as the clinical laboratory tests before dosing, where applicable. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
30. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of the study treatment administration and 1 hour (±10 minutes) after the end of the study drug administration) to monitor for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed. In addition, delayed hypersensitivity will be monitored after 24 hours of study drug administration, including serum sickness-like reaction (myalgia with fever or rash, arthralgia,

lymphadenopathy, skin eruption or edema).

31. Additional serum samples for complement (C3, C4) and total hemolytic complement will be assessed if delayed hypersensitivity occurs after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
32. If the investigator deems hospitalization necessary for the blood sample collection, patients should remain in the hospital until blood samples for pharmacokinetic analysis have been collected. If the investigator deems hospitalization unnecessary and sampling can be adequately obtained without hospitalization, the patient does not have to remain hospitalized. Blood samples for pharmacokinetic analysis will be obtained at following time point;

Visit (Day)	Arm 1	Arm 2			
		Group A	Group B	Group C	Group D
Week 22 (Day 154)	• Pre-dose* • After EOI (+15 min) • 1 hr (±15 min) after EOI • 8 hr (±15 min) after SOI • 24 hr (±15 min) after SOI • 48±2 hr after SOI • 168±6 hr after SOI	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection	• Pre-dose**	• Pre-dose**	• Pre-dose**
Week 24 (Day 168)	• 14 days (±12 hr) after SOI at Week 22	• Pre-dose**	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection	• N/A	• N/A
Week 26 (Day 182)	• 28±1 days after SOI at Week 22	• N/A	• Pre-dose**	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection	• N/A

Visit (Day)	Arm 1	Arm 2			
		Group A	Group B	Group C	Group D
Week 28 (Day 196)	• 42±1 days after SOI at Week 22	• N/A	• N/A	• Pre-dose**	• Pre-dose** • 24±2 hr after injection • 48±2 hr after injection • 72±2 hr after injection • 96±4 hr after injection • 120±4 hr after injection • 144±4 hr after injection • 168±6 hr after injection • 216±4 hr after injection • 264±4 hr after injection
Week 30 (Day 210)	• Pre-dose*	• Pre-dose**	• Pre-dose**	• Pre-dose**	• Pre-dose**

EOI, End of the infusion; hr, hours; min; minutes; N/A, not applicable; SOI, Start of the infusion.
*prior to the beginning of study treatment administration on dosing day (or 56 days after previous dosing day only if patient has not received study treatment on each relevant dosing day)
**prior to the beginning of study treatment administration on dosing day (or 14 days after previous dosing day only if patient has not received study treatment on each relevant dosing day)
Note: If a patient in Arm 2 is not able to attend any of the sampling visits, it should be discussed with the Sponsor in advance.

33. CRP samples should be drawn at the same time as the clinical laboratory blood samples.
34. Blood samples of patients who sign a separate informed consent form will be collected.
35. Blood samples and consumption time of foods or drinks containing protein will be collected.
36. Use of all prior and concomitant medications for the treatment of Crohn's disease or Ulcerative colitis, from the diagnosis of disease until the last assessment date or EOS Visit, will be recorded in the patient's eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) patient enrolment until the last assessment date or EOS Visit, will be recorded. All concomitant medications will also be recorded when any serious adverse drug reactions occur after the EOS Visit.
37. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB, and interferon-γ release assay or chest x-ray can be performed at the investigator's discretion based on the judgment on the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
38. Adverse events will be assessed from the date the ICF is signed until the last assessment date or EOS Visit. Where AEs are ongoing at the EOS Visit, the patient should be followed up for a further 30 days regardless of the relationship to study drug. The related AEs will be followed until resolution or improvement to baseline, relationship reassessed as unrelated, confirmed by the investigator that no further improvement could be expected, no more collection of clinical or safety data, or final database closure. Serious adverse drug reactions occurring up to 8 weeks after last dose of study drug will be reported and followed up until 8 weeks after last dose of study drug. In addition, if it is ongoing until 8 weeks after last dose of study drug, it should be followed up for a further 30 days. Adverse events of special interest (i.e. administration-related reaction, injection site reaction, delayed hypersensitivity, infection and malignancy) should be closely monitored.

Table 10-3 Sampling Time points for Part 2

Study Week		Screening	0	2	6	14	22	30	38	46	54	EOS
Study Day		–42 ~	0	14	42	98	154	210	266	322	378	
Safety	IGRA	X						Pre-treatment[1]			Pre-treatment[1]	X[8]
	Hepatitis B and HBV-DNA	X					(Pre-treatment[1])			(Pre-treatment[1])		(X)
	Clinical laboratory tests	X	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	X
	ESR	X	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	X
	Complement (C3, C4) and Total Hemolytic Complement[2]		Pre-treatment[1]									
	Immunogenicity		Pre-treatment[1]		Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	X
PD	Fecal Calprotectin	X	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	X[8]
	CRP[3]	X	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	X
Efficacy	Hematocrit[4]	X		Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	X
Biomarker	Genotypes (optional)[5]		Pre-treatment[1]									
	Amino acids[6]		Pre-treatment[1]		Pre-treatment[1]		Pre-treatment[1]				Pre-treatment[1]	
PK[7]			Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	Pre-treatment[1]	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EOS, End-of-Study; HBV, hepatitis B virus; IGRA, inteferone-γ release assay; PD, pharmacodynamics; PK, pharmacokinetics.

1. Pre-treatment: Blood samples will be obtained prior to the study drug administration.
2. Additional serum samples for complement (C3, C4) and total hemolytic complement will be assessed if delayed hypersensitivity occurs after 24 hours of study drug administration to determine serum sickness.
3. CRP samples should be drawn at the same time as the clinical laboratory blood samples.
4. For CDAI assessment at Screening and during the study period, hematocrit results from local laboratory within the 7 days prior to the CDAI assessment date will be used.
5. Blood samples of patients who sign a separate informed consent form will be collected.
6. Blood samples and consumption time of foods or drinks containing protein will be collected.
7. PK sampling time points between Week 22 and Week 30 is specified in Table 5-2.
8. End-of-study assessment will only be performed if the assessment was not done at Week 54, or in patient with discontinuation before Week 54.

10.2 Diabetes Mellitus Assessment

Diabetes mellitus is defined by the criteria for the diagnosis of diabetes mellitus according to the American Diabetes Association. Patients are to be excluded from the study if they have uncontrolled diabetes mellitus even after insulin treatment. Details of the American Diabetes Association criteria for the diagnosis of diabetes mellitus are provided in Table 10-4.

Table 10-4 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 of anhydrous glucose dissolved in water.

Abbreviations: 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.
Source: American Diabetes Association2006.

10.3 New York Heart Association Functional Classification

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

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

10.4 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 Crohn's Disease Activity Index

No.	Items	Factor
1	Number of liquid or very soft stools[1]	×2
2	Abdominal pain[1] (0=none, 1=mild, 2=moderate, 3=severe)	×5
3	General well-being[1] (0=generally well, 1=slightly under par, 2=poor, 3=very poor, 4=terrible)	×7
4	Number of 6 listed categories patient now has:	×20
	1) Arthritis/arthralgia 2) Iritis/uveitis 3) Erythema nodosum/pyoderma gangrenosum/aphthous stomatitis 4) Anal fissure, fistula, or abscess 5) Other fistula 6) Fever over 100℉ (37.8℃) during past week	
5	Taking lomotil/opiates for diarrhea (0=no, 1=yes)	×30
6	Abdominal mass (0=none, 2=questionable, 5=definite)	×10
7	Hematocrit[2] (Males: [47-hematocrit], Females: [42-hematocrit])	×6
8	Percentage deviation from standard weight[3] ([Standard weight – Patient weight]/Standard weight) × 100 (%)	×1

1. Sum of 7 days.
2. Only for CDAI assessment at Screening and during the study period, the hematocrit results from local laboratory within the 7 days prior to the CDAI score assessment will be used.
3. If the calculated subtotal is less than '-10', then it will be set to '-10'.

Source: Best et al.1976.

10.6 SES-CD Score

		Rectum	Left Colon	Transverse Colon	Right Colon	Ileum	Total
Was this section of the intestine	Explored						
	Resected						
	Inaccessible						
Presence and size of ulcers	0 = None						
	1 = Aphthous ulcers (0.1 to 0.5 cm)						
	2 = Large ulcers (0.5 to 2 cm)						
	3 = Very large ulcers (> 2cm)						
Extent of ulcerated surface	0 = None						
	1 = < 10%						
	2 = 10—30%						
	3 = > 30%						
Extent of affected surface	0 = Unaffected segments						
	1 = < 50%						
	2 = 50—75%						
	3 = > 75%						
Presence and type of narrowing	0 = None						
	1 = Single, can be passed						
	2 = Multiple, can be passed						
	3 = Cannot be passed						
SES - CD Total							

Source: Daperno et al. 2004

10.7 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 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

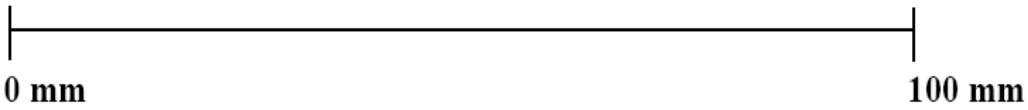
Total Mayo score ranges from 0 to 12, with higher scores indicating more severe disease .

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.
3. Endoscopy subscore of the Mayo Score is modified in accordance with United States Food and Drug Administration guidance so that a value of 1 does not include friability.
4. The physician's global assessment acknowledged the three other criteria; the patient's daily record 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

10.8 Visual Analogue Scale (VAS): Local Site Pain

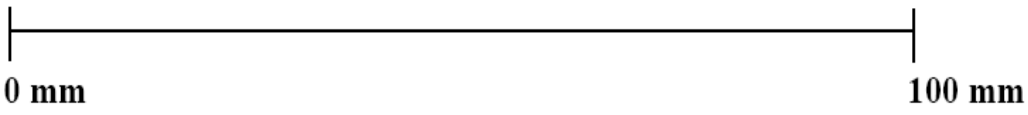
Patient assessment of local site pain is measured by the patient indicating the extent of their pain by marking a line (|) through the 100 mm line (0 mm equals no pain and 100 mm equals extreme pain). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient's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



None Extreme

10.9 Visual Analogue Scale (VAS): Patient Overall Satisfaction

Patient assessment of overall satisfaction about procedure and duration of the study drug administration on that visit day, regardless of other external conditions (e.g., interaction with doctor/nurse, distance from home to hospital, transportation, etc.) is measured by the patient indicating his or her overall satisfaction of the study drug administration by marking a line (|) through the 100 mm line (0 mm equals “extremely unsatisfied” and 100 mm equals “extremely satisfied”). The length of the line is measured from the left (in mm) and the value (in mm) recorded in the patient’s case report form.



Extremely unsatisfied Extremely satisfied

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