

CELLTRION Inc.
CT-P13 3.8

**A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study to Evaluate the
Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as
Maintenance Therapy in Patients With Moderately to Severely Active Crohn's Disease**

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Statistical Analysis Plan

Final Version 1.0

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Upon review of this document, including table, listing and figure shells, the undersigned approves the final statistical analysis plan. The analysis methods and data presentation are acceptable, and the table, listing and figure production can begin.

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List of Abbreviations

Abbreviation	Definition
ADA	Anti-Drug Antibody
ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AI	Auto-Injector
ANCOVA	Analysis of Covariance
AP	Abdominal Pain
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BSFS	Bristol Stool Form Scale
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
C _{max}	Observed Maximum Serum Concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	Trough Concentration
CT-P13	Infliximab (CELLTRION, Inc.)
CT-P13 SC	Subcutaneous Injection of CT-P13
CV%	Percent Coefficient of Variation
DRM	Data Review Meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End-of-Study
ESR	Erythrocyte Sedimentation Rate
FC	Fecal Calprotectin
HCV-RNA	Hepatitis C virus - RNA
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV-DNA	Hepatitis B Virus - DNA
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
ICF	Informed Consent Form
IGRA	Interferon Gamma Release Assay
IRR	Infusion-Related Reaction
ISR	Injection Site Reaction
ITT	Intent-to-treat
IV	Intravenous
IWRS	Interactive Web Response System
JAK	Janus kinase
LLN	Lower Limit of Normal
LLT	Lowest Level Term

LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MNAR	Missing Not at Random
N/A	Not Applicable
NAb	Neutralizing Antibody
NRR	Not Reported Result
NYHA	New York Heart Association
PD	Pharmacodynamic
PFS	Pre-filled Syringe
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan [REDACTED]
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SES-CD	Simplified Endoscopic Activity Score for Crohn's Disease
SF	Stool Frequency
SI	System International
SIAQ	Self-Injection Assessment Questionnaire
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SIR	Systemic Injection Reaction
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Table, Listing and Figure
ULN	Upper Limit of Normal
USA	United States of America
VAS	Visual Analogue Scale
WHO	World Health Organization

1. ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of CELLTRION, Inc (hereinafter referred to as “CELLTRION”). The clinical monitoring, medical writing and bioanalytical lab analysis are being performed under contract with [REDACTED], in collaboration with CELLTRION. Endoscopic image analysis is being performed under contract with [REDACTED] in collaboration with CELLTRION. Pharmacokinetics analysis is being performed under contract with [REDACTED] in collaboration with CELLTRION. The data management and statistical analysis are being performed by CELLTRION.

2. INTRODUCTION

This statistical analysis plan (SAP) defines the statistical methods and data presentations to be used by CELLTRION Clinical Statistics team in the analysis and presentation of data for CELLTRION study number CT-P13 3.8, entitled as “A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study to Evaluate the Efficacy and Safety of the Subcutaneous Injection of CT-P13 (CT-P13 SC) as Maintenance Therapy in Patients With Moderately to Severely Active Crohn’s Disease”.

The following clinical study reports (CSR) will be generated during the entire study period:

- A report of all data for each patient up to Week 54 including the usability and exposure data for patient who self-injected a study drug via auto-injector (AI) and has usability assessments for AI up to Week 62. The following data will be included.

	Ongoing at Week 54	Withdrawal on or before Week 54
Scheduled Visit (excluding EOS)	Up to Week 54	All available data
EOS	Not Applicable	
Unscheduled Visit	On or before Week 54 visit date for each patient *	All available data up to the latest date of the all patients' Week 54 visit date.
Non-visit based data (e.g. adverse events and medications)	All available data having a start date/or imputed start date on or before the Week 54 visit date for each patient *.	

Note: In case of usability and exposure for AI data for patient who self-injected a study drug via AI and has usability assessments for AI up to Week 62, “Week 54” above will be replaced to “Week 62”. Exposure for AI data will be presented in listing. Exceptionally, colonoscopy data that is performed between Week 54 and Week 56 study drug administration date could be included in the analysis as a result at Week 54 based on determination during the blinded DRM.

* For patients who are ongoing and skip the Week 54 visit, the latest of the Week 54 visit date for other patients will be used instead of the Week 54 visit date for each patient.

- A report of all data for each patient after completion of all visits

This SAP covers all specified analysis and is based on the following documents:

- Study Protocol Version 6.0 – 3rd August 2020
- Study Protocol Version 6.0 Country specific A.0 – 4th August 2020
- Study Protocol Version 6.0 Country specific B.0 – 4th August 2020
- Study Protocol Version 6.0 Country specific C.0 – 4th August 2020
- Study Protocol Version 6.0 Country specific D.2 – 8th July 2021
- Unique Case Report Form (CRF) Version 5.1 – 28th January 2021

Table, Listing and Figure (TLF) mock shells will be presented as an addendum to this document.

3. STUDY OBJECTIVES

Primary and secondary objectives are described as below.

3.1. Primary Objective

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

3.2. Secondary Objective

The secondary objective of this study is to evaluate additional efficacy, PK, PD, usability (excluding Protocol including Country Specific A and C), and overall safety including immunogenicity.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This is a randomized, placebo-controlled, double-blind, multicenter, parallel group, Phase 3 study, designed to evaluate the efficacy, PK, PD, usability (excluding Protocol country specific A and C), and safety of CT-P13 SC as maintenance therapy in patients with moderately to severely active Crohn's Disease (CD) who have had an inadequate response to conventional therapy. Approximately 600 patients with moderately to severely active CD will be enrolled in the open-label Induction Phase. All enrolled patients will receive induction doses of CT-P13 5 mg/kg via IV infusion at Weeks 0, 2, and 6. After the patients receive 3 full doses of CT-P13 via IV infusion, those patients classified as a Crohn's Disease Activity Index (CDAI)-100 responder at Week 10, and also have no safety concerns at the investigator's discretion will be randomly assigned before Week 10

treatment in a 2:1 ratio into either CT-P13 SC or Placebo SC treatment arms. Patients classified as non-responders at Week 10 will not continue the study drug treatment.

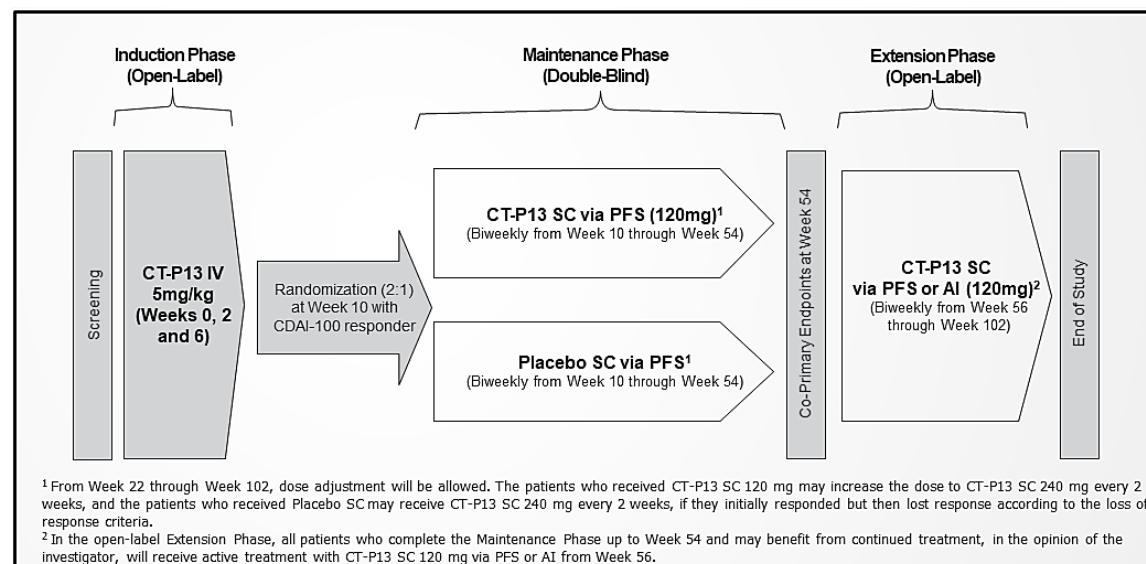
It is estimated that at least 360 patients (240 in CT-P13 SC group and 120 in Placebo SC group) will enter the double-blind Maintenance Phase. The Maintenance Phase treatment will continue up to Week 54 and the subsequent open-label Extension Phase treatment will continue up to Week 102. In the open-label Extension Phase, all patients will receive CT-P13 SC.

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

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

The overview of study design is illustrated in [Figure 1](#).

Figure 1. Study Design Overview



Abbreviations: AI, auto-injector; CDAI, Crohn's Disease Activity Index; IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

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

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

Treatment Period:

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

In the open-label Induction Phase, the patients who meet all of the inclusion criteria and none of the exclusion criteria will be enrolled on Day 0 (Week 0). All enrolled patients will receive a 2-hour CT-P13 IV infusion (5 mg/kg) during onsite visits at Weeks 0, 2, and 6 as induction treatments. Patients who are classified as a CDAI-100 responder at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and for whom there are no safety concerns based on the investigator's discretion will be randomly assigned to receive either CT-P13 SC or Placebo SC, before treatment on Day 70 (Week 10).

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

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

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

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

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

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

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

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

Loss of response is defined as following: an increase in CDAI of ≥ 100 points from the Week 10 CDAI score with a total score ≥ 220 . On the day of initiation of dose adjustment, blood samples for PK and immunogenicity analysis will be collected before study drug administration. The patients whose dose adjust to CT-P13 SC 240 mg prior to Week 54 will be considered as non-remitter or non-responder at Week 54 in the analysis of co-primary endpoints and key secondary endpoints.

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

Patients will comply with all appropriate visits and assessments. Patients will return to the study center at predefined time intervals for clinical assessments and blood sampling. At each visit, patients will be questioned about adverse events (AEs) and concomitant medications and will be monitored for the clinical signs and symptoms of tuberculosis (TB) and/or cardiovascular disease. The efficacy, PK, PD, usability (excluding Protocol country specific A and C), and safety assessments will be performed at the time points specified in the schedule of events ([Appendix 1](#) and [Appendix 2](#)).

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

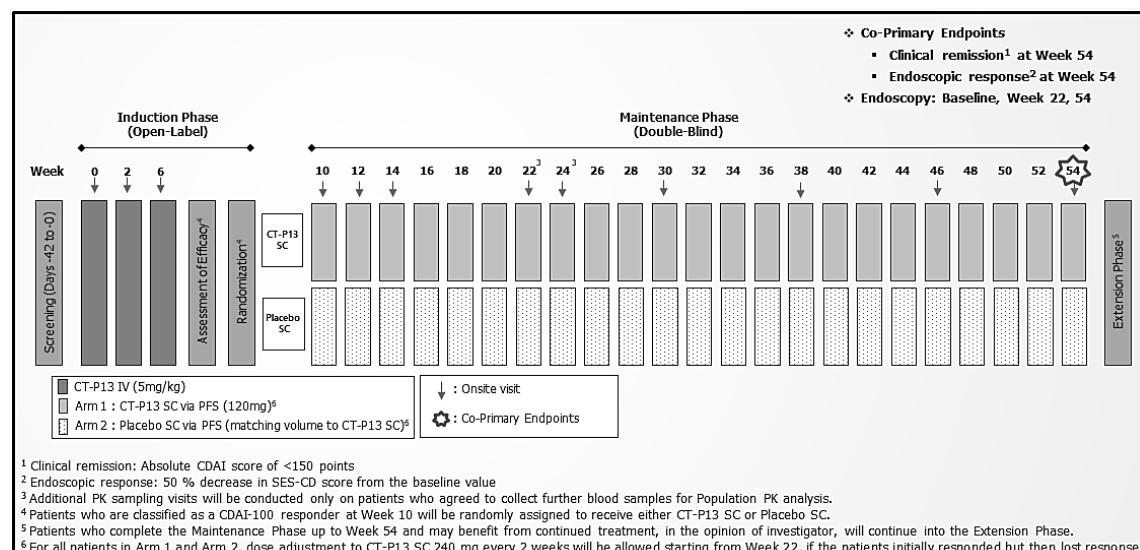
CT-P13 SC via AI will be self-injected in at least 50 patients who are entered into the Extension Phase. The Week 56 visit will be only reserved for the patients who will self-inject CT-P13 SC via AI. For the patients who will self-inject CT-P13 SC via AI, the initial training for self-injection of CT-P13 SC via AI will be conducted at Week 56 prior to the first AI injection. After proper training in AI injection technique, patient will self-inject with CT-P13 SC via AI at home or study center at the scheduled administration week in the Extension Phase. If investigator or designee determines or the patient requests it, additional training can be given prior to the self-injection of CT-P13 SC via AI.

End-of-Study visit: The EOS visit will occur 4 weeks after the last dose of study drug is received. For patients who early discontinue the study drug before administration of CT-

P13 SC or Placebo SC at Week 10, the EOS visit will occur 8 weeks after the last dose of CT-P13 IV is received.

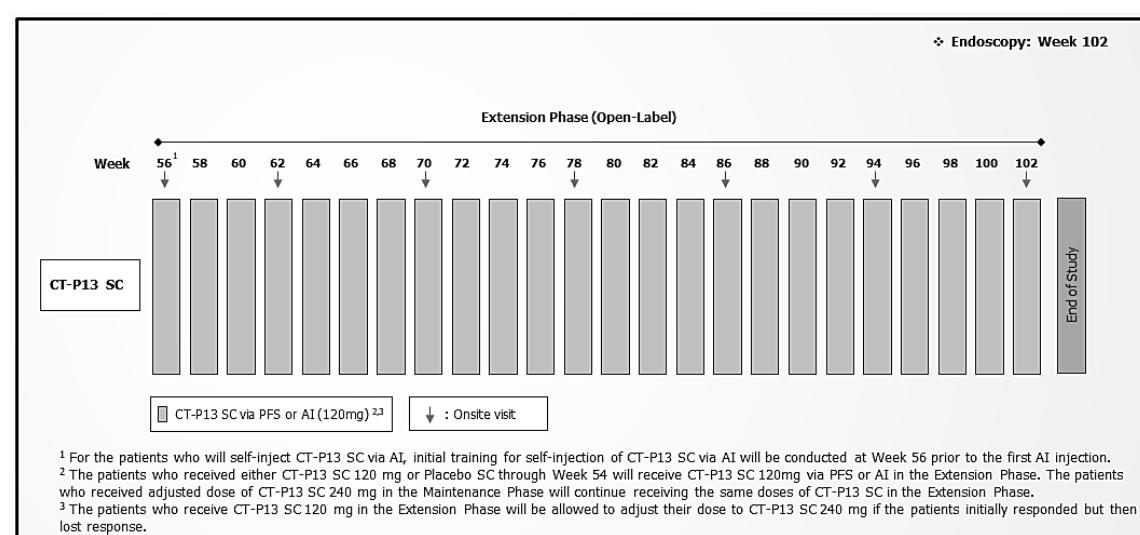
The study design for each treatment phase is illustrated in [Figure 2](#) and [Figure 3](#).

Figure 2. Study Design for Induction and Maintenance Phase



Abbreviations: CDAI, Crohn's Disease Activity Index; IV, intravenous; PFS, pre-filled syringe; PK, pharmacokinetics; SES-CD, simplified Endoscopic Activity Score for Crohn's Disease; SC, subcutaneous

Figure 3. Study Design for Extension Phase



Abbreviations: AI, auto-injector; PFS, pre-filled syringe; SC, subcutaneous

4.2. Country Specific Study Design

The changes in study design compared to Section 4.1 and differences in usability assessment by country specific protocol are described in this section.

4.2.1. Protocol including Country Specific A

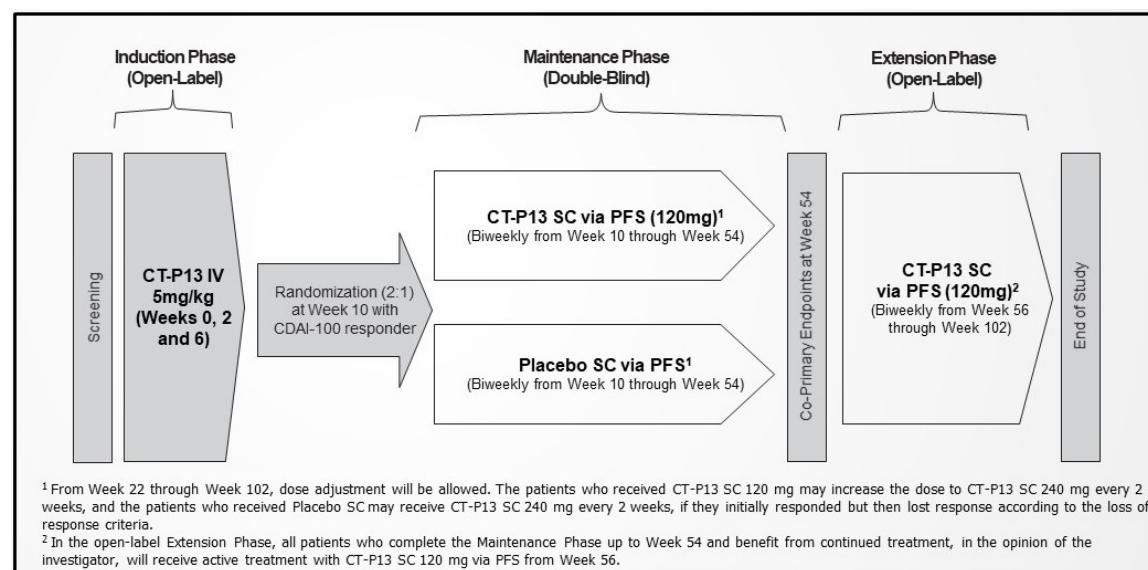
The changes in study design are excluding contents for AI (excluding contents are marked with “-”):

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

~~CT-P13 SC via AI will be self injected in at least 50 patients who are entered into the Extension Phase. The Week 56 visit will be only reserved for the patients who will self inject CT-P13 SC via AI. For the patients who will self inject CT-P13 SC via AI, the initial training for self injection of CT-P13 SC via AI will be conducted at Week 56 prior to the first AI injection. After proper training in AI injection technique, patient will self inject with CT-P13 SC via AI at home or study center at the scheduled administration week in the Extension Phase. If investigator or designee determines or the patient requests it, additional training can be given prior to the self injection of CT-P13 SC via AI.~~

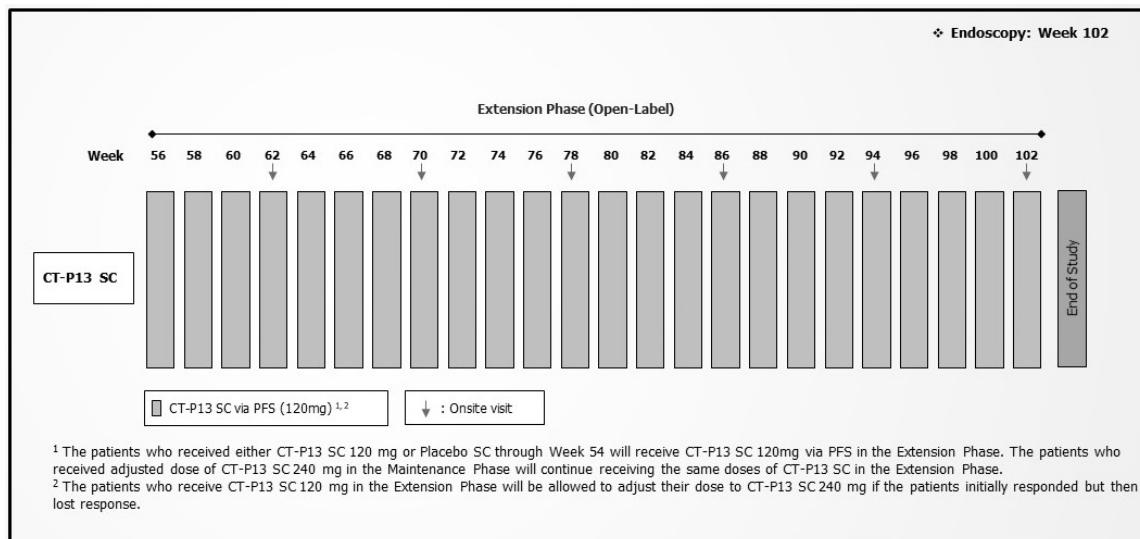
The overview of study design and study design for extension phase are illustrated in [Figure 4](#) and [Figure 5](#).

Figure 4. Study Design Overview (Protocol including Country specific A)



Abbreviations: CDAI, Crohn's Disease Activity Index; IV, intravenous; PFS, pre-filled syringe; SC, subcutaneous

Figure 5. Study Design for Extension Phase (Protocol including Country specific A)



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

Usability assessment for PFS and AI will be not performed.

4.2.2. Protocol including Country Specific B

There is no change in study design.

Usability assessment for PFS and AI will be performed.

4.2.3. Protocol including Country Specific C

The changes in study design are same as protocol including country specific A ([Section 4.2.1](#)).

Usability assessment for PFS and AI will be not performed.

4.2.4. Protocol including Country Specific D

The changes in study design are same as protocol including country specific A ([Section 4.2.1](#)) and additionally excluding the contents for injection by another person (excluding contents are marked with “-”):

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

~~be administered by another person, such as a family member or friend who is trained properly by investigator or designee.~~

Usability assessment only for PFS (not AI) will be performed.

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized by using descriptive statistics: the number of observations (n), mean, standard deviation (SD), median, minimum and maximum unless otherwise specified. The descriptive statistics will be calculated using raw data before rounding although rounded values are listed. The following rules will be followed with regard to the number of decimal places:

- Minimum and maximum will be displayed without rounding from values in the source listing.
- Mean, median, geometric mean and percent coefficient of variation (CV%) will be rounded to one more decimal place than the maximum decimal place of values in the source listing. If the minimum value from the data is zero, then the geometric mean will not be calculated.
- SD and Standard Error (SE) will be rounded to one more decimal place than mean.

Categorical data will be summarized in a frequency table showing the numbers and percentages of patients. Percentages will be rounded to one decimal place and will be suppressed when the count is zero. The denominator for all percentages will be the number of patients within the treatment group for the population of interest, unless otherwise specified.

Point estimate and confidence interval (CI) obtained from statistical procedures will be presented using the same number of decimal places as mean for continuous data or percentage for categorical data. P-value obtained from statistical procedures will be displayed to four decimal places if the value is greater than 0.0001, otherwise <.0001.

In addition, data collected at unscheduled and EOS visits will also not be summarized in visit-based tables, unless otherwise specified. But all data will be displayed in listings. Unless otherwise specified, listings will be sorted by the treatment group, patient number, and visit, if applicable. In cases where more ordering is required, other variables will be included in the sort order as applicable.

For the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality sign will be displayed, unless otherwise specified.

5.1. Software

All analyses will be conducted using [REDACTED]

[REDACTED] PK parameters will be calculated by noncompartmental methods using the appropriate validated software such as [REDACTED]

5.2. Sample Size

The sample size of 360 patients (240 in the CT-P13 SC group and 120 in the Placebo SC group) is estimated to provide at least 90% statistical power to detect a statistically significant clinical effectiveness of CT-P13 SC in comparison with Placebo SC in the following co-primary endpoints at the 1-sided significance level of 2.5%.

- Clinical remission at Week 54, defined as an absolute CDAI score of <150 points, assuming a treatment difference of 18% and placebo rate of 19%
- Endoscopic response at Week 54 assuming a treatment difference of 26% and placebo rate of 2%

Considering a 40% non-responder rate of CDAI-100 at Week 10 before randomization, a total of approximately 600 patients will be enrolled at Week 0. The number of enrolled patients may be adjusted based on the actual number of randomized patients at Week 10.

A total sample size of 360 patients provides 89% statistical power for CDAI-100 response at Week 54, one of the key secondary endpoints, under the assumption of a treatment difference of 18% and placebo rate of 28% at the 1-sided significance level of 2.5%. Key secondary endpoints other than CDAI-100 response at Week 54 are not applicable for power calculation due to lack of relevant references. However, minimum detectable effect sizes with the sample size of 360 patients and at least 80% statistical power for other key secondary endpoints are as follows at the 1-sided significance level of 2.5%:

- 11% for clinical remission at Week 54, defined as an average worst daily abdominal pain score of ≤ 1 (using 4-point scale) and an average loose/watery stool frequency score of ≤ 3 (of Type 6 or Type 7 on Bristol Stool Form Scale [BSFS]) with no worsening in either score compared with the baseline value, assuming a placebo rate of 6%
- 9% for endoscopic remission at Week 54 assuming a placebo rate of 3%

For corticosteroid-free remission at Week 54, minimum detectable effect size with the sample size of 90 patients and at least 80% statistical power is 29% at the 1-sided significance level of 2.5% assuming a placebo rate of 10%.

5.3. Randomization, Stratification, and Blinding

An Interactive Web Response System (IWRS) will be used for the randomization. Biostatistician will generate the randomization schedule for the IWRS, which will link sequential patient randomization numbers to treatment codes. Patients classified as a CDAI-100 responder at Week 10 after receiving 3 full doses of CT-P13 via IV infusion and have no safety concern based on the investigator's discretion will be randomized in a 2:1 ratio to receive either CT-P13 SC or Placebo SC, before starting treatment on Week 10. The randomization will be stratified by previous exposure to biologic agent and/or JAK inhibitors (used or not used), use of treatment with oral corticosteroids at Week 0 (used or not used) and clinical remission at Week 10 (remitter or non-remitter by CDAI score). Permuted block design will be used to randomize patients to treatment groups, where within each block the same pre-specified ratio of patients will be allocated to the treatment groups. The block size will not be revealed.

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

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

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

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

5.4. Population of Analysis

The following patient analysis populations are defined: Intent-to-Treat (ITT), All-randomized, Per-protocol (PP), Pharmacokinetic (PK), Pharmacodynamics (PD), Usability for PFS, Usability for AI and Safety.

Determinations on the population will be made at the blinded Data Review Meeting (DRM) held in accordance with International Council for Harmonisation Technical Requirements for Registration of Pharmaceuticals for Human Use harmonised tripartite guideline E9.

Analysis of the Safety and PP Populations will be performed according to actual treatment group. The populations except for Safety and PP Populations will be analyzed according to the treatment they were randomized to at Week 10. The actual treatment group will be assigned according to their treatment actually administered during Double-blind Maintenance Phase even if there is a discrepancy between the treatment actually administered and the randomized group. If there is a patient with such a discrepancy, the patient receiving at least one dose of CT-P13 SC prior to initiation of dose adjustment during Double-blind Maintenance Phase will be treated as CT-P13 SC treatment group. All other patients will be treated as Placebo SC treatment group.

For randomized patients, data before randomization at Week 10 will be displayed under the treatment group based on randomized or actual administered study drug. If a patient discontinues the study before the randomization at Week 10, the patient will be listed under treatment group of ‘Not Applicable’ and will not be included in summary tables.

The number of patients in each analysis population will be tabulated by the treatment group. A listing will also be produced displaying data on ITT Population.

5.4.1. Intent-to-Treat Population

The ITT Population is defined as all enrolled patients. A patient will be considered to have enrolled if it is recorded as ‘Yes’ to ‘Is the patient eligible to be enrolled in this study?’ on the ‘Screening Pass/Fail’ page of the eCRF. Some of listings will be generated on the ITT population to include patients who discontinued the study prior to randomization at Week 10.

5.4.2. All-randomized Population

The All-randomized Population is defined as all randomly assigned patients at Week 10, regardless of whether or not any study drug dosing was completed. This will therefore include all patients who have been allocated randomization ID at Week 10 based on ‘Randomization’ page of eCRF. The All-randomized Population will be used for analysis of co-primary and key secondary endpoints.

5.4.3. Per-protocol Population

The PP Population is defined as all randomly assigned patients who receive at least one full dose of study drug at Week 10 or thereafter prior to Week 54 and who have at least one efficacy evaluation result after Week 10 treatment and who do not have any major protocol deviation that is relevant to efficacy analysis. The PP Population will be used to provide supportive results of co-primary and key secondary endpoints.

A patient will be considered as receiving full dose if the total dose administered (mg) of the patient is equal to prescribed dose (mg) based on ‘Study Drug Administration for SC’ page of eCRF.

A patient will be considered as having an efficacy evaluation result if the patient has a non-missing result from at least one of the following assessments:

- CDAI score
- Average Worst Daily Abdominal Pain (AP) and Loose/Watery Stool Frequency (SF) score
- Simplified Endoscopic Activity Score for Crohn’s Disease (SES-CD) score
- Patient Global Scale
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

5.4.4. Pharmacokinetic Population

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

5.4.5. Pharmacodynamic Population

The PD Population is defined as all randomly assigned patients who receive at least one full dose of study drug at Week 10 or thereafter and who have at least one PD result (Fecal calprotectin [FC] or C-reactive protein [CRP]) after Week 10 treatment.

5.4.6. Usability Population for PFS

The Usability Population for PFS is defined as all randomly assigned patients who self-injected at least one (partial or full) dose of study drug via PFS from Week 14 to 22 and who have at least one usability assessment in Maintenance Phase.

Usability assessments are as below:

- PRE- Self-Injection Assessment Questionnaire (SIAQ)
- POST-SIAQ
- Self-injection Assessment Checklist
- Device Integrity

A patient will be considered to have self-injected a study drug if the following conditions are met based on the ‘Study Drug Administration for SC’ page of the eCRF.

- Patient is checked ‘Self injection’ in first and/or second injection type
- Patient is recorded as study drug administered or Date of administration is recorded

5.4.7. Usability Population for AI

The Usability Population for AI is defined as all randomly assigned patients who self-injected at least one (partial or full) dose of study drug via AI from Week 56 to 62 and who have at least one usability assessment in Extension Phase.

5.4.8. Safety Population

The Safety Population is defined as all randomly assigned patients who receive at least one (partial or full) dose of study drug at Week 10 or thereafter. A patient will be considered to have received a study drug if the patient is recorded as study drug administered or if a date of administration is recorded on the ‘Study Drug Administration for SC’ page of the eCRF.

5.5. Definition of Baseline

The baseline value will be considered to be the last non-missing value before the first administration, unless otherwise specified. Post-baseline values will be considered to be all values collected after the first administration.

5.6. Protocol Deviations

Protocol deviation will be categorized as “major” or “minor”. Category of protocol deviation will be identified during the blinded DRM. A major protocol deviation is one that may affect the interpretation of efficacy results or the patient’s rights, safety or welfare.

Major protocol deviations and population to be excluded are defined as follow (but not limited to):

- Mis-randomizations (PK and PP Population): Patients who received the other treatment (prior to initiation of dose adjustment) than that to which they are assigned before Week 54 will be defined as mis-randomized.
- Significant GCP non-compliance (All populations): CELLTRION will identify the sites which have been closed or patients who have been affected due to suspected scientific misconduct and/or serious GCP non-compliance.
- Non-compliance of inclusion or exclusion criteria which affect the efficacy results (PP Population): CELLTRION will identify via review of data sourced from the site monitoring database.
- Randomization without CDAI-100 response at Week 10 (PP Population): Patients who are classified as non-responder at Week 10 after applying the data handling

rules defined in [Section 5.7.2](#) regardless of eCRF data, among the patients randomized at Week 10.

- Prohibit Therapy during Treatment Period which affect the efficacy results (PP Population): Patients who have received them which affect the efficacy results, among the prohibit medications or treatments described in Section 5.9 of the protocol. The list of prohibit medications or treatments which affect the efficacy results will be determined during the blinded DRM.
- Other deviation which affect the efficacy results (PP Population): The list of other deviation which affect the efficacy results will be determined during the blinded DRM.

The major protocol deviations will be summarized for the All-randomized Population by treatment group. A listing of major protocol deviations for each patient will also be provided by treatment group for the ITT Population.

5.7. Data Handling Rules

5.7.1. Dose Adjustment

For patients with dose adjustment, data of the patients will be included in the summary as following [Table 1](#), unless otherwise specified:

Table 1. Data Analysis Scope by endpoints

Endpoint	CT-P13 SC group *	Placebo SC group *
Efficacy, PK and PD	Only data collected before initiation of dose adjustment	
Safety and Immunogenicity (Including Treatment and Medication)	All data collected regardless of dose adjustment	Only data collected before initiation of dose adjustment
Usability and ADE	All data collected regardless of dose adjustment	

* The randomized or actual treatment group will be determined by the analysis population.

Data collected before initiation of dose adjustment will be identified using the following [Table 2](#):

Table 2. Rule of data collected before initiation of dose adjustment

		Time collected	Time not collected
Visit based data (including EOS, Unscheduled)	Assessments to be performed at Pre-dose	Assessment date/time <= Initiation of dose adjustment date/time *	Assessment date <= Initiation of dose adjustment date *
	Assessments to be performed at Post-dose **	Assessment date/time < Initiation of dose adjustment date/time *	Assessment date < Initiation of dose adjustment date *

Non-visit based data (e.g. adverse events and medications)	Event start date/time (or imputed start date/time) < Initiation of dose adjustment date/time *	Event start date (or imputed start date) <= Initiation of dose adjustment date *
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* Date (or Date/time) of initiation of dose adjustment will be taken as the earliest date (or date/time) of CT-P13 SC administration satisfying the following two conditions:

- Recorded as '240 mg' to 'Total Dose Administered' on the 'Study Drug Administration for SC' page of the eCRF
- Recorded as 'Yes' to 'Does a patient adjust the dose at this visit? or Did a patient adjust the dose at least once?' on the 'Visit Date' page of the eCRF.

** including electrocardiograms

All data will be displayed in listing along with a flag indicating data after initiation of dose adjustment.

5.7.2. Calculation of the CDAI score

The CDAI score is composed of 8 components for the patient's CDAI diary entries (worst daily abdominal pain, number of liquid (watery) or very soft (loose) stools and general well-being), hematocrit results, and assessments performed by the site investigator including but not limited to physical examination, vital signs, and weight.

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 at least 7 consecutive days immediately prior to diary review and CDAI assessment date, except when the CDAI assessment is performed on the same date of colonoscopy procedure.

A patient is given the CDAI Diary at each scheduled visit. Patient is asked to complete the CDAI diary for 7 consecutive days prior to the next scheduled visit except when CDAI assessment is performed at the same date as colonoscopy procedure. If bowel preparation is planned for colonoscopy procedure, patient is asked to complete the CDAI diary for 7 consecutive days not overlapping with 3 days of colonoscopy procedure. In order to secure diary compliance, information on the date of next visit schedule as well as the date when the diary should be completed is provided with the CDAI diary. In case of change in the visit schedule, patient can complete the diary for more than 7 days using spare pages within the diary. However, site staff should only enter the most recent 7 days of CDAI diary to the eCRF. If any of the most recent 7 days in the diary overlap with the dates of colonoscopy procedure, site staff should replace the overlapped dates with the other recent diary dates in case there are replaceable dates.

To minimize missing data, even if the date of some CDAI diaries collected in eCRF as above is out of the diary instruction, the CDAI diaries will be considered valid for the CDAI score calculation if the following conditions are met:

- Screening: CDAI diaries are recorded within 14 days prior to the date of CDAI assessment.

- Other scheduled visits: CDAI diaries are recorded after the date of study drug administration of the previous visit.
- CDAI diary dates do not overlap with either the day of bowel preparation (the day before colonoscopy procedure) or the day of colonoscopy procedure.

Subscores for the components of Worst daily Abdominal pain, Number of liquid (watery) or very soft (loose) stools and General well-being will be calculated as (sum of valid diary scores \times (7 / number of valid diary days)). The number of valid diary days should be 7 for Screening and 4 or more for other visits. Otherwise, the subscores will be considered missing.

When calculating the CDAI score, local hematocrit results calculated locally using device supplied will be used. For missing results, the local hematocrit result at the last non-missing assessment before a visit for the patient will be used.

If at least one component of CDAI score is missing at a visit after applying the data handling rule, the CDAI score will be considered missing.

5.7.3. Calculation of average worst daily abdominal pain score and average daily loose/watery stool frequency score

The rule of valid diary will be same as calculation of CDAI score (Section 5.7.2). Average scores for the worst daily abdominal pain and daily loose/watery stool frequency from the patient's CDAI diary will be calculated using valid diary scores. The number of valid diary days should be 7 for Screening and 4 or more for other visits. Otherwise, average scores will be considered missing.

5.7.4. Week 54 Colonoscopy Data

When the colonoscopy is not performed at Week 54, another colonoscopy data that is performed between Week 50 and Week 54 study drug administration date will be used as the data for Week 54 in the relevant summary. Colonoscopy data that is performed between Week 54 and Week 56 study drug administration date could be included in the analysis as a result at Week 54 based on the determination during the blinded DRM. In a listing, a flag will be added to the data used instead of the missed Week 54 colonoscopy data.

6. PATIENT DISPOSITION

The total number of patients who were screened and screening failure will be displayed along with the primary reason for screening failure based on the 'Screening Pass/Fail' page of the eCRF.

The reasons for screening failure will be displayed using the following categories and ordering:

- Inclusion/Exclusion Criteria Not Met

- Subject Withdrew Consent
- Other

A listing of patients reported as screening failures will be provided.

The number of patients who were enrolled, treated in each phase, randomized, discontinued in each phase and completed the study will also be displayed on the All-randomized Population along with percentage, if applicable.

Patient disposition will be defined as follows:

- A patient will be considered to have enrolled if it is recorded as ‘Yes’ to ‘Is the patient eligible to be enrolled in this study?’ on the ‘Screening Pass/Fail’ page of the eCRF.
- A patient will be considered to have been treated in the Induction Phase if it is recorded as at least one ‘Yes’ to ‘Was study drug administered?’ on the ‘Study Drug Administration for IV’ page of the eCRF at Week 0, Week 2 and/or Week 6.
- A patient will be considered to be randomized if the patient was allocated a randomization ID at Week 10 based on the ‘Randomization’ page of the eCRF.
- A patient will be considered to have been treated in the Maintenance Phase if it is recorded as at least one ‘Yes’ to ‘Was study drug administered?’ on the ‘Study Drug Administration for SC’ page of the eCRF from Week 10 to Week 54.
- A patient will be considered to have been treated in the Extension Phase if it is recorded as at least one ‘Yes’ to ‘Was study drug administered?’ on the ‘Study Drug Administration for SC’ page of the eCRF on or after Week 56.
- A patient will be considered to have completed the study if it is recorded that they completed (‘Yes’ box checked) on the ‘Study Treatment Termination’ page of the eCRF. Conversely, a patient is considered to have discontinued the study if it is recorded in the ‘Study Treatment Termination’ page of the eCRF that they did not complete (‘No’ box checked). If the patient who is considered to have discontinued the study has received a study drug administration on or after Week 56, the patient will be considered to have discontinued in the Extension Phase, else if the patient who is considered to have discontinued the study has been randomized at Week 10 and has not received a study drug administration on or after Week 56, the patient will be considered to have discontinued in the Maintenance Phase, otherwise, in the Induction Phase.

The total number of patients who discontinued the study in the Induction Phase will be presented by primary reason. The number and percentage of patients who discontinued the study in the Maintenance Phase and Extension Phase will also be displayed by primary

reason for discontinuation and treatment group. The reasons for discontinuation will be displayed using the following categories and ordering:

- Progressive Disease
- Non-responder at Week 10 (Only for Induction Phase)
- Adverse Event
- Protocol Deviation
- Lost to Follow-up
- Death
- Physician Decision
- Withdrawal by Subject
- Pregnancy
- Study Terminated by Sponsor
- Other

In addition, the time on study drug prior to discontinuation will also be summarized using descriptive statistics by treatment group, if applicable, for those patients who have discontinued study treatment prematurely in the Induction Phase, Maintenance Phase or Extension Phase, respectively. The treatment duration in days will be calculated as (Date of last administration - date of first administration + 1).

The date of first administration will be taken as the earliest date recorded on the ‘Study Drug Administration for IV’ page of the eCRF. The date of last administration will be taken as recorded on the ‘Study Treatment Termination’ page of the eCRF.

The patient disposition data collected for the ITT Population will be listed by treatment group.

7. DEMOGRAPHICS, BASELINE, AND BACKGROUND CHARACTERISTICS

7.1. Demographics and Stratification Details

The following demographic measures will be summarized for the All-randomized Population by treatment group: Age (years); Gender (male, female); Female fertility status (Pre-Menarche, Surgically Sterilized, Post-Menopausal, Potentially Able to bear Children, Other); Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not allowed by investigator country regulations, Other); Ethnicity (Hispanic or Latino, Non-Hispanic or non-Latino, Unknown); Height (cm), Weight (kg) and Body Mass Index (BMI) (kg/m²) as recorded at the screening.

The following stratification details will also be summarized for the All-randomized Population by treatment group: Previous exposure to biologic agent and/or JAK inhibitors (used or not used); Use of treatment with oral corticosteroids at Week 0 (used or not used); Clinical remission at Week 10 (remitter or non-remitter by CDAI score). If there is a

difference for data entered between IWRS and eCRF, the stratification factors will be summarized using the final data collected on the eCRF.

Demographics will be listed for the ITT Population by treatment group. Stratification details will be listed for the All-randomized Population by treatment group.

7.2. Hepatitis B and C and Human Immunodeficiency Virus 1 and 2

The following assessments will be performed at each scheduled visit:

- Hepatitis B Surface Antigen (HBsAg)
- Hepatitis B Surface Antibody (HBsAb)
- Hepatitis B Core Antibody (HBcAb)
- Hepatitis B virus (HBV)- DNA
- Hepatitis C Antibody
- Hepatitis C virus (HCV)- RNA
- Human Immunodeficiency Virus (HIV) 1&2

Viral serology results will be summarized at Baseline by treatment group and parameter for the All-randomized Population. A listing will be produced by treatment group for the ITT Population. If confirmatory test is conducted, the result of the confirmatory test will be used for the summary. All collected results will be listed.

7.3. Medical History

Medical history is captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 25.0 or higher). Medical history will be summarized by treatment group, system organ class (SOC) and preferred term (PT) for the All-randomized Population. The total number of medical history and the number and percentage of patients with at least one medical history will also be presented in the table by treatment group. Medical history will also be listed for the ITT Population by treatment group.

7.4. Crohn's Disease History

Active Crohn's Disease (CD) history is captured at the Screening. The time since active CD diagnosis will be tabulated for the All-randomized Population by treatment group. Time (years) since active CD diagnosis will be calculated as [(date of first administration – date of diagnosis)/365.25]. If an incomplete active CD diagnosis date is recorded for a patient this will be imputed using the latest possible date. That is, if the day is missing (i.e. XXMAR2022) the date will be the last day of the month (i.e. 31MAR2022). If the day and month are missing (i.e. XXXXX2022), the date will be set to the 31st December (i.e. 31DEC2022). If the imputed date is later than date of first administration, then it will be imputed using the date of first administration. If the whole date is missing, the date will not be imputed and time since active CD diagnosis will not be calculated. Active CD history will also be listed by treatment group for the ITT Population.

7.5. Stool Microbiology

Stool microbiology (enteric pathogens, ova and parasites, and *clostridium difficile* toxin test) will be performed at Screening and at any point in the study when a patient becomes symptomatic, including worsening or return of disease activity, at the investigator's discretion. Analysis will be performed at the central laboratory. All collected results will be listed by treatment group for the ITT Population.

7.6. Inclusion and Exclusion Criteria

Details of Inclusion and Exclusion criteria can be found in Sections 4.2 and 4.3 of the protocol. Inclusion and Exclusion criteria for each patient including date of informed consent will be presented for the ITT Population by treatment group.

The listing will indicate which protocol the patient was recruited under and hence which criteria applied.

8. TREATMENTS AND MEDICATIONS

For patients with dose adjustment, all data collected regardless of dose adjustment for CT-P13 SC group and data collected before initiation of dose adjustment for Placebo SC group will be included in the summary, unless otherwise specified. All data will be displayed in listing along with a flag indicating data after initiation of dose adjustment.

8.1. Prior and Concomitant Medications

All prior and concomitant medications for the treatment of CD, latent TB, and/or hepatitis C (if applicable) from the diagnosis of disease until the EOS visit, will be collected on the eCRF. All medications for other purposes, from within 30 days prior to the first study drug administration (Day 0) or from when the ICF is signed, whichever is earlier, will be collected on the eCRF until the EOS visit. All concomitant medications will also be recorded when any Adverse Drug Reaction (ADR) is ongoing at the EOS visit. All medications will be coded according to the World Health Organization drug dictionary (WHODrug Dictionary Global B3 version March, 2022 or later version).

Medications will be classed as either prior or concomitant. For the purpose of inclusion in prior or concomitant medication tables, incomplete medication start and stop dates will be imputed as follows:

If the stop date is incomplete the following rules will be applied:

- Missing day: Assume the last day of the month.
- Missing day and month: Assume December 31st.
- Missing day, month and year: Leave it as Missing.

In the case of the death of a patient, and the imputed stop date is after the date of death, the stop date will be imputed as the date of death. In addition, if a medication, checked as 'Yes' to 'If stop date is unknown, was this drug stopped before the first administration of study drug (Day 0)?' on the 'Prior & Concomitant Medications' page of the eCRF, has

imputed stop date on or after the date of the first study drug administration, the stop date will be set to one day before the date of the first study drug administration.

If the start date is incomplete the following rules will be applied. If the stop date is incomplete, imputed stop date will be used instead of actual stop date:

- Missing day: Assume the first day of the month.
However, if the partial date and the date of the first study drug administration lie within the same month and year and the date of the first study drug administration is not after the stop date of the medication, set to the date of the first study drug administration. Otherwise, set to stop date of the medication.
- Missing day and month: Assume January 1st.
However, if the partial date and the date of the first study drug administration lie within the same year and the date of first administration is not after the stop date of the medication, set to the date of the first study drug administration. Otherwise, set to stop date of the medication.
- Missing day, month and year: Assume date of the first study drug administration, if not after the stop date for the medication. Otherwise, set to stop date for the medication.

For the missing day imputation, the following examples should be used for reference:

- Example 1:
Medication start: UNJUN2022
Medication stop: 20OCT2022
Date of the first study drug administration: 16OCT2022
Medication start imputed: 01JUN2022
- Example 2:
Medication start: UNOCT2022
Medication stop: 20OCT2022
Date of the first study drug administration: 16OCT2022
Medication start imputed: 16OCT2022
- Example 3:
Medication start: UNOCT2022
Medication stop: 20OCT2022
Date of the first study drug administration: 24OCT2022
Medication start imputed: 20OCT2022

A prior medication is defined as following, and all other medications will be defined as concomitant medication.

- A medication having actual/imputed stop date of medication before date of the first study drug administration, or
- A medication checked as yes to “If stop date is unknown, was this drug stopped before the first administration of study drug (Day 0)” on eCRF.

The prior and concomitant medications will be summarized by treatment group, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and PT along with the total number of prior/concomitant medications and the number and percentage of patients with at least one prior/concomitant medication for the Safety Population. When ATC level 2 for drug class is not available, level 1 will be used instead. The summaries will be repeated in separate tables for concomitant medications in Maintenance Phase. A concomitant medication in Maintenance Phase is defined as follows:

- 1) Patients treated in the Maintenance Phase and not treated in the Extension Phase: a concomitant medication with actual/imputed stop date on or after the Week 10 study drug administration date or marked as ongoing or missing
- 2) Patients treated in both the Maintenance and Extension Phase: a concomitant medication with actual/imputed stop date on or after the Week 10 study drug administration date or marked as ongoing or missing, and actual/imputed start date before the first study drug administration date in the Extension Phase

All prior and concomitant medications will be listed separately along with the Maintenance Phase flag by treatment group for the ITT Population.

8.2. Exposure to Study Drug

The number and percentage of patients with dose administered at each scheduled visit will be summarized by treatment group for the Safety Population. For patients who are not administered with the study drug, the number and percentage of patients with each reason why the dose was not administered (AE, Other) will be displayed by scheduled visit. For patients who were administered the study drug, a table will be provided displaying descriptive statistics of the prescribed dose and actual dose administered by treatment group at each scheduled dose.

Prescribed and actual administered dose per weight (mg/kg) for IV infusion and prescribed and actual administered dose (mg) for SC injection will be summarized. The dose per weight (mg/kg) for IV infusion will be calculated using the Prescribed Dose (mg) and Total Dose Administered (mg) based on the ‘Study Drug Administration for IV’ page of eCRF and Weight (kg) on the ‘Vital Signs’ page of eCRF.

In addition, the total number of doses received and total administered dose (mg) of each patient during the Induction Phase, Maintenance Phase and Extension Phase will be summarized using descriptive statistics by treatment group for the Safety Population.

The number and percentage of patients who received adjusted dose during the Maintenance Phase and Extension Phase on or after Week 22 will be additionally summarized in a table by treatment group and scheduled visit for the Safety Population. The number and percentage of patients who received at least one adjusted dose during each phase will also be included in this summary. A patient will be considered to receive adjusted dose if the actual administered dose that the patient received on or after the date of initiation of dose adjustment is more than CT-P13 SC 120 mg.

A listing will be provided by treatment group for the ITT Population showing the details of study drug administration. This listing will include data collected on the “Kit Number Dispensation” page of eCRF, “Study Drug Administration for IV” page of eCRF and “Study Drug Administration for SC” page of eCRF.

9. EFFICACY ANALYSIS

Efficacy will be assessed by CDAI score, SES-CD score, average AP and SF score, patient global scale and SIBDQ at each scheduled visit.

Colonoscopy will be evaluated at central and local level. Statistical test for the co-primary and key secondary efficacy endpoints based on the colonoscopy (SES-CD) will be conducted using the colonoscopy reading results of central level. Other secondary efficacy endpoints based on the colonoscopy (SES-CD) will be assessed using the both colonoscopy reading results of central and local level.

For the efficacy endpoints related remission or response, the following patients will be considered as non-remitter or non-responder:

- Patients who do not meet the remission or response criteria
- Patients with missing or incomplete data for the evaluation of each endpoint at their scheduled visit of interest, even after applying the data handling rule defined in [Section 5.7](#) (if applicable)
- Patients with dose adjustment to CT-P13 SC 240 mg prior to their scheduled visit of interest

For patients with dose adjustment, only data collected before initiation of dose adjustment for both treatment groups will be included in the summary, unless otherwise specified. All data will be displayed in listing along with a flag indicating data after initiation of dose adjustment.

9.1. Co-primary Efficacy Analysis

The following efficacy parameters are determined as the co-primary efficacy endpoints:

- Clinical remission at Week 54, defined as an absolute CDAI score of <150 points
- Endoscopic response at Week 54, defined as a 50% decrease in SES-CD score from the baseline value

The co-primary endpoints will be tested at the 2-sided significance level of 5% on the All-randomized Population using the p-value from Cochran-Mantel-Haenszel (CMH) test stratified by Previous exposure to biologic agent and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by CDAI score). If both p-values are ≤ 0.05 ,

the statistical significance of both co-primary endpoints will be concluded. If the co-primary endpoints are significant, the fixed sequence procedure will be used for key secondary endpoints in order to preserve the Type I error. For the supportive analysis, the co-primary endpoints analysis will be performed on the PP Population.

The co-primary endpoints will be summarized using frequency table along with the p-value from stratified CMH test, respectively. Difference in proportion between two treatment groups estimated using CMH weights and corresponding 95% stratified Newcombe CI with CMH weights will also be provided.

In addition, for the descriptive comparison of the treatment effect between patients with and without dose adjustment to CT-P13 SC 240 mg prior to Week 54 within CT-P13 SC treatment group, the co-primary endpoints will be summarized by patients with/without dose adjustment in CT-P13 SC treatment group using frequency table without the statistical test, respectively. In this analysis, remitter or responder will be determined as per remission or response criteria regardless of dose adjustment.

9.1.1. Sensitivity Analysis

A sensitivity analysis will be performed on the co-primary efficacy endpoints, utilizing Fisher's exact test and a logistic regression model.

Fisher's exact test will be performed on the All-randomized Population. The difference of proportions between two treatment groups and corresponding 95% exact CI ([Chan and Zhang 1999](#)) will be presented along with p-value obtained from the Fisher's exact test.

A logistic regression model with treatment as a fixed effect and Previous exposure to biologic agent and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by CDAI score) as covariates will also be performed on the All-randomized Population. Difference in proportion and its 95% CI estimated using Delta method will be presented along with p-value for treatment obtained from the logistic regression model.

In addition, to assess robustness of co-primary efficacy findings with respect to missing data, tipping point analysis will be conducted on the All-randomized Population. The following patients will be considered as having missing result.

- Patients with missing or incomplete data for the evaluation of each endpoint at Week 54, even after applying the data handling rule defined in [Section 5.7](#) (if applicable)
- Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54

Stratified CMH test, the same method for the co-primary endpoints analysis, will be performed by gradually increasing the number of remitter or responder for each group starting with the scenario where all patients with missing result are non-remitters or non-

responders up to the scenario where all patients with missing result are remitters or responders. All p-values calculated from the stratified CMH test for the difference between two proportions (CT-P13 SC and Placebo SC) will be displayed as a shift table. The results from tipping point analysis will also be presented using 2-dimensional plot.

In order to evaluate the impact of the war in Ukraine, a sensitivity analysis will be performed on the co-primary endpoints by excluding war-affected patients in Ukraine and excluding all patients in Ukraine, respectively. The analysis will be performed using the same method as co-primary endpoints on the All-randomized Population. War-affected patients in Ukraine will be defined as patients who meet the following two conditions:

- Site location: Study site located in Ukraine
- Randomization date: Randomization date within 44 weeks (308 days) before Russian invasion of Ukraine on 24 February 2022

9.1.2. Subgroup Analysis

For the co-primary endpoints, subgroup analyses will be performed using the same method for the co-primary endpoints on the All-randomized Population. For each specific subgroup, if there are not enough patients (i.e., <5% All-randomized Population), the corresponding analyses will not be performed. The following are the pre-defined subgroups:

- Gender (Male, Female)
- Age (<35 years, \geq 35 years)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Not Allowed by Investigator Country Regulations, Other)

9.2. Key secondary Efficacy Analysis

The following efficacy parameters are determined as the key secondary efficacy endpoints, and the fixed sequence procedure will be used for key secondary endpoints in order to preserve the Type I error in the following order in case the statistical significance of the co-primary efficacy endpoints is declared:

- CDAI-100 response at Week 54, defined as a decrease in CDAI score of 100 points or more from the baseline value
- Clinical remission at Week 54, defined as an average worst daily abdominal pain score of ≤ 1 (using 4-point scale) and an average daily loose/watery stool frequency score of ≤ 3 (of Type 6 or Type 7 on BSFS) with no worsening in either average score compared with the baseline value

- Endoscopic remission at Week 54, defined as an absolute SES-CD score of ≤ 4 and at least 2-point reduction from the baseline value with no Segment sub-score of >1
- Corticosteroid-free remission at Week 54, defined as being in clinical remission (by an absolute CDAI score of <150) in addition to not receiving corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at Baseline. The corticosteroid is defined as follows:
 - 1) ATC level 2 = “CORTICOSTEROIDS FOR SYSTEMIC USE” or Preferred Term in (“BUDESONIDE”, “DEXAMETHASONE”, “METHYLPREDNISOLONE ACEPONATE”, “PREDNISOLONE”, “DEXAMETHASONE DIPROPIONATE”, “DEXAMETHASONE”, “BECLOMETASONE”, “HYDROCORTISONE”), and
 - 2) Indication not including “Premedication”, and
 - 3) Route:
 - 3-1) Route for Baseline: including oral only
 - 3-2) Route for Week 54: all route excluding topical administration (RESPIRATORY[INHALATION])

For the comparison between treatment groups, the key secondary endpoints will be tested at the 2-sided significance level of 5% on the All-randomized Population using the p-value from the CMH test stratified by Previous exposure to biologic agent and/or JAK inhibitors (used or not used), Use of treatment with oral corticosteroids at Week 0 (used or not used) and Clinical remission at Week 10 (remitter or non-remitter by CDAI score). The first key secondary endpoint will be tested only if the co-primary endpoints are statistically significant, and the next key secondary endpoint will be tested only if the previous key secondary endpoint is statistically significant. For the supportive analysis, the key secondary endpoints analysis will be performed on the PP Population.

The key secondary endpoints will be summarized using frequency table along with the p-value from stratified CMH test, respectively. Difference in proportion between two treatment groups estimated using CMH weights and corresponding 95% stratified Newcombe CI with CMH weights will also be provided.

In order to evaluate the impact of the war in Ukraine, a sensitivity analysis will be performed on the key secondary endpoints by excluding war-affected patients in Ukraine and excluding all patients in Ukraine, respectively. The analysis will be performed using the same method as key secondary endpoints on the All-randomized Population.

For the subgroup analyses, the key secondary endpoints will be performed on the All-randomized Population using the same method as key secondary endpoints and pre-defined subgroups as co-primary endpoints ([Section 9.1.2](#)).

For the descriptive comparison of the treatment effect between patients with and without dose adjustment to CT-P13 SC 240 mg prior to Week 54 within CT-P13 SC treatment group, the key secondary endpoints will be summarized by patients with/without dose adjustment in CT-P13 SC treatment group using frequency table without the statistical test, respectively. In this analysis, remitter or responder will be determined as per remission or response criteria regardless of dose adjustment.

9.3. Other Secondary Efficacy Analysis

The following secondary efficacy endpoints will be assessed at each scheduled visit:

- Clinical remission, defined as an absolute CDAI score of <150 points
- Maintenance of clinical remission at Week 54, defined as being in clinical remission by CDAI score of <150 points, among the patients in clinical remission at Week 10
- Sustained clinical remission at both Week 22 and Week 54, defined as an average worst daily abdominal pain score of ≤ 1 (using 4-point scale) and an average loose/watery stool frequency score of ≤ 3 (of Type 6 or Type 7 on BSFS) at both Week 22 and Week 54 with no worsening in either average score compared with the baseline value
- 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
- Maintenance of clinical response at Week 54, defined as being in CDAI-100 response at Week 54, among the patients in CDAI-100 response at Week 10
- Sustained clinical response at both Week 22 and Week 54, defined as a reduction from the baseline value in average worst daily abdominal pain score (using 4-point scale) and/or in average daily loose/watery stool frequency score (of Type 6 or Type 7 on BSFS) at both Week 22 and Week 54
- Endoscopic remission, defined as an absolute SES-CD score of ≤ 4 and at least 2 point reduction from the baseline value with no Segment sub-score of >1
- Endoscopic response, defined as a 50% decrease in SES-CD score from the baseline value
- Patient global scale, defined as a question that asks a patient's position on achieving remission from his or her CD symptoms (Yes or No)

- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The secondary efficacy endpoints listed in this section will be analyzed at each scheduled visit by treatment group on the All-randomized Population. Confidence interval and p-value will be presented for comparison between treatment groups in a descriptive manner with no adjustments for multiple testing.

Binary endpoints will be summarized using frequency table, and difference of proportions between two treatment groups estimated using CMH weights and corresponding 95% stratified Newcombe CI with CMH weights will be presented along with p-value from stratified CMH test. The same stratified analysis used for the analysis of co-primary endpoints will be applied.

Continuous endpoint will be summarized using descriptive statistics of actual value and change from baseline and analyzed using Analysis of Covariance (ANCOVA) presenting a point estimate, p-value and 95% CI for the treatment difference. Covariates for ANCOVA will include stratification factors used for the analysis of co-primary endpoints.

The point estimate, 95% CI and p-value for the difference between treatment groups will be presented only for results after Week 10 randomization.

9.4. Crohn's Disease Activity Index (CDAI)

Clinical response and remission will be assessed by the CDAI score including average AP and SF score. The CDAI score will be calculated at scheduled visits. The 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. The components of CDAI and weighting factors are the following:

Table 3. Crohn's Disease Activity Index

No.	Items	Factor
1	Number of liquid (watery) or very soft (loose) stools ¹	×2
2	Worst daily 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: 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°F (37.8°C) during past week	×20
5	Taking antidiarrheal drugs (including Lomotil, Loperamide or opiates) (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 local hematocrit results 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’.

Adapted from: Best et al.1976

Data handling rules (as defined in [Section 5.7.2](#) and [Section 5.7.3](#)) will be applied for calculation of CDAI score, average AP and SF score. CDAI scores range from 0 - 600. If the weighted sum of components of CDAI score is more than 600, it will be set to 600. Else if the weighted sum of components of CDAI score is less than 0, it will be set to 0.

Descriptive statistics for actual and change from baseline of CDAI score at each scheduled visit will be presented by treatment group for the All-randomized Population.

Also, descriptive statistics for actual and change from baseline of average AP and SF score at each scheduled visit will be presented by treatment group for the All-randomized Population.

All CDAI score information including AP and SF score will be listed by treatment group for the All-randomized Population. AP and SF score will be listed separately.

9.5. Simplified Endoscopic Activity Score for Crohn’s Disease (SES-CD)

Endoscopic response and remission will be assessed by colonoscopy (endoscopic examination of luminal surface of the gastrointestinal tract that may include the rectum, colon, and terminal ileum) using the SES-CD score. SES-CD score is obtained as follows:

Table 4. SES-CD Score

		Rectum	Left Colon	Transverse Colon	Right Colon	Ileum	Subtotal score
Was this section of the intestine	Explored						
	Resected						
	Inaccessible						
Q1. 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)					
Q2. Extent of ulcerated surface	0 = None					
	1 = <10%					
	2 = 10—30%					
	3 = >30%					
Q3. Extent of affected surface	0 = Unaffected segments					
	1 = <50%					
	2 = 50—75%					
	3 = >75%					
Q4. Presence and type of narrowing	0 = None					
	1 = Single, can be passed					
	2 = Multiple, can be passed					
	3 = Cannot be passed					
Segment sub-score						SES-CD

Source: Daperno et al. 2004

Subtotal score consists of the sum of scores for all individual segments: Small Intestine (Ileum) and Large Intestine (Left Colon, Transverse Colon, Right Colon, Rectum) at each assessment. Segment sub-score consists of the sum of scores for all assessments (Q1, Q2, Q3, Q4) at each individual segments. SES-CD score consists of the sum of Segment sub-score for each of the individual segments (Ileum, Left Colon, Transverse Colon, Right Colon, Rectum). When calculating the sum of scores for Subtotal score, Segment sub-score or SES-CD, the missing result due to inaccessible or resected exploration result will be considered as zero. For the central level of colonoscopy, a reader's final SES-CD score which was selected based on the central reading adjudication process will be used in analysis. If the prior segment's section of the intestine is inaccessible or prior segment's presence and type of narrowing is 'Cannot be passed' then subsequent segments will be considered inaccessible.

For the colonoscopies evaluated at central level, the endoscopic videos at Screening, Week 22, Week 54, and, if applicable, EOS (Maintenance Phase) and Unscheduled Visit (Maintenance Phase) will be read in a batch after Week 54. Real-time reading will also be performed for Screening, Week 102, EOS (Extension Phase) and/or Unscheduled visit (Extension Phase). Baseline will be determined using results from batch reading. Summary for Week 22 and Week 54 and summary for Week 102 will use results from batch reading and real-time reading, respectively. Also, data handling rule (as defined in [Section 5.7.4](#)) will be applied for Week 54 Colonoscopy data.

For the central and local level of colonoscopy, descriptive statistics for actual and change from baseline of SES-CD score at each scheduled visit will be presented by treatment for the All-randomized Population, respectively.

For the central and local level of colonoscopy, SES-CD information will be listed by treatment group for the All-randomized Population, respectively.

9.6. Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

The SIBDQ is a quality-of-life questionnaire for patients with inflammatory bowel disease. It has 10 questions measuring physical (systemic and bowel), social, and emotional status. Scores for this questionnaire range from 1 (poorest quality of life) to 7 (best quality of life). The total score will be the sum of the scores obtained for physical, social and emotional status for each patient and visit.

All SIBDQ information will be listed by treatment group for the All-randomized Population.

10. PHARMACOKINETIC ANALYSIS

All PK analysis will be conducted on the PK population unless otherwise specified. For patients with dose adjustment, only data collected before initiation of dose adjustment for both treatment groups will be included in the summary. All data will be displayed in listing along with a flag indicating data after initiation of dose adjustment.

10.1. Serum Concentrations

Blood samples for PK analysis will be collected at pre-dose (prior to the beginning of the study drug administration) of Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102, and within 15 minutes after the end of the study drug infusion of Week 6. In case of initiation of dose adjustment other than scheduled visits, additional blood samples will be collected at pre-dose.

In addition, for patients who agreed to collect further blood samples, additional blood samples for further population PK analysis will also be collected at the following time points.

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

Additional blood samples for further population PK analysis and for initiation of dose adjustment other than scheduled visits will not be used to summarize in tables and figures. In other words, the blood samples collected only at scheduled visits (pre-dose of Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102 and within 15 minutes after the end of the study drug infusion of Week 6) will be used to summarize in tables and figures. However, all data will be presented in the data listing.

Individual serum concentrations, scheduled visit and actual sampling time will be presented in the data listing by treatment group for the All-randomized Population.

Serum concentrations of Infliximab will be summarized using descriptive statistics (n, mean, SD, CV%, geometric mean, minimum, median, and maximum) by treatment group at each scheduled visit and time point for the PK Population. All concentrations below the lower limit of quantification (BLQ) will be indicated in the data listing.

For summary of serum concentration, BLQ prior to the first administration (Week 0) will be set to zero. All other BLQs after study drug exposure will be set equal to Lower Limit of Quantification (LLoQ).

Mean serum concentration versus scheduled visit plots for study drugs will also be presented on both linear and semi-logarithmic scales by treatment group for the PK Population.

10.2. Pharmacokinetic Parameters

The serum PK parameters will be calculated by non-compartmental methods using

The C_{trough} will be assessed up to Week 100 and C_{max} will be assessed at Week 6.

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

To derive PK parameter, all BLQs after the first administration will be set equal to LLoQ. The results of additional blood samples for further Population PK analysis and for initiation of dose adjustment other than scheduled visits will not be used to calculate the C_{trough} . In other words, the C_{trough} will be calculated only using the blood samples collected at scheduled visits (pre-dose of Weeks 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94 and 102).

The PK parameters will be summarized by treatment group using descriptive statistics (n, mean, median, SD, CV%, geometric mean, minimum, maximum) for the PK Population. All data for PK parameters will be listed by treatment group for the All-randomized Population.

11. PHARMACODYNAMIC ANALYSIS

The CRP and FC will be recorded as numeric PD parameters. Descriptive statistics will be provided for the CRP and FC (actual value and change from baseline) for the PD population by treatment group at each scheduled visit. Descriptive statistics will consist of n, mean, SD, SE, CV%, geometric mean, minimum, median and maximum. All PD information will be listed by treatment group for the All-randomized population. In addition, a plot will be presented showing the mean (\pm SE) concentration of the CRP and FC at each scheduled visit for the PD Population by treatment group. In the case where

duplicate measurement are recorded within the same visit, the highest value will be used for summary.

For patients with dose adjustment, only data collected before initiation of dose adjustment for both treatment groups will be included in the summary. All data will be displayed in listing along with a flag indicating data after initiation of dose adjustment flag.

12. USABILITY ANALYSIS

For usability analysis, the experience of self-SC injected medication will be recorded in both the source documents and the eCRF. All usability tables and listings will be generated using all data for the Usability Population – PFS/or AI. Usability will be assessed by the evaluation of PRE- and POST- SIAQ, the observer rating of successful self-injections and completion of all instructions using Self-Injection Assessment Checklist, and device integrity of used PFS and AI by the observer (using a question that asks clear evidence of damage and/or compromised structural or mechanical integrity based on a visual examination [Yes or No]) at each time points specified in the schedule of events. The usability assessment for AI will be performed on at least 50 patients who are entered into the Extension Phase.

For patients with dose adjustment, all data collected regardless of dose adjustment for both treatment groups will be included in the summary and listing.

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

Usability will be assessed using the SIAQ prior to and after self-injection of the study drug. The PRE-SIAQ module and POST-SIAQ module should be completed by the patients.

The PRE-SIAQ module is a 7-item questionnaire that investigates 3 domains of feelings about injections, self-confidence (regarding self-injection), and satisfaction with self-injection. The patients will complete PRE-SIAQ immediately (not exceeding 1 hour) before the administration of the study drug.

The POST-SIAQ module is a 27-item questionnaire that assesses 6 domains of feelings about injections, self-image, self-confidence (regarding self-injection), pain and skin reactions during or after the injection (localized injection site reactions), ease of use of PFS or AI, and satisfaction with self-injection. The patients will complete POST-SIAQ immediately (not exceeding 1 hour) after the administration of the study drug.

Item score will be transformed to obtain a score ranging from 0 (worst experience) to 10 (best experience) for each item, based on below algorithm:

- 1) For 5-point semantic Likert-type scale: Transformed = ([raw score]-1) x 2.5
- 2) For 6-point semantic Likert-type scale: Transformed = ([raw score]-1) x 2

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

The domain scores of PRE and POST module of SIAQ will be summarized using descriptive statistics by each scheduled visit and domain for the Usability population – PFS/or AI, separately. A listing for PRE and POST module of SIAQ will be presented showing the raw scores for each question and domain scores. The domain scores will be displayed to one decimal places.

12.2. Self-injection Assessment Checklist

The patient's ability to successfully follow the steps in the printed instruction for use to self-administer the study drugs will be assessed using the self-injection assessment checklist. The investigator or designee will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection.

The self-injection assessment for PFS will be coded as successful if instructions (P8, P9, and P10), which ask complete dose delivery in the Self-Injection Assessment Checklist, are checked as Yes. The self-injection assessment for AI will be coded as successful if instructions (P8, P9, P10, and P11), which ask complete dose delivery in the Self-Injection Assessment Checklist, are checked as Yes. In addition, the completion of all 13 instructions for PFS and 14 instructions for AI will be assessed from the self-injection assessment checklist.

The summary table will display proportion of patient's successful self-injection and proportion of patient's completion of all instructions, respectively for the Usability population – PFS/or AI. A listing for Self-injection Assessment Checklist will be presented.

12.3. Device Integrity

The structural or mechanical integrity issues of used PFS and AI after the completion of the self-injection will be assessed by the observer using a question that asks clear evidence of damage and/or compromised structural or mechanical integrity based on a visual examination (Yes or No).

The summary table will display proportion of used PFS/or AI devices having structural or integrity issues for the Usability population – PFS/or AI. Only the data from each scheduled visit where patient has self-injected will be included in the summary. A listing for data integrity will be presented along with a flag indicating whether the patient has self-injected.

13. SAFETY ANALYSIS

All safety analyses will be performed in the Safety Population by treatment group presenting data on AEs, clinical laboratory results (clinical chemistry, hematology and urinalysis [including microscopy]), complement (C3, C4) and total hemolytic complement, vital sign measurements, weight, hypersensitivity monitoring via vital sign measurements

(including blood pressure, heart and respiratory rates and body temperature), 12-lead electrocardiograms (ECGs), physical examination findings, signs and symptoms of tuberculosis (TB monitoring, Interferon- γ Release Assay [IGRA] and chest X-ray), monitoring of cardiovascular disease related signs and symptoms, local site pain (using 100 mm Visual Analogue Scale [VAS]), pregnancy tests, NYHA functional classification assessment, and immunogenicity tests.

For patients with dose adjustment, all data collected regardless of dose adjustment for CT-P13 SC group and only data collected before initiation of dose adjustment for Placebo SC group will be included in the summary, unless otherwise specified. All safety data will be listed along with a flag indicating data after initiation of dose adjustment for the ITT Population unless otherwise specified.

13.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug.

A treatment-emergent adverse event (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsen in either intensity or frequency after exposure to study drug.

The Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 or the higher version will be used to code all AEs. AEs will be graded for intensity according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0

If the stop date of an AE is partial or missing the following rules will be applied.

- Missing day (e.g. XXJAN2022): Assume the last day of the month. (e.g. 31JAN2022)
- Missing day and month (e.g. XXXXX2022): Assume December 31st. (e.g. 31DEC2022)
- Missing day, month and year (e.g. XXXXXXXXXX): Leave it as Missing.

If the start date of an AE is partial or missing the following rules will be applied. If the stop date of the AE is partial, imputed stop date will be used instead of actual stop date.

- If the day of an Adverse Event is missing (e.g. XX JAN2022), the month and year of the partial date will be compared to the date of the first exposure to study drug.
 - If the month and year are equal for both dates, the AE start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE.
 - If the month and year are not equal, the AE start date will be imputed as the first day of the month (e.g. 01 JAN2022).

- If the day and month is missing (e.g. XXXXX2022), the year of the partial date will be compared to the date of the first exposure to study drug.
 - If the years of both dates are equal, start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE.
 - If the year is not equal, start date will be imputed as the 1st of January of the partial date year (e.g. 01JAN2022).
- If the AE start date is missing (e.g. XXXXXXXXXX), start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the stop date of the AE.

Listings for AEs will include the following information: SOC, PT and Verbatim term; start and stop date; TEAE flag, study phase (Induction Phase, Maintenance Phase, Extension Phase); intensity (CTCAE Grade 1 to 5); frequency (continuous, intermittent, transient); outcome (recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown); type of sequelae (if result of outcome is Recovered/Resolved with Sequelae); relationship to study drug (unrelated, possible, probable, definite); action taken with study drug (dose not changed, dose increased, dose reduced, drug interrupted, drug withdrawn); any treatment received (no, medication, non-medication treatment: specify, both medication and non-medication treatment: specify the non-medication treatment); whether the event was serious (yes, no); whether the AE is infusion-related reaction/systemic injection reaction (hypersensitivity/anaphylactic reaction) (IRR/SIR), delayed hypersensitivity, localized injection site reaction (ISR), infection, malignancy, adverse device effect (ADE) and Coronavirus Disease 2019 (COVID-19). All AEs will be listed.

In summaries, adverse events will be considered to be related if the relationship is possible, probable, or definite. If relationship or intensity is missing, it will be summarized separately under a missing category.

13.1.1. Incidence of Treatment-Emergent Adverse Events

The TEAEs during the study will be summarized by treatment group and SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the worst intensity recorded at each level of summarization. The total number of events and number of patients with at least one TEAE over all SOCs will also be displayed. The summaries will be repeated in separate tables for TEAEs occurred in Maintenance Phase and Extension Phase, respectively. TEAEs occurred in Maintenance Phase are defined as follows:

- 1) Patients treated in the Maintenance Phase and not treated in the Extension Phase: TEAEs with actual/imputed start date on or after date of Week 10 study drug administration
- 2) Patients treated in both the Maintenance Phase and the Extension Phase: TEAEs with actual/imputed start date on or after date of Week 10 study drug

administration and before the first study drug administration date in the Extension Phase.

TEAEs occurred in Extension Phase are defined as TEAEs with actual/imputed start date on or after the first study drug administration date in the Extension Phase.

The summary will also be repeated in a separate table for TEAEs classified as COVID-19. TEAEs coded with Preferred Terms of ‘COVID-19’, ‘Asymptomatic COVID-19’, ‘COVID-19 pneumonia’ and ‘Coronavirus test positive’ will be included. Detailed information on patients infected with COVID-19 will be presented in an additional information listing.

In addition, TEAEs with PT reported for at least 5% of incidence rate which is rounded to one decimal place in any treatment group will be summarized separately.

Furthermore, the summary will also be repeated in a separate table for TEAEs occurred in the Maintenance Phase by comparing patients with/without dose adjustment to CT-P13 SC 240 mg during Maintenance Phase in CT-P13 SC treatment group.

13.1.2. Deaths

All patients who have a Serious Adverse Event (SAE) with serious criteria of “Death” will be presented in a listing and the following variables will be included; date of first/last dose, date of last visit, date of death, time to death from first/last dose, days on study, TEAE flag, study phase (Induction Phase, Maintenance Phase, Extension Phase), SOC/ PT/ cause of death, whether an autopsy was performed (yes, no), whether a death certificate was completed (yes, no), relationship to study drug. Time (days) to death from first/last dose will be calculated as (date of death – date of first/last dose + 1). In case of death during the study, days on study will be calculated as (date of death – date of first dose +1). Otherwise, days on study will be calculated as (date of last visit – date of first dose +1).

13.1.3. Serious Adverse Events

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

Treatment-Emergent Serious Adverse Events (TESAEs) will be summarized by treatment group and SOC, PT, relationship and intensity/serious criteria, displaying the number and percentage of patients with at least one TESAE using only the most severe SAE recorded at each level of summarization. The total number of events and number of patients with at least one TESAE over all SOCs will also be displayed. The summaries will be repeated in a separate table for TESAEs occurred in Maintenance Phase and Extension Phase, respectively.

The summary will also be repeated in a separate table for TESAEs classified as COVID-19.

All SAEs will be listed including the variables detailed in [Section 13.1](#). Serious criteria and SAE description will be presented in an additional information listing.

13.1.4. Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation

All patients who have a TEAE with an action taken with study drug of “Drug Withdrawn” will be summarized by treatment group and by SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE leading to study drug discontinuation, using only the most severe TEAE recorded at each level of summarization. The total number of events and number of patients with at least one TEAE which led to study drug discontinuation will also be displayed. The summaries will be repeated in a separate table for TEAEs leading to study drug discontinuation and occurred in Maintenance Phase and Extension Phase, respectively.

The summary will also be repeated in a separate table for TEAEs leading to study drug discontinuation classified as COVID-19.

All TEAEs leading to study drug discontinuation will be listed including the variables detailed in [Section 13.1](#).

13.1.5. Treatment-Emergent Adverse Events of Special Interest

The AEs of special interest are as following:

- Infusion-related reaction/systemic injection reaction (hypersensitivity/anaphylactic reaction)
AEs which are classified as Infusion related reaction/Systemic injection reaction will be captured on eCRF pages, and the AE term will be reported Infusion related reaction/Systemic injection reaction, respectively. Cases that are additionally determined as delayed hypersensitivity will be excluded.
- Delayed hypersensitivity
Delayed hypersensitivity will be determined on a case-by-case occasion among IRR/SIR reported case on eCRF prior to the database lock
- Localized injection site reactions
AEs classified as Localized ISR in the eCRF will be included.
- Infection
AEs coded with a System Organ Class of ‘Infections and Infestations’ will be included.
- Malignancies

AEs coded with a System Organ Class of ‘Neoplasms benign, malignant and unspecified (incl cysts and polyps)’ excluding terms which includes ‘benign’ in High Level Group Term (HLGT), High Level Term (HLT), PT and Lowest Level Term (LLT).

The IRR/SIR and delayed hypersensitivity will be summarized together in one table, and other TEAEs of special interest will be summarized in separate tables. These are displayed by treatment group, SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE using only the most severe TEAE recorded at each level of summarization. The total number of events and number of patients with at least one TEAE of special interest will also be displayed. In addition, tables for signs and symptoms regarding IRR/SIR and delayed hypersensitivity and localized ISR will be provided separately by SOC, PT (as coded by MedDRA version 25.0 or higher version) and intensity. All summaries will be repeated in separate tables for TEAEs of special interest occurred in Maintenance Phase and Extension Phase, respectively.

All TEAEs of special interest will be flagged in listings for AEs. TEAEs classified as IRR/SIR, Delayed hypersensitivity and localized ISR will be presented in separate listings including the variables detailed in [Section 13.1](#). Experienced Signs and symptoms will be presented in additional information listings for IRR/SIR and delayed hypersensitivity and localized ISR, separately.

13.1.6. Adverse Device Effect

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

All patients who have a TEAE classified as an ADE will be summarized by treatment group and by SOC, PT, relationship and intensity, displaying the number and percentage of patients with at least one TEAE classified as an ADE, using only the most severe TEAE recorded at each level of summarization. The total number of events and number of patients with at least one TEAE which classified as an ADE will also be displayed.

For patients with dose adjustment, all data collected regardless of dose adjustment for both treatment groups will be included in the summary. All ADEs will be flagged in listings for AEs.

13.2. Clinical Laboratory Evaluations

Clinical laboratory (clinical chemistry, hematology and urinalysis [including microscopy]) test samples will be analyzed at the central laboratory at each scheduled visit. Erythrocyte Sedimentation Rate (ESR) samples will be analyzed at the local laboratory using kits supplied. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity to determine serum sickness. All summaries will be based on the SI (System International) units provided by the central laboratory. Result of clinical laboratory parameters of the central laboratory and ESR will be tabulated by

treatment group at each scheduled visit. All clinical laboratory results will be presented in listings.

Actual value and change from baseline for clinical chemistry, hematology and urinalysis will be summarized using descriptive statistics by treatment group, test parameter and scheduled visit, respectively. For the purpose of summarization, any numeric values recorded below the lower limit or above the upper limit of quantification will be set to the respective limit for all related summaries. In listings, original results containing inequality signs will be displayed. In the case where duplicate measurements are recorded within the same visit, the highest value will be used for summary.

Shift tables from baseline visit to each scheduled post-baseline visit will be generated for urinalysis results using “Normal” or “Abnormal” classification as appropriate by treatment group.

Some clinical laboratory parameters will be labeled with a CTCAE term, and grading will be applied to post-baseline values for numeric parameters where possible according to CTCAE v 5.0. Grades that require clinical input only will not be assigned to these parameters. Grades which are part numeric and part clinical input will be assigned based on the numeric portion only. If different grades share the same criteria due to exclusion of clinical input, lower grade will be used. The CTCAE terms and ranges for applicable parameters are listed in [Appendix 3](#). The CTCAE grades for this analysis will be Grade 1 (Mild), Grade 2 (Moderate), Grade 3 (Severe) and Grade 4 (Life-threatening). The CTCAE Grade 5 (Death) will not be applied in this analysis since death cannot be determined from a numeric laboratory result. If the post-baseline result for a patient does not satisfy any CTCAE grade, it will be classified as “No Grade”.

The number and percentage of patients with a result for each grade will be summarized by laboratory category, treatment group, CTCAE term and scheduled visit.

In addition, the table for the most severe grade in Treatment Period and Maintenance Phase will be generated. For the summary in Treatment Period, all post-baseline results including unscheduled and EOS visits (prior to initiation of dose adjustment for Placebo SC group) will be used. For the summary in Maintenance Phase, following results will be used:

- 1) Patients treated in the Maintenance Phase and not treated in the Extension Phase:
All post-baseline results including unscheduled and EOS visits (prior to initiation of dose adjustment for Placebo SC group) collected after the date of Week 10 study drug administration
- 2) Patients treated in both the Maintenance and Extension Phase:
All post-baseline results including unscheduled visit (prior to initiation of dose adjustment for Placebo SC group) collected after the date of Week 10 study drug administration and on or before the first study drug administration date in the Extension Phase.

Clinical chemistry, hematology and urinalysis data will be presented in separate listings along with interpretation (Normal, Abnormal, High or Low), if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters.

13.2.1. Incidence of Liver Biochemistry Elevation Potentially Related to Liver Injury

The incidence of abnormalities in AST and ALT levels potentially related to liver injury will be analyzed.

The number and percentages of patients with at least one liver biochemistry elevation which occurred after the first study drug administration in Maintenance Phase using only the worst elevation case at each level of summarization will be summarized.

- Any elevations of AST (>3x-, 5x-, 10x-, and 20xULN)
- Any elevations of ALT(>3x-, 5x-, 10x-, and 20xULN)
- Any elevations of ALT or AST (>3x-, 5x-, 10x-, and 20xULN)

The clinical chemistry listing will include a flag indicating the above elevation potentially related to liver injury.

13.3. Complement (C3, C4) and Total Hemolytic Complement

Complement (C3, C4) and total hemolytic complement will be assessed at Week 0. Additional assessment for complement (C3, C4), total hemolytic complement will be assessed if delayed hypersensitivity occurs to determine serum sickness. All complement tests data will be presented in a listing by treatment group for the ITT Population.

13.4. Vital Signs and Weight

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature) and weight will be assessed at scheduled visits. For hypersensitivity monitoring, vital signs will also be assessed at the following time points of scheduled visit:

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

Vital signs data and weight assessed will be summarized using descriptive statistics of actual value and change from baseline by treatment group, parameter at each scheduled visit for the Safety Population. Baseline will be obtained using only data from the “Vital Signs” page of the eCRF or data of “VITAL SIGN - Prior to study drug administration” time point from “Vital Signs and Hypersensitivity Monitoring” page of the eCRF.

The number and percentage of patients who have clinically notable hypersensitivity result will be summarized in a table by treatment group, scheduled visit, time points and parameter for the Safety Population. The criteria for clinically notable results are defined as follows:

Table 5. Hypersensitivity Classification for Vital Signs

Parameter	Low	High
Systolic blood pressure (mmHg)	<= 90	>= 160
Diastolic blood pressure (mmHg)	<= 50	>= 90
Heart rate (beats per minute)	<= 50	>= 100
Respiratory rate (breaths per minute)	<= 12	>= 20
Body temperature (°C)	<= 35.0	>= 38.0

All vital signs data including hypersensitivity monitoring results, weight will be listed for each patient by treatment group, visit, time points and parameter for the ITT Population. High and low flags will also be presented in the listing to show whether a value is outside of the normal range.

13.5. Electrocardiograms

Findings of 12-Lead ECG will be classified as either “Normal”, “Abnormal, not clinically significant”, or “Abnormal, clinically significant”. The number and percentage of patients will be summarized by treatment group and scheduled visit for the Safety Population, in the form of a shift table to detect changes from baseline. All 12-Lead ECG data will be listed for each patient by treatment group and visit for the ITT Population.

13.6. Physical Examination

Physical examinations will be performed on scheduled visit before the beginning of the study drug administration (on the same visit day as the study drug administration). The following body systems will be examined:

- General Appearance
- Head, Ears, Eyes, Nose, Throat
- Neck and Thyroid
- Skin
- Cardiovascular System
- Respiratory System
- Abdominal System
- Neurological System
- Musculoskeletal System
- Lymph Nodes
- Other

Findings of physical examination will be collected as either “Normal”, “Abnormal, not clinically significant” or “Abnormal, clinically significant”. The number and percentage of patients will be summarized in a table by treatment group, scheduled visit and body system for the Safety Population, in the form of a shift table to detect changes from baseline. All physical examination data will be listed for each patient by treatment group, visit and body system for the ITT Population.

13.7. Tuberculosis Assessment

TB will be assessed using IGRA, Chest X-ray and clinically monitored throughout the study.

Results for IGRA will be classified as either “Positive”, “Indeterminate” or “Negative”. If retest is conducted because the IGRA result is indeterminate, the result of the retest will be used for the summary. Both first and retest results will be listed. The baseline value for IGRA will be considered to be the last non-missing value before the first administration during Screening Period. If there are no values during Screening Period, the value at Week 0 will be used for the baseline determination. In Treatment Period and Maintenance Phase, the IGRA results at baseline, in each Period will be summarized displaying the number and percentage of patients for the Safety Population. For the summary in Treatment Period and Maintenance phase, results will be determined using the following methodology, based on data from the same visits included in the summary of the most severe grade of CTCAE ([Section 13.2](#)):

- If a patient has at least one result of “Positive” in the Treatment Period/Maintenance Phase, the patient will be considered as “Positive”.
- If a patient has no “Positive” results and at least one result of “Indeterminate” in the Treatment Period/Maintenance Phase, the patient will be considered as “Indeterminate”
- If a patient has only “Negative” results in the Treatment Period/Maintenance Phase, the patient will be considered as “Negative”

Results for Chest X-ray will be classified as either “Normal”, “Abnormal, Not Clinically Significant” or “Abnormal, Clinically Significant”. The patients will be monitored throughout the study to confirm the presence of any signs or symptoms indicative of tuberculosis.

Each patient’s IGRA, Chest X-ray and TB clinical monitoring results will be separately listed by treatment group and visit for the ITT Population.

13.8. Local Site Pain

Local site pain measurements using 100 mm Visual Analogue Scale (VAS) will be performed immediately (not exceeding 15 minutes) after the end of the study drug administration at scheduled visits. Local site pain data (scale standardized) will be summarized using descriptive statistics by treatment group and scheduled visit for the Safety Population. All local site pain data will be listed by treatment group and visit for the ITT Population.

13.9. Pregnancy Test

Pregnancy tests will be conducted and summarized only for female patients of childbearing potential. Pregnancy tests consist of serum and urine pregnancy tests. Serum pregnancy tests will be performed by a central laboratory at Screening and EOS. Urine pregnancy

tests will be performed locally at scheduled visits. Serum pregnancy test results will be classified as “Positive”, “Inconclusive” or “Negative”. Urine pregnancy test results will be classified as “Positive” or “Negative”. If a urine pregnancy test result is “Positive”, a confirmatory serum pregnancy test should be performed at the central laboratory. The number and percentage of female patients who have pregnancy test results will be summarized by treatment group, scheduled visit (including Baseline and EOS) and test for the Safety Population. For patients with dose adjustment, all data collected regardless of dose adjustment for both treatment groups will be included in the summary. All pregnancy test results will be listed for each patient tested by treatment group, visit and test for the ITT Population.

13.10. Cardiovascular Disease Assessment

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

All cardiovascular disease assessment data will be presented in a listing by treatment group and visit for the ITT Population.

13.11. New York Heart Association Functional Classification

Heart failure will be assessed by New York Heart Association (NYHA) functional criteria at scheduled visits. If a patient had heart failure, corresponding NYHA class will be selected. The criteria for heart failure are defined as [Table 6](#).

Table 6. New York Heart Association Functional Classification

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

The number and percentage of patients will be summarized by treatment group, scheduled visit and NYHA results for the Safety Population. All NYHA criteria assessment data will be presented in a listing by treatment group and visit for the ITT Population. Patients who have no heart failure will be classed as “No Class”.

13.12. Immunogenicity

Serum sample for immunogenicity will be collected before study drug administration at each scheduled visit. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after study drug administration. On the day of initiation of dose adjustment, serum samples for immunogenicity analysis will be collected before study drug administration. Immunogenicity assessment consists of both anti-drug antibody (ADA) and neutralizing antibody (NAb) assays.

The ADA assay will follow a three tiered approach consisting of (i) screening assay, (ii) confirmatory assay, and (iii) titration. The test outcome for the screening assay will be “Potential Positive” or “Negative”. Samples that are “Potential Positive” in the screening assay will be undergone further testing in the confirmatory assay to determine if samples are a true positive. The test outcome for the confirmatory assay will be: “Reactive”, “Negative” or “Not applicable (N/A)”. “Reactive” indicates a true positive test outcome and will be labeled as “Positive” in outputs, “Negative” is considered negative and “N/A” indicates the assay was negative at the screening phase of the process. Patients with a “Negative” test outcome for either screening or confirmatory assays will be considered negative for the overall ADA assessment. For further characterization, the antibody level will be assessed by titration in confirmed positive samples.

Samples that are positive in the ADA assay will be analyzed further to conduct a NAb assessment. The test outcome for the screening assay will be: “Positive” or “Negative”.

The results of the final ADA and the screening NAb assay will be summarized. The number and percentage of patient will be presented by treatment group and test at each scheduled visit for the Safety Population.

In addition, the number of patients and percentages with positive ADA and NAb conversion in Treatment Period and Maintenance Phase will be summarized for the Safety Population. For the summary in Treatment Period and Maintenance phase, data from the same visits included in the summary of the most severe grade of CTCAE ([Section 13.2](#)) will be used to determine the conversion. The rule of ADA and NAb conversion is following:

- ADA Conversion is defined as patients who reported at least one ADA positive result after Week 0 administration in patients who
 - 1) Have at least one immunogenicity result (including Not Reported Result [NRR]) after Week 0 administration. And
 - 2) Have not any ADA positive result before Week 0 administration.
- NAb Conversion is defined as patients who reported at least one Nab positive result after Week 0 administration in patients who

- 1) Have at least one immunogenicity result (including NRR) after Week 0 administration. And
- 2) Have not any NAb positive result before Week 0 administration.

A listing showing immunogenicity test results for each patient will be provided by treatment group and visit for the ITT Population.

The ADA titer values will be determined as the lowest concentration of the diluted sample that is detected at or above titer cut point and be reported as the reciprocal of that dilution. Descriptive statistics of ADA titer will be displayed by treatment group and scheduled visit for the Safety Population. The results of ADA titer for each visit will also be presented in the listing of immunogenicity results for the ITT Population.

14. Changes in the Planned Analysis

14.1. Changes in the Protocol

- PP population definition

According to study protocol, PP population was defined as “who receive all doses (full) of study drug prior to Week 54 and who have at least 1 efficacy evaluation after Week 10 treatment and who do not have any major protocol deviation that is relevant to efficacy analysis”.

However, due to the safety concerns from global pandemic of COVID-19, numerous dose skip cases have occurred. In addition, it is expected that numerous patients assigned to placebo group will be dropped out prior to Week 54.

As a result, these patients will be excluded from PP population although patients comply with the study protocol well throughout the study period. But CELLTRION believes that it is appropriate to include these patients if they follow study protocol well and do not have any major deviation throughout the study period even though they drop out before Week 54 or do not receive all doses.

To include these patients in PP population, the definition of PP population was changed as “who receive at least one full dose of study drug at Week 10 or thereafter prior to Week 54 and who have at least 1 efficacy evaluation”.

- Data scope of first CSR

According to study protocol, first CSR was planned to be generated based on the data for each patient up to Week 54 including the data for patient who has usability assessments for AI up to Week 62. However, considering the purpose of the first CSR is to see the efficacy and safety of CT-P13 SC in maintenance phase through week 54 and usability of AI, first CSR will include data up to week 54 for each patient. For patients who have usability assessments for AI, usability assessment and exposure data up to week 62 will be included in first CSR exceptionally.

- Statistical analysis method for Co-primary and Key secondary endpoints

As described in the study protocol, the main analysis for the co-primary and key secondary endpoints was planned to be conducted using fisher's exact test. However, in consideration of IND 140478 Preliminary Comments to Pre-BLA Type B Meeting (13Jun2022), the method was changed to the stratified CMH test that could account for covariates (i.e., the randomization stratification factors). Instead, Fisher's exact test will be performed as a sensitivity analysis. In accordance with the change of the main analysis method, the significance level of the test was also changed from one-sided 2.5% to two-sided 5%.

- Corticosteroid-free remission definition

According to study protocol, corticosteroid-free remission at Week 54 was defined as “being in clinical remission (by an absolute CDAI score of <150) in addition to not receiving oral corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at Baseline.”. However, considering that steroid use through the other routes as well as the oral route can affect clinical remission, the usage of the other route of corticosteroid was also restricted to achieve steroid-free remission at week 54. As a result, the definition of corticosteroid-free remission was changed as “being in clinical remission (by an absolute CDAI score of <150) in addition to not receiving corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at Baseline.”.

15. Reference List

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16. APPENDICES

Appendix 1: Schedule of Events for Induction and Maintenance Phase

Study Week	Screening	Induction Phase			Maintenance Phase								EOS ¹		
		0	2	6	10 ²	12 ²	14	22 ³	24 ³	30	38	46			
Study Day	-42 ~ 0	0	14	42	70	84	98	154	168	210	266	322	378		
Dosing Window ⁴		N/A	± 3 days		± 3 days										
Arm 1 treatment ⁵		CT-P13 IV			CT-P13 SC			CT-P13 SC ⁶							
Arm 2 treatment ⁷					Placebo SC			Placebo SC ⁶							
Informed consent	X														
Demography	X														
Medical history	X														
Hepatitis B and HBV DNA ⁸	X						(X ⁹)			(X ⁹)		(X ⁹)	(X)		
Hepatitis C and HCV RNA ¹⁰	X						(X ⁹)			(X ⁹)		(X ⁹)	(X)		
HIV -1 & -2	X														
Stool microbiology ¹¹	X														
Serum pregnancy test ¹²	X												X		
Chest X-ray ¹³	X														
IGRA ¹⁴	X	X ⁹		X ⁹			X ⁹			X ⁹		X ⁹	X		
Inclusion and exclusion criteria	X	X ⁹													
Randomization					X ⁹										
Efficacy assessments															
CDAI score ¹⁵	X ¹⁶		X ⁹	X ⁹	X ⁹		X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X		
AP & SF score ¹⁵	X ¹⁶		X ⁹	X ⁹	X ⁹		X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X		
Colonoscopy (SES-CD) ¹⁷	X							X ⁹					X ⁹		
Patient global scale ¹⁸			X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X		
SIBDQ			X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X		
Usability assessments															
PRE- and POST-SIAQ for PFS ¹⁹								X ¹⁹	X ¹⁹						
Self-injection assessment checklist for PFS ²⁰								X	X						
Device integrity ²¹								X	X						
Safety and other assessments															
Urine pregnancy test ²²			X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X ⁹		

Study Week	Screening	Induction Phase			Maintenance Phase								EOS ¹
		0	2	6	10 ²	12 ²	14	22 ³	24 ³	30	38	46	
Study Day	-42 ~ 0	0	14	42	70	84	98	154	168	210	266	322	378
Dosing Window ⁴		N/A	± 3 days			± 3 days							
Clinical laboratory tests ²³	X	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X ⁹
Physical examinations	X	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X ⁹
Vital signs and weight ²⁴	X	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X ⁹
NYHA class assessment	X	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X ⁹
12-lead ECG ²⁵	X			X	X		X			X			X
Hypersensitivity monitoring ²⁶			X	X	X	X	X	X		X	X	X	X
Immunogenicity ²⁷			X ⁹			X ⁹	X ⁹			X ⁹	X ⁹	X ⁹	X ⁹
C3, C4 and total hemolytic complement ²⁸		X ⁹											
PK blood samples ²⁹			X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ^{9, 28}	X ^{9, 28}	X ⁹	X ⁹	X ⁹
PD blood sampling (CRP) ³⁰	X	X ⁹	X ⁹	X ⁹	X ⁹		X ⁹	X ⁹		X ⁹	X ⁹	X ⁹	X
Fecal calprotectin	X				X ⁹			X ⁹					X ⁹
VAS local site pain ³¹					X	X	X	X		X	X	X	X
Prior, concomitant medications ³²									X				
TB clinical monitoring ³³									X				
Cardiovascular disease monitoring ³⁴									X				
AE monitoring ³⁵									X				

Abbreviations: AE, adverse event; AP, abdominal pain; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ECG, electrocardiogram; EOS, End-of-Study; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IGRA, interferon- γ release assay; IV, intravenous; N/A, not applicable; NYHA, New York heart association; PD, pharmacodynamic; PFS, pre-filled syringe; PK, pharmacokinetic; SC, subcutaneous; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; SF, stool frequency; SIAQ, self-injection assessment questionnaire; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TB, tuberculosis; VAS, Visual Analogue Scale.

1. All EOS assessments will be completed after 4 weeks (± 3 days) after the last dose of CT-P13 SC or Placebo SC is received, if a patient withdraws prior to Week 102 treatment. For patients who early discontinue the study drug before administration of CT-P13 SC or Placebo SC at Week 10, the EOS visit will be completed after 8 weeks (± 3 days) from the last dose of CT-P13 IV is received.
2. At Weeks 10 and 12, initial training for self-injection of CT-P13 SC or Placebo SC via PFS will be conducted. If needed, the patient or caregiver will be retrained during this time on how to perform the injection of the study drug.
3. Between Week 22 and Week 24, additional PK sampling visits will be conducted only on patients who agreed to collect further blood samples for Population PK analysis.
4. A dosing window of ± 3 days is allowed, including self-injection. The minimal dose interval of 11 days is allowed from Week 10.

5. For Arm 1 Treatment group, CT-P13 IV (5 mg/kg) will be administered at Weeks 0, 2, and 6. CT-P13 IV will be then switched to CT-P13 SC (120 mg) at Week 10. Further doses of study drug with CT-P13 SC will be given every 2 weeks via PFS through Week 54.
6. From Week 22, dose adjustment will be allowed. The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria. The patients who received Placebo SC may receive CT-P13 SC 240 mg every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria.
7. For Arm 2 Treatment group, CT-P13 IV (5 mg/kg) will be administered at Weeks 0, 2, and 6. CT-P13 IV will be then switched to Placebo SC (matching volume to CT-P13 SC 120 mg) at Week 10. Further doses of study drug with Placebo SC will be given every 2 weeks via PFS through Week 54.
8. At Screening, HBsAg, HBsAb, and HBcAb must be assessed in all patients (mandatory). If the HBsAg test result is positive, the patient cannot be enrolled. If a patient has results of HBsAg (negative), HBsAb (negative or positive), and HBcAb (positive), a HBV-DNA test will be performed at Screening. If the HBV DNA test result is positive, the patient cannot be enrolled. (Protocol country specific D: If a patient has results of HBsAg (negative), HBsAb (positive), and HBcAb (negative) except for the patient who has received the hepatitis B vaccine, a HBV DNA test will be performed at Screening as well.) If the HBV DNA test result is negative and the patient does not have any evidence of liver cirrhosis, the patient can be enrolled. For patients enrolled based on the HBV DNA test, tests for HBsAg, HBsAb, HBV DNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94 and EOS visits. In patients who develop hepatitis B reactivation, study drug should be stopped and the patient must be withdrawn from the study. Hepatitis B analysis will be performed at the central laboratory.
9. Assessed prior to study drug administration.
10. At Screening, hepatitis C antibody and HCV RNA must be assessed in all patients (mandatory). If the HCV RNA test result is positive, the patient cannot be enrolled. If the hepatitis C antibody and HCV RNA test results are both negative, the patient can be enrolled. If the hepatitis C antibody result is positive and HCV RNA test result is negative, the patient can be enrolled as long as the patient does not have liver cirrhosis and achieved a SVR for at least 12 weeks after the completing the hepatitis C infection treatment. For enrolled patients who have result of hepatitis C antibody (positive), the tests for HCV RNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94 and EOS visits. In patients who develop hepatitis C activation, study drug should be stopped, and the patient must be withdrawn from the study. Hepatitis C analysis will be performed at the central laboratory.
11. Stool microbiology (enteric pathogens, ova and parasites, and *Clostridium difficile* toxin test) will be performed at Screening and at any point in the study when a patient becomes symptomatic, including worsening or return of disease activity, at the investigator's discretion. Analysis will be performed at the central laboratory.
12. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS visit. Patients who are of childbearing potential with only negative results from a serum pregnancy test can be enrolled.
13. A chest X-ray (both posterior-anterior and lateral views) is not required at Screening if a chest X-ray result from within the 42 days prior to the first administration of the study drug (Day 0) is available.
14. The IGRA analysis will be performed at the central laboratory.

15. Patients will complete the CDAI diary for at least 7 consecutive days immediately prior to the CDAI (including worst daily abdominal pain score and loose/watery stool frequency) assessment date, except when the CDAI assessment is performed on the same date as a colonoscopy procedure. If the patient is planned to have bowel preparation for a colonoscopy procedure, the patient should complete the CDAI diary for 7 consecutive days not to overlap with 3 days over the colonoscopy procedure (i.e, from the day before and up to the next day of the colonoscopy procedure).
16. 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). The CDAI score, average worst daily abdominal pain score, and average daily loose/watery stool frequency score will be calculated at Day 0.
17. Colonoscopies will be evaluated at central level to confirm eligibility, and evaluated at central and local level for reporting purpose. Video endoscopies will be assessed centrally by independent reviewer that will be blinded treatment assignment. If a colonoscopy video from within the 42 days prior to the first administration of the study drug (Day 0) is available and meets the appropriate criteria for the evaluation at central level, a colonoscopy is not required to be performed at Screening, and the result will be recorded in both the source documents and the eCRF. For colonoscopy after Screening, an assessment window of -14 days is allowed.
18. Patient global scale will be assessed by a question that asks a patient's position on achieving remission from his or her CD symptoms (Yes or No).
19. (excluding Protocol country specific A and C) The usability assessment for PFS will be performed. PRE-SIAQ will be completed by patient prior to self-injection of CT-P13 SC or Placebo SC and POST-SIAQ will be completed by patient after self-injection of CT-P13 SC or Placebo SC (Weeks 14, 16, 18, 20, and 22). (Protocol country specific D: However, if the patient is still not properly trained after the training sessions at Week 10 and 12, the PRE-SIAQ and POST-SIAQ for PFS will be performed 5 consecutive times from the first PFS self-injection after the completion of the training.) Patients will complete PRE-SIAQ immediately (not exceeding 1 hour) before the administration of study drug and POST-SIAQ immediately (not exceeding 1 hour) after the administration of study drug.
20. (excluding Protocol country specific A and C) The investigator or designee will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection at Weeks 14 and 22. (Protocol country specific D: However, if the patient is still not properly trained after the training sessions at Week 10 and 12, the self-injection assessment checklist for PFS will be performed for the first and the fifth PFS self-injections after the completion of the training.)
21. (excluding Protocol country specific A and C) The structural or mechanical integrity issues of used PFS and AI after the completion of the self-injection will be assessed by the observer using a question that asks clear evidence of damage and/or compromised structural or mechanical integrity based on a visual examination (Yes or No). (Protocol country specific D: However, if the patient is still not properly trained after the training sessions at Week 10 and 12, the device integrity assessment for used PFS will be performed for the first and the fifth PFS self-injections after the completion of the training.)
22. A urine pregnancy test for women of childbearing potential will be used to confirm that patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation. 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.
23. To determine eligibility, retesting will be allowed once during Screening period based on the investigator's discretion. Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples except erythrocyte sedimentation rate will be analyzed at the central laboratory. The ESR samples will be analyzed locally using kits supplied. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity to determine serum sickness.

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

24. Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting). In addition, measurement of height will be documented once at Screening.
25. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the investigator's discretion.
26. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of study drug administration, within 15 minutes after the end of study drug administration, and 1 hour [+10 minutes] after the end of study drug administration) will be monitored for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available; in addition, any type of ECG can be performed. Delayed hypersensitivity will be monitored, which includes serum sickness-like reactions (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption, or edema).
27. Serum samples for immunogenicity testing will be drawn at the same time as the clinical laboratory tests before dosing, where applicable. On the day of initiation of dose adjustment, serum samples for immunogenicity analysis will be collected before study drug administration. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity to determine serum sickness. Analysis will be performed at the central laboratory.
28. Additional serum samples for complement (C3, C4), total hemolytic complement will be assessed if delayed hypersensitivity occurs to determine serum sickness. Analysis will be performed at the central laboratory.
29. Blood samples for PK analysis will be collected at pre-dose (prior to the beginning of study drug administration) of Weeks 0, 2, 6, 10, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, and 102 and within 15 minutes after the end of the study drug infusion of Week 6. On the day of initiation of dose adjustment, blood samples for PK analysis will be collected at pre-dose. For patients who agreed to collect further blood samples, additional blood samples for further Population PK analysis will be collected at following time points; any time between 48 hours and 72 hours after study drug administration of Week 22, any time between 120 hours and 168 hours after study drug administration of Week 22, and pre-dose of Week 24.
30. C-reactive protein samples will be drawn at the same time as the clinical laboratory blood samples.
31. All patients will assess local site pain using 100 mm VAS immediately (not exceeding 15 minutes) after the end of administration of study drug.
32. Use of all prior and concomitant medications for the treatment of CD, latent TB, and/or hepatitis C (if applicable) from the diagnosis of disease until the EOS visit, will be recorded in both the source documents and the eCRF. Use of all concomitant medications for other purposes, from within 30 days prior to the first administration of the study drug (Day 0) or from when the ICF is signed, whichever is earlier, will be recorded until the EOS visit. All concomitant medications will also be recorded when any ADR is ongoing at the EOS visit.

33. Throughout the study, patients will be monitored for the clinical signs and symptoms of TB. An additional IGRA or chest X-ray can be performed at the investigator's discretion based on the judgment per the signs and symptoms of TB monitoring. The investigator will confirm the absence of active TB prior to the subsequent dose administration.
34. Throughout the study, patients will be monitored for the cardiovascular disease related signs and symptoms such as but not limited to shortness of breath, palpitations, chest pain, chest discomfort and/or fainting.
35. Adverse events will be assessed from the date the patient signs the ICF until the last assessment date or EOS visit. Where an ADR (e.g., related to study drug) is ongoing at the EOS visit, the ADR will be followed up until one of the following: resolution or improvement from baseline, relationship reassessed as unrelated, confirmation from the investigator that no further improvement can be expected, end of collection of clinical or safety data, or final database closure. AEs of special interest (i.e., infusion-related reaction/systemic injection reaction, infection, delayed hypersensitivity, localized injection site reaction, and malignancy) should be closely monitored.

Appendix 2: Schedule of Events for Extension Phase

Study Week	Open-label Extension Phase							EOS ¹
	56 ²	62	70	78	86	94	102	
Study Day	392	434	490	546	602	658	714	
Dosing Window³	± 3 days							
Study Treatment⁴	CT-P13 SC							
Hepatitis B and HBV DNA ⁵		(X ⁶)		(X ⁶)		(X ⁶)		(X)
Hepatitis C and HCV RNA ⁷		(X ⁶)		(X ⁶)		(X ⁶)		(X)
Serum Pregnancy Test ⁸								X
IGRA ⁹			X ⁶		X ⁶		X ⁶	X ¹⁰
Efficacy assessments								
CDAI score ¹¹		X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ¹⁰
AP & SF score ¹¹		X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ¹⁰
Colonoscopy (SES-CD) ¹²							X ⁶	X ¹⁰
Patient global scale ¹³		X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ¹⁰
SIBDQ			X ⁶		X ⁶		X ⁶	X ¹⁰
Usability assessments								
PRE- and POST-SIAQ for AI ¹⁴	X ¹⁴	X ¹⁴						
Self-injection assessment checklist for AI ¹⁵	X	X						
Device integrity ¹⁶	X	X						
Safety and other assessments								
Urine pregnancy test ¹⁷	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	
Clinical laboratory tests ¹⁸	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X
Physical examinations	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X
Vital signs and weight ¹⁹	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X
NYHA class assessment	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X
12-lead ECG ²⁰			X		X		X	X
Hypersensitivity monitoring ²¹	X	X	X	X	X	X	X	
Immunogenicity ²²		X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X
C3, C4 and total hemolytic complement ²³								
PK blood samples ²⁴		X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	
PD blood sampling (CRP) ²⁵		X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X ⁶	X
Fecal calprotectin			X ⁶		X ⁶		X ⁶	X ¹⁰

VAS local site pain ²⁶	X	X	X	X	X	X	X	
Prior, Concomitant medications ²⁷					X			
TB clinical monitoring ²⁸					X			
Cardiovascular disease monitoring ²⁹					X			
AE monitoring ³⁰					X			

Abbreviations: AE, adverse event; AI, auto injector; AP, abdominal pain; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; ECG, electrocardiogram; EOS, End-of-Study; HBV, hepatitis B virus; HCV, hepatitis C virus; IGRA, interferon- γ release assay; NYHA, New York heart association; PD, pharmacodynamics; SC, subcutaneous; SES-CD, Simplified Endoscopic Activity Score for Crohn's Disease; SF, stool frequency; SIAQ, self-injection assessment questionnaire; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; TB, tuberculosis; VAS, Visual Analogue Scale.

1. All EOS assessments will be completed 4 weeks (± 3 days) after the last dose of CT-P13 SC is received.
2. (excluding Protocol country specific A, C and D) The Week 56 visit will be only reserved for the patients who will self-inject CT-P13 SC via AI. For the patients who will self-inject CT-P13 SC via AI, initial training for self-injection of CT-P13 SC via AI will be conducted at Week 56 prior to the first AI injection. CT-P13 SC via AI will be self-injected on at least 50 patients who are entered into the Extension Phase. If the patient requests it, additional training can be provided during the visits to the study center.
3. A dosing window of ± 3 days is allowed, including self-injection. The minimal dose interval of 11 days is allowed.
4. All patients will receive active treatment with CT-P13 SC 120 mg via PFS or AI from Week 56. The patients who received CT-P13 SC 240 mg in the Maintenance Phase will continue receiving the same doses of CT-P13 SC for the study treatment in the Extension Phase. During the Extension Phase, dose adjustment will be allowed. The patients who received CT-P13 SC 120 mg may increase the dose to CT-P13 SC 240 mg every 2 weeks, if patients initially responded but then lost response according to the loss of response criteria. CT-P13 SC via AI will be self-injected on at least 50 patients.
5. For patients enrolled based on the HBV DNA test, tests for HBsAg, HBsAb, HBV DNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94 and EOS visits (Protocol country specific D: at Weeks 6, 14, 22, 30, 38, 46, 54, 62, 70, 78, 86, 94, 102 and EOS visits). In patients who develop hepatitis B reactivation, study drug should be stopped and the patient must be withdrawn from the study. Hepatitis B analysis will be performed at the central laboratory.
6. Assessed prior to study drug administration.
7. For enrolled patients who have result of hepatitis C antibody (positive), tests for HCV RNA, AST, ALT and total bilirubin will be additionally performed at Weeks 14, 30, 46, 62, 78, 94 and EOS visits. In patients who develop hepatitis C activation, study drug should be stopped and the patient must be withdrawn from the study. Hepatitis C analysis will be performed at the central laboratory.
8. A serum pregnancy test for women of childbearing potential should be conducted at Screening and at the EOS visit.
9. The IGRA analysis will be performed at the central laboratory.
10. End-of-Study assessment will only be performed if the assessment was not done at Week 102, or on patient with discontinuation before Week 102.

11. Patients will complete the CDAI diary for at least 7 consecutive days immediately prior to the CDAI (including worst daily abdominal pain score and loose/watery stool frequency) assessment date, except when the CDAI assessment is performed on the same date as a colonoscopy procedure. If the patient is planned to have bowel preparation for a colonoscopy procedure, the patient should complete the CDAI diary for 7 consecutive days not to overlap with 3 days over the colonoscopy procedure (i.e., from the day before and up to the next day of the colonoscopy procedure).
12. Colonoscopies will be evaluated at central level to confirm eligibility, and evaluated at central and local level for reporting purpose. Video endoscopies will be assessed centrally by independent reviewer that will be blinded treatment assignment. For colonoscopy after Screening, an assessment window of -14 days is allowed.
13. Patient global scale will be assessed by a question that asks a patient's position on achieving remission from his or her CD symptoms (Yes or No).
14. (excluding Protocol country specific A, C and D) The usability assessment for AI will be performed on at least 50 patients. PRE-SIAQ will be completed by patient prior to self-injection of CT-P13 SC and POST-SIAQ will be completed by patient after self-injection of CT-P13 SC injection (Weeks 56, 58, 60, and 62). Patients will complete PRE-SIAQ immediately (not exceeding 1 hour) before the administration of study drug and POST-SIAQ immediately (not exceeding 1 hour) after the administration of study drug.
15. (excluding Protocol country specific A, C and D) The investigator or designee will observe the patient's self-injection and complete the checklist within 15 minutes after patient's self-injection at Weeks 56, and 62.
16. (excluding Protocol country specific A, C and D) The structural or mechanical integrity issues of used PFS and AI after the completion of the self-injection will be assessed by the observer using a question that asks clear evidence of damage and/or compromised structural or mechanical integrity based on a visual examination (Yes or No).
17. A urine pregnancy test for women of childbearing potential will be used to confirm that patients are not pregnant before study drug administration on each visit day or more frequently if required by country-specific legislation. 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.
18. Clinical laboratory (clinical chemistry, hematology, and urinalysis including microscopy) test samples except erythrocyte sedimentation rate will be analyzed at the central laboratory. The ESR samples will be analyzed locally using kits supplied. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity to determine serum sickness.

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

19. Vital signs (including systolic and diastolic blood pressure, heart and respiratory rates, and body temperature) and weight will be measured after 5 minutes of rest (sitting).
20. All scheduled 12-lead ECGs must be performed locally after the patient has rested quietly for at least 5 minutes in the supine position. Regardless of the 12-lead ECG result, further cardiological evaluation can be done at the investigator's discretion.

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

Appendix 3: Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Blood bilirubin increased	Serum Bilirubin (Total) *	High	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
Alanine aminotransferase increased	Alanine aminotransferase (ALT) *	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Aspartate aminotransferase increased	Aspartate aminotransferase (AST) *	High	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline Phosphatase *	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
GGT increased	γ -Glutamyl Transferase *	High	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Creatinine increased	Creatinine	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
CPK increased	Creatine Kinase	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Hypoalbuminemia	Albumin	Low	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	-
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L;	>155 - 160 mmol/L;	>160 mmol/L;
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	125-129 mmol/L	120-124 mmol/L	<120 mmol/L;
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L;	>6.0 - 7.0 mmol/L;	>7.0 mmol/L;
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; #	<3.0 - 2.5 mmol/L;	<2.5 mmol/L;

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Hypercalcemia	Calcium	High	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; @	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; @	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; @	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; @
Hypocalcemia	Calcium	Low	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; @	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; @	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; @	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; @
Hypoglycemia	Glucose	Low	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L;
Blood lactate dehydrogenase increased	Lactate Dehydrogenase	High	>ULN	-	-	-
Cholesterol high	Total Cholesterol	High	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Hypertriglyceridemia	Triglyceride	High	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L;
Leukocytosis	Total White Blood Cell Count	High	-	-	>100,000/mm ³	-
White blood cell decreased	Total White Blood Cell Count	Low	<LLN - 3000/mm ³ ; <LLN - 3.0 x 10 ⁹ /L	<3000 - 2000/mm ³ ; <3.0 - 2.0 x 10 ⁹ /L	<2000 - 1000/mm ³ ; <2.0 - 1.0 x 10 ⁹ /L	<1000/mm ³ ; <1.0 x 10 ⁹ /L
Neutrophil count decreased	Absolute Neutrophil Count	Low	<LLN - 1500/mm ³ ; <LLN - 1.5 x 10 ⁹ /L	<1500 - 1000/mm ³ ; <1.5 - 1.0 x 10 ⁹ /L	<1000 - 500/mm ³ ; <1.0 - 0.5 x 10 ⁹ /L	<500/mm ³ ; <0.5 x 10 ⁹ /L
Lymphocyte count decreased	Lymphocyte Count	Low	<LLN - 800/mm ³ ; <LLN - 0.8 x 10 ⁹ /L	<800 - 500/mm ³ ; <0.8 - 0.5 x 10 ⁹ /L	<500 - 200/mm ³ ; <0.5 - 0.2 x 10 ⁹ /L	<200/mm ³ ; <0.2 x 10 ⁹ /L
Lymphocyte count increased	Lymphocyte Count	High	-	>4000/mm ³ - 20,000/mm ³	>20,000/mm ³	-
Platelet count decreased	Platelet Count	Low	<LLN - 75,000/mm ³ ; <LLN - 75.0 x 10 ⁹ /L	<75,000 - 50,000/mm ³ ; <75.0 - 50.0 x 10 ⁹ /L	<50,000 - 25,000/mm ³ ; <50.0 - 25.0 x 10 ⁹ /L	<25,000/mm ³ ; <25.0 x 10 ⁹ /L
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	<8.0 g/dL; <4.9 mmol/L; <80 g/L	-
Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 g/dL from ULN	Increase in >2 - 4 g/dL from ULN	Increase in >4 g/dL from ULN	-
Eosinophilia	Eosinophils	High	>ULN and >Baseline	-	-	-
Glucosuria	Glucose	N/A	Present	-	-	-

Note: LLN = lower limit of normal, ULN = upper limit of normal. The LLN and ULN values will be the lower and upper limits of the normal ranges as provided by the central laboratory.
N/A = Not Applicable.

* indicates that baseline results will be considered abnormal only when the baseline result is abnormal and high, otherwise normal.

indicates that this grade will not be used because this grade shares the same criteria due to exclusion of clinical input.

@ indicates that corrected calcium (mg/dL) = measured total calcium (mg/dL) + 0.8 (4.0 – serum albumin [g/dL]), where 4.0 represents the average albumin level. For SI units as: Corrected calcium (mmol/l) = total calcium (mmol/l) + 0.02 (40 –serum albumin [g/l]). The LLN and ULN values of total calcium will be used.