CELLTRION Inc.
CT-P13 1.6

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

20th July 2018
Statistical Analysis Plan

Part 1 – Final Version 4.0

Prepared by:

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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
ARR	Administration-Related Reaction
ADA	Anti-Drug Antibody
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC_{τ}	Area Under the Concentration-Time Curve at Steady State
AZA	Azathioprine
BA	Bioavailability
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CI	Confidence Interval
CL	Clearance
C_{max}	Observed Maximum Serum Concentration
CRP	C-Reactive Protein
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Concentration
CT-P13	Infliximab (CELLTRION, Inc.)
CV%	Percent Coefficient of Variation
DRM	Data Review Meeting
ECG	Electrocardiogram
EOI	End of Infusion
eCRF	Electronic Case Report Form
EOS	End-of-Study
ESR	Erythrocyte Sedimentation Rate
FC	Fecal Calprotectin
GCL	Global Central Lab
HBcAb	Hepatitis B Core Antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
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
LLN	Lower Limit of Normal
LLT	Lowest Level Term
LLoQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean Residence Time
MTX	Methotrexate

N/A	Not Applicable
NAb	Neutralizing Antibody
NRR	Not Reported Result
NYHA	New York Heart Association
PD	Pharmacodynamic
PFS	Pre-filled Syringe
PK	Pharmacokinetic
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SD	Standard Deviation
SE	Standard Error
SES-CD	Simplified Endoscopic Activity Score for Crohn's Disease
SI	System International
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SOC	System Organ Class
SOI	Start of Infusion
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLF	Table, Listing and Figure
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization
6-MP	6-mercaptopurine

1. ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of CELLTRION, Inc. The clinical monitoring, medical writing and pharmacokinetics analysis are being performed under contract with [redacted], in collaboration with CELLTRION, Inc. The data management and statistical analysis are being performed by CELLTRION, Inc.

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 Part 1 of CELLTRION study number CT-P13 1.6, entitled as "An Open-label, Randomized, Parallel-Group, Phase I Study to Evaluate Pharmacokinetics, Efficacy and Safety between Subcutaneous CT-P13 and Intravenous CT-P13 in Patients with Active Crohn's Disease and Active Ulcerative Colitis".

The clinical study report (CSR) will be generated to report all efficacy, pharmacokinetics (PK), pharmacodynamics (PD) and safety data after completion of all visits of all patients.

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

- Study Protocol Version 3.0 – 9th January 2018
- Unique CRF for Part 1 Version 2.0 – 4th July 2017

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 for Part 1 is to find the optimal dose of CT-P13 Subcutaneous (SC) over the first 30 weeks as determined by the area under the concentration-time curve at steady state (AUC_{τ}) between Week 22 and 30.

3.2. Secondary Objective

The secondary objective of this study for Part 1 is to evaluate efficacy, PK, PD and overall safety of CT-P13 SC in comparison with CT-P13 IV up to Week 54.

4. INVESTIGATIONAL PLAN

4.1. Overall Study Design and Plan

This study is an open-label, randomized, multicenter, parallel group, phase I study designed to evaluate PK, PD, efficacy and safety between CT-P13 SC and CT-P13 IV in patients with active Crohn's Disease (CD) and active Ulcerative Colitis (UC).

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

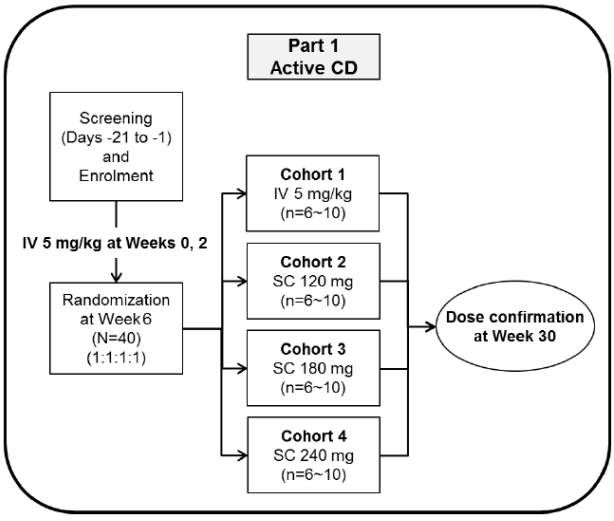
Table 1. Study Cohort

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

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

Part 1 of this study is designed to find the optimal dose of CT-P13 SC. The overview of study design is illustrated in Figure 1.

Figure 1. Overview of Study Design



IV, intravenous; SC, subcutaneous; CD, Crohn's disease;

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

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

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

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

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

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

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

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

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

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

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

Figure 2. Patient Assessment Overview for Part 1

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

Efficacy	X	X	X		X	X	X	X
Secondary Pharmacokinetic	←							→
Pharmacodynamic	X	X	X		X	X	X	X
Safety Evaluation	←							→

1. Additional visits will only be made by patients who need extra training for CT-P13 SC injection.
2. A visit window of ±3 days is allowed up to and including Week 30; a visit window of ±5 days is allowed thereafter, including the End-of-Study Visit.
3. Only patients from Cohorts 2, 3, and 4 will make visits for additional pharmacokinetic assessment.
4. Visit window for primary PK assessment is allowed according to Section 9.

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

End-of-Study Visit: An End-of-Study Visit will occur 8 weeks after the last dose is received, either at the end of the Maintenance Phase or earlier if the patient withdraws from the study. The schedule of events is presented in Appendix 1.

5. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics: n, mean, standard deviation (SD), minimum, median and maximum unless otherwise specified. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data. SD will be presented to two more decimal places than the raw data. If the geometric mean and percent coefficient of variation (CV%) are to be presented, it will be set to the same decimal places as the mean. Confidence intervals (CI) obtained from statistical procedures will be displayed to two decimal places. In summary tables, all available decimal places will be used although rounded value is listed.

Categorical data will be summarized using numbers and percentages of patients. Percentages will be presented 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.

All data will be displayed in listings. Unless otherwise specified, listings will be sorted by the treatment group, patient number, and assessment date or visit date, 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. In addition, EOS and Unscheduled visit will not be summarized for visit-based tables, unless otherwise specified.

When combining data from eCRF and analytical facilities such as [redacted], discrepancy will be handled as following:

1) Recorded as collecting sample in eCRF but no corresponding results from analytical facility – listing will display only sample collection visit/date/time from eCRF;

2) No corresponding records in eCRF for results from analytical facility – listing will display only specimen collection visit/date and results from analytical facility;

3) Discrepancy in sample collection date from eCRF and analytical facility – listing will display results from analytical facility and visit/date/time from eCRF if not missing; if sample collection date/time is missing in eCRF then use specimen collection visit/date from analytical facility.

All available results from analytical facilities will be included in the summary table.

5.1. Software

All analyses will be conducted using [redacted]
PK parameters will be calculated by noncompartmental methods using the appropriate validated software such as [redacted]

5.2. Sample Size

No formal sample size estimation was performed because no confirmatory analyses are planned in the study. Approximately 24 to 40 patients (6 to 10 patients per cohort) are considered to be sufficient to investigate the primary objective of this study (Section 3.1).

5.3. Randomization, Stratification, and Blinding

An Interactive Web Response System (IWRS) will be used for the randomization. Clinical Statistics team will generate the randomization schedule for IWRS, which will link sequential patient randomization numbers to treatment codes. The randomization at Week 6 will be stratified by region (European or non-European), current use of treatment with Azathioprine (AZA) or 6-mercaptopurine (6-MP) or Methotrexate (MTX) (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease) and body weight at Week 6 (≤70 kg or >70 kg). The randomization numbers will be blocked, and within each block the same number of patients will be allocated to each cohort group. The block size will not be revealed. Blinding is not included in this study because it is an open-label study.

5.4. Population of Analysis

Population to be used in analysis will be specified in related sections. The following patient populations are defined: Intent-to-Treat (ITT), All-randomized, Pharmacokinetic (PK), Pharmacodynamics (PD), Efficacy and Safety Populations. Patients who have any major protocol deviations (as defined in Section 5.6) may be excluded from the PK Population. The relevant decision will be taken at the Data Review Meeting (DRM).

Analysis of the ITT Population and All-randomized Population will be performed according to the treatment they were randomized to at Week 6. The other populations will be analyzed according to actual treatment group. The actual treatment group will be assigned according to their actual treatment, not according to the randomized cohort, even if there is a discrepancy between the actual administered dose and the randomized cohort. If there is a patient who has the discrepancy, the patient will be discussed during the DRM. Administration after adjusting to the optimal dose will not be used for determination of treatment group.

For randomized patients, data before randomization at Week 6 will be displayed by the treatment group based on randomized or actual administered study drug. If a patient discontinues the study before the randomization at Week 6, 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 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 will consist of all enrolled patients. A patient will be considered to be enrolled if the patient is successfully screened based on the 'Screening Pass YES/NO' page of the eCRF. In addition, a patient can be enrolled by an investigator's decision. Some of listings will be generated on the ITT Population to include patients who discontinued the study prior to randomization at Week 6.

5.4.2. All-randomized Population

The All-randomized Population will consist of all randomly assigned patients at Week 6, 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 6 based on 'Randomization' page of eCRF.

5.4.3. Pharmacokinetic Population

The PK Population will consist of the All-randomized Population who receive at least one full dose of study drug at Week 6 or thereafter and who have at least one PK concentration result after Week 6 treatment. The primary PK endpoint of the AUC_{τ} at steady state between Week 22 and Week 30 will be analyzed in patients who received all doses (full) of study drug up to Week 30 (prior to Week 30) in the PK Population. A patient will be considered as receiving full dose if the actual administered dose (mg) of the patient is greater than or equal to prescribed dose (mg) based on 'Study Drug Administration' page of eCRF. If a patient doesn't receive full dose, the patient will be discussed during the DRM to confirm whether the patient can be considered as receiving full dose or not.

5.4.4. Pharmacodynamic Population

The PD Population will consist of the All-randomized Population who receive at least one full dose (as defined in Section 5.4.3) of study drug at Week 6 or thereafter and who have at least one PD result (Fecal calprotectin [FC] or C-reactive protein [CRP]) after Week 6 treatment.

5.4.5. Efficacy Population

The Efficacy Population will consist of the All-randomized Population who receive at least one full dose (as defined in Section 5.4.3) of study drug at Week 6 or thereafter and who have at least one efficacy evaluation result after Week 6 treatment. A patient will be considered as having an efficacy evaluation result if the patient is recorded as performing at least one of any assessment of the followings.

- CDAI
- Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD)
- Short Inflammatory Bowel Disease Questionnaire (SIBDQ)

5.4.6. Safety Population

The Safety Population will consist of all patients who received at least one (partial or full) dose of study drug at Week 6 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' 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. 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 DRM. A major protocol deviation is one that may affect the interpretation of study results or the patient's rights, safety or welfare.

Major protocol deviations are defined as follows:

- Mis-randomizations (defined as patients who received another treatment to which they were assigned at any point during the study)

Patients who were mis-randomized may be excluded from the PK Population. The major protocol deviations used for exclusion 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. Outliers

Any outliers that are detected during the review of the data will be investigated and discussed during the DRM. In general, outliers will not be excluded. Sensitivity analyses and exploratory analyses may be conducted using imputation or excluding outliers to ensure robustness of study conclusions. Details of outliers detected will be presented in the footnotes of the relevant outputs.

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.

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

- Inclusion/Exclusion Criteria Not Met
- Subject Withdrew Consent
- Others

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 the patient is successfully screened based on the 'Screening Pass YES/NO' page of the eCRF.
- A patient will be considered to have been treated in the Dose-loading Phase if it is recorded as 'Yes' on the 'Study Drug Administration' page of the eCRF at Week 0 and/or Week 2.
- A patient will be considered to be randomized if the patient was allocated a randomization ID at Week 6 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 'Yes' on the 'Study Drug Administration' page of the eCRF on or after Week 6.
- 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 at Week 6, the patient will be considered to have discontinued in the Maintenance Phase, otherwise, in the Dose-loading Phase.

The total number of patients who discontinued the study in the Dose-loading Phase will be presented by primary reason. The number and percentage of patients who discontinued the study in the Maintenance 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:

- Patient develops signs of disease progression in the judgement of the investigator
- Patient withdrew consent to continue participation

- AE(s) that, in the opinion of the investigator, precludes further participation in the study
- Significant protocol violation
- Patient lost to follow-up
- Patient died
- Pregnancy
- Investigator decision
- Others

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 Dose-loading Phase or Maintenance 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' 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. DEMOCRAPHICS, 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); Sex (male, female); Female fertility status (Pre-Menarche, Surgically Sterilized, Post-Menopausal, Potentially Able to bear Children, Other); Race (Not allowed by investigator country regulations, Asian/Oriental, Caucasian/White, African/Black, Other); Ethnicity (Hispanic or Latino, Non-Hispanic or non-Latino, Unknown); Height (cm), Weight (kg) and Body Mass Index (BMI) (kg/m^2) as recorded at the screening visit.

Age will be automatically calculated in the eCRF system based on the date of the informed consent visit and the year of birth considering whether birth date has passed the informed consent date or not.

The following stratification details will also be summarized for the All-randomized Population by treatment group: region (European or non-European), current use of treatment with AZA or 6-MP or MTX (used or not used), clinical response at Week 6 (responder or non-responder by CDAI-70 for Crohn's disease) and body weight at Week 6 ($\leq$70 kg or >70 kg). 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. Congestive Heart Failure Assessment

Congestive heart failure will be assessed by New York Heart Association (NYHA) functional criteria at Screening. The criteria for congestive heart failure is defined as Table 2.

Table 2. New York Heart Association Functional Classification

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

All NYHA criteria assessment data will be presented in a listing by treatment group for the ITT Population. Patients without signs or symptoms of cardiac dysfunction will be classed as "No Class" in the listing.

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

At Screening, the following assessments will be performed:

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

Viral serology results will be summarized at Baseline (as defined in Section 5.5) by treatment group for the All-randomized Population. A listing will be produced by treatment group for the ITT Population.

7.4. Medical History

Medical history is captured at Screening and will be coded using Medical Dictionary for Regulatory Activities (MedDRA Version 20.0 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.

7.5. Crohn's Disease History

Crohn's Disease history is captured at the screening visit. The time since CD diagnosis will be tabulated for the All-randomized Population by treatment group. Time (years) since CD diagnosis will be calculated as [(date of first administration – date of diagnosis)/365.25]. If an incomplete 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. XXMAR2017) the date will be the last day of the month (i.e. 31MAR2017). If the day and month are missing (i.e. XXXXX2017) the date will be set to the 31st December (i.e. 31DEC2017). 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 CD diagnosis will not be calculated. CD history will also 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 (CT-P13 SC 1.6). Inclusion and Exclusion criteria for each patient will be presented in separate listings for the ITT Population by treatment group.

A number of inclusion and exclusion criteria may be modified during protocol revisions. The listing will indicate which protocol the patient was recruited under and hence which criteria applied.

8. TREATMENTS AND MEDICATIONS

8.1. Prior and Concomitant Medications

All medications for the treatment of CD, from the diagnosis of disease until the last assessment date or EOS visit, will be collected on the eCRF. All medications except for the treatment of CD used during the study taken within 30 days before date of first administration and until the last assessment date or EOS visit will be collected on the eCRF. All medications will be coded according to the World Health Organization drug dictionary (WHO Drug Dictionary September 1, 2017 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 end date is after the date of death, the end date will be imputed as the date of death.

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

- Missing day: Assume the first day of the month.
  However, if the partial date and the date of first administration (defined as the earliest date recorded on the "Study Drug Administration" page of eCRF) lie within the same month and year and the date of first administration is not after the stop date of the medication, set to the date of first 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 first 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 first administration. Otherwise, set to stop date of the medication.

- Missing day, month and year: Assume date of first 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: UNJUN2017
  Medication end: 20OCT2017
  Date of first administration: 16OCT2017
  Medication start imputed: 01JUN2017
- Example 2:
  Medication start: UNOCT2017
  Medication end: 20OCT2017
  Date of first administration: 16OCT2017
  Medication start imputed: 16OCT2017
- Example 3:
  Medication start: UNOCT2017
  Medication end: 20OCT2017
  Date of first administration: 24OCT2017
  Medication start imputed: 20OCT2017

A prior medication is defined as any medication where the start and stop dates or imputed start and stop dates are before the date of first administration. A concomitant medication is defined as any medication that has an actual or imputed stop date are on or after the date of first administration, marked as ongoing or missing. The actual or imputed start date of a concomitant medication can be before or after the date of first administration.

The prior medications will be summarized by treatment groups, drug class (using Anatomical Therapeutic Chemical [ATC] level 2), and PT along with the total number of prior medications and the number and percentage of patients with at least one prior medication for the Safety Population. The summaries will be repeated in separate tables for concomitant medications and just for concomitant medications in Maintenance Phase. A concomitant medication in Maintenance Phase is defined as a medication that has an actual or imputed stop date on or after the Week 6 administration date, marked as ongoing or missing in patients who are administered on or after Week 6.

All prior and concomitant medications will be listed separately 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 dose week 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 visit. For patients who administered with 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) will be calculated using the Prescribed Dose (mg) and Actual Administered Dose (mg) based on the 'Study Drug Administration' page of eCRF and Weight (kg) on the 'Vital Signs' page of eCRF. If the patient's weight on the 'Vital Signs' page of eCRF is missing at the applicable visit, then the weight on the 'CDAI' page of eCRF at applicable visit will be used. If the weight is still missing at the applicable visit, then weight at the last non-missing assessment before the applicable visit date (applicable administration date) for the patient will be used.

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

Dose escalation occurs when the intended dose (mg/kg) is greater than 5mg/kg and it will be allowed for IV infusion since Week 30. The number of patients with escalated dose and descriptive statistics of intended dose (mg/kg) will be displayed by treatment group at each scheduled dose (since Week 30) for the Safety Population. Since Week 30, descriptive statistics for total number of escalated dose and average administered escalated dose (mg/kg) of each patient will be displayed along with the number of patients with at least 1 escalated dose for the Safety Population.

A listing will be provided by treatment group for the ITT Population showing the details of study drug administration. This listing will include all data collected on the "Study Drug Administration" page of eCRF.

9. PHARMACOKINETIC ANALYSIS

All pharmacokinetic tables, listings and figures will be generated using all data on the PK Population by treatment group unless otherwise specified.

9.1. Serum Concentrations

PK samples will be collected at pre-dose (prior to the beginning of the study treatment administration on dosing day) of the scheduled sampling time points. In addition, PK samples will also be collected at specific PK monitoring visit period (between Week 22 and Week 30) presented in Table 3.

All patients in SC cohorts (Cohorts 2, 3 and 4) will be randomly assigned at Week 14 in a 1:1 ratio to either of Group A or B to collect blood samples in the PK monitoring visit period:

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

Table 3. Steady state PK sampling time points

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

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

Individual serum concentrations, scheduled time, actual sampling time and deviations from scheduled time will be presented in a data listing by treatment group for the Safety 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 collection visit and time point for the PK Population. Geometric mean will not be reported if the dataset includes zero values. All concentrations below the lower limit of quantification (BLQ) will be indicated in the data listing. For summary of serum concentration and calculation of PK parameters, BLQ prior to the first administration (Week 0, Dose 1) 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 sample time plots for study drugs will also be presented on both linear and semi-logarithmic scales by treatment group for the PK Population. Additional plots showing the data collected during the PK monitoring visit period will be provided separately for better comparison between treatment groups for the PK Population.

9.2. Pharmacokinetic Parameters

Individual serum concentration data over actual time data will be used to calculate PK parameters of infliximab by standard non-compartmental methods using [redacted] For the calculation of PK parameters, BLQ will be handled using the rules in Section 9.1. Actual time after dose (most recent dose) will be used for all PK analyses. However, for ease of presentation, scheduled sampling times will be used to present results in summary tables and figures.

Table 4. Pharmacokinetic Parameters for Infliximab

Primary Parameter (calculated between Week 22 and Week 30): AUC_{τ} will be calculated at Week 22 for Cohort 1 (IV), Week 22 and 26 for Group A of Cohort 2, 3 and 4 (SC), and Week 24 and 28 for Group B of Cohort 2, 3 and 4 (SC).	
$AUC_{\tau(SC)}$	Area under the concentration-time curve at steady state between over the actual SC dosing interval (14 days), calculated using the linear trapezoidal rule.
$AUC_{\tau(IV)}$	Area under the concentration-time curve at steady state between over the actual IV dosing interval (56 days), calculated using the linear trapezoidal rule.
Secondary Parameters (calculated between Week 22 and Week 30, if data allows): Secondary parameters except for $C_{trough,ss}$ will be calculated at Week 22 for Cohort 1 (IV), Week 22 and 26 for Group A of Cohort 2, 3 and 4 (SC), and Week 24 and 28 for Group B of Cohort 2, 3 and 4 (SC). $C_{trough,ss}$ will be calculated at Week 22 for Cohort 1 (IV), Week 22, 24, 26, 28 for Group A and B of Cohort 2, 3 and 4 (SC).	
AUC_{ss8W}	AUC exposure normalized to an 8-week interval, calculated over actual dosing interval (observed [τobs]), according to the following formula: IV group: AUCτ [ng·h/mL]/ τobs [h]×1344 [h] SC (A) group: mean of $\left(\frac{AUC\tau \text{ at } W22}{\tau obs \text{ at } W22}, \frac{AUC\tau \text{ at } W26}{\tau obs \text{ at } W26}\right)$×1344 [h] SC (B) group: mean of $\left(\frac{AUC\tau \text{ at } W24}{\tau obs \text{ at } W24}, \frac{AUC\tau \text{ at } W28}{\tau obs \text{ at } W28}\right)$ ×1344 [h]
$C_{max,ss}$	Observed maximum serum concentration after dose administration
$T_{max,ss}$	Time of observed maximum serum concentration
$T_{1/2}$	Terminal half life
$C_{trough,ss}$	Trough concentration, calculated from the pre-dose of the next dose observed, if available.
MRT	Mean residence time, calculated as: MRT = ([$AUMC_{\tau}$ + τ (AUC_{inf} - AUC_{τ})]/ AUC_{τ}) – 0.5 × (administration time) for IV infusion and

	MRT = ([AUMC$_\tau$ + τ (AUC$_{inf}$ - AUC$_\tau$)]/ AUC$_\tau$) for SC administration Where AUC$_{inf}$ is the area under the concentration-time curve from 0 extrapolated to infinity (AUC$_{inf}$= AUC$_\tau$+$\frac{Last\ observed\ concentration\ over\ the\ dosing\ interval}{slope\ of\ the\ terminal\ phase}$) AUMC$_\tau$ is the area under the moment curve over the dosing interval, and τ is the dosing interval.
CL$_{ss}$	Clearance after IV dosing, calculated as: CL = Dose$_{IV}$ / AUC$_{\tau(IV)}$
CL/F$_{ss}$	Apparent clearance after SC dosing, calculated as: CL/F = Dose$_{SC}$ / AUC$_{\tau(SC)}$
DNC$_{max,ss}$	Dose normalized peak exposure at steady state, calculated as: C$_{max}$/total dose administered
Secondary Parameter (obtained over Week 0 to Week 54): C$_{trough}$ will be obtained at all scheduled visit except Week 22 for Cohort 1 (IV), except Week 22, 24, 26, 28 for Group A and B of Cohort 2, 3 and 4 (SC).	
C$_{trough}$	Trough concentration, calculated from the pre-dose of the next dose observed, if available.

ss, steady state

The PK parameters will be presented in listings and summarized in tables by treatment group for the PK Population. The PK primary parameter of the AUC$_\tau$ at steady state between Week 22 and Week 30 will also be summarized (n, mean, SD, CV%, geometric mean, minimum, median, and maximum) in patients who received all doses (full) of study drug up to Week 30 by treatment group for the PK population. Unreliable estimate values will be excluded from summary but listed with a flag.

10. PHARMACODYNAMIC ANALYSIS

The CRP and FC will be recorded as numeric PD parameters. Any numeric values recorded below the lower limit of quantification or above the upper limit of quantification will be set to the respective limit for all summaries. In listing, original results containing inequality signs will be displayed.

Descriptive statistics will be provided for the CRP and Fecal calprotectin (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 PD population. In addition, a plot will be presented showing the mean concentration and SE of the CRP and Fecal calprotectin at each scheduled visit for the PD Population by treatment group.

11. EFFICACY ANALYSIS

All efficacy tables and listings will be generated using all data for the Efficacy Population by treatment group unless otherwise specified.

Efficacy will be assessed by the evaluation of CDAI, colonoscopy (SES-CD) and SIBDQ at each time points specified in the schedule of events.

11.1. Crohn's Disease Activity Index (CDAI)

11.1.1. Clinical Response and Remission

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. CDAI is defined as follows:

Table 5. Crohn's Disease Activity Index

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

1. Sum of 7 days.
2. Only for CDAI assessment at Screening and during the study period, the hematocrit results from local laboratory within the 7 days prior to the CDAI score assessment will be used.
3. If the calculated subtotal is less than '-10', then it will be set to '-10'.
Source: Best et al.1976.

Descriptive statistics for actual and change from baseline of CDAI score at each scheduled visit will be calculated by treatment for the Efficacy Population. If there is a incomplete component, CDAI score will not be calculated.

The number and percentage of patients achieving clinical response according to CDAI criteria (CDAI-70 or CDAI-100) will be summarized at each scheduled visit by treatment group for the Efficacy Population. A patient is defined as having a CDAI-70 (or CDAI-100) response if there is a decrease in CDAI score of 70 points or more (100 points or more for CDAI-100 response) from the baseline value (as defined in Section 5.5).

The number and percentage of patients achieving clinical remission will be summarized at each scheduled visit by treatment group for the Efficacy Population. Clinical remission is defined as an absolute CDAI score of less than 150 points.

All CDAI information will be listed by treatment group for the Efficacy Population.

11.2. Colonoscopy (SES-CD)

The degree of mucosal ulceration will be assessed by colonoscopy (endoscopic examination of luminal surface of gastrointestinal tract which may include the rectum, colon and terminal ileum) using the SES-CD. SES-CD score is obtained as follows:

Table 6. SES-CD Score

		Rectum	Left Colon	Transverse Colon	Right Colon	Ileum	Subtotal SES-CD
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						
Total SES - CD							**Overall SES-CD**

Source: Daperno et al. 2004

Subtotal SES-CD Score consists of the sum of scores for all individual components: Small Intestine (Ileum) and Large Intestine (Left Colon, Transverse Colon, Right Colon, Rectum) at each assessment. Total SES-CD Score consists of the sum of scores for all assessments (Q1, Q2, Q3, Q4) at each individual components. Overall SES-CD Score consists of the sum of Subtotal SES-CD Scores for each of the assessments (Q1, Q2, Q3, Q4), or sum of all Total SES-CD Scores for each individual components.

Descriptive statistics for actual and change from baseline of overall SES-CD score at each study visit will be calculated by treatment for the Efficacy Population. At each visit, if any of the individual components for a subject has an inaccessible or missing exploration result, then the subject's overall SES-CD score will be excluded from this summary table; but if any of the individual components for a subject at each visit has a resected exploration result (provided that no inaccessible exploration results exist at that visit), then the overall SES-CD score will be included in this summary table with the actual score value.

Endoscopic response is defined as a decrease in 50% or more of Overall SES-CD Score from the baseline value using colonoscopy date (as defined in Section 5.5) without inaccessible or missing exploration result. The number and percentage of patients achieving endoscopic response in patients who have confirmed mucosal abnormalities (Overall SES-CD Score is greater than 0) without inaccessible or missing exploration result at baseline and have Overall

SES-CD Score without inaccessible or missing exploration result at each visit will be summarized by treatment group for the Efficacy Population.

Endoscopic remission is defined as an absolute Overall SES-CD Score of 2 points or less without inaccessible or missing exploration result. The number and percentage of patients achieving endoscopic remission in patients who have confirmed mucosal abnormalities (Overall SES-CD Score is greater than 0) regardless of exploration result or Overall SES-CD score of 0 with inaccessible exploration result or with missing exploration result at baseline will be summarized by treatment group for the Efficacy Population.

All colonoscopy (SES-CD) information will be listed by treatment group for the Efficacy Population.

11.3. 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, 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. Descriptive statistics for actual and change from baseline of SIBDQ total score at each study visit will be tabulated by treatment group for the Efficacy Population. All SIBDQ information will be listed by treatment group for the Efficacy Population.

12. 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), complement (C3, C4) and total hemolytic complement, vital sign measurements, 12-lead electrocardiograms (ECGs), hypersensitivity monitoring via vital sign measurements (including blood pressure, heart and respiratory rates and body temperature), physical examination findings, signs and symptoms of tuberculosis (Interferon-γ Release Assay [IGRA] and chest X-ray), local site pain (Visual Analogue Scale [VAS]), pregnancy tests, and immunogenicity tests. All safety data will be listed for the ITT Population unless otherwise specified.

12.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study by signing the ‘Informed Consent’ page of eCRF, 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 20.0 or 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) v4.03.

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

- Missing day (e.g. XXFEB2017): Assume the last day of the month. (e.g. 28FEB2017)
- Missing day and month (e.g. XXXXX2017): Assume December 31st. (e.g. 31DEC2017)
- Missing day, month and year (e.g. XXXXXXXXX): 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 reported stop date.

- If the day of an Adverse Event is missing (e.g. XXFEB2017), 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 end 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. 01FEB2017).
- If the day and month is missing (e.g. XXXXX2017), 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 end 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. 01JAN2017).
- If the AE start date is missing (e.g. XXXXXXXXX), start date will be imputed as the earlier date of: (i) the date of the first exposure to study drug, and (ii) the end date of the AE.

Listings for AEs will include the following information: SOC, PT and Verbatim term; start and stop date; TEAE flag, study period (Dose-loading Phase, Maintenance 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); relationship with study drug (unrelated, possible, probable, definite); action taken with study drug (dose not changed, dose reduced, dose increased, drug interrupted, drug withdrawn); any treatment required (no, yes with specified treatment); whether the event was serious (Yes, No); whether the AE is administration-related reaction (ARR) or injection site reaction (ISR) and infection/malignancy. All AEs will be listed.

In summaries, adverse events will be considered to be related if the relationship is possible, probable, or definite.

12.1.1. 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. TEAEs occurred in Maintenance Phase is defined as any event not present before study drug administration at Week 6 or any event already present that worsens in either intensity or frequency after study drug administration at Week 6.

12.1.2. Deaths

All patients who have an 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 dose, date of last dose, date of last visit, date of death, time to death from first dose, time to death from last dose, days on study, TEAE flag, SOC/ PT/ cause of death, whether an autopsy was performed (yes, no), whether a death certificate was completed (yes, no) and 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).

12.1.3. 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.

All SAEs will be listed including the variables detailed in Section 12.1. Serious criteria and SAE description will be presented in an additional information listing.

12.1.4. 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 discontinuation occurred in Maintenance Phase.

All TEAEs leading to study drug discontinuation will be listed including the variables detailed in Section 12.1.

12.1.5. Treatment-Emergent Adverse Events of Special Interest

The following TEAEs of special interest except for ARR and delayed hypersensitivity will be summarized in separate tables and ARR and delayed hypersensitivity will be summarized together in one table. 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 levels of summarization. The total number of events and number of patients with at least one TEAE of special interest will also be displayed. The summaries will be repeated in separate tables for TEAEs of special interest that occurred in Maintenance Phase. In addition, tables for signs and symptoms regarding ARR and ISR will be provided separately by SOC, PT (as coded by MedDRA version 20.0 or higher version) and intensity. The summaries will be repeated in separate tables for TEAEs of special interest that occurred in Maintenance Phase.

- Infusion-related reactions/hypersensitivity/anaphylactic reactions [administration related reactions]

  AEs classified as IRR in the eCRF and that occurred between start of administration and 24 hours from the study drug administration will be included. Stop time for IV infusion and start time for SC injection will be used for calculating time to ARR occurrence after study drug administration. If administration time or ARR start time is unknown, only administration date and ARR start date will be considered and AEs that occurred within 1 day after study drug administration will be classified as ARR.

  Note: IRR in the eCRF means administration related reaction (ARR).

- Delayed hypersensitivity

  AEs classified as IRR in the eCRF and that occurred of hypersensitivity after 24 hours from the study drug administration will be included. Stop time for IV infusion and start time for SC injection will be used for calculating time to ARR occurrence after study drug administration. If administration time or ARR start time is unknown, only administration date and ARR start date will be considered and AEs that occurred 2 or more days after study drug administration will be classified as Delayed hypersensitivity.

- Injection site reactions (ISR)

  AEs classified as 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). And it will be determined by medical review and included.

TEAEs classified as ARR and ISR will be presented in separate listings including the variables detailed in Section 12.1. Experienced Signs and symptoms will be presented in additional information listings for ARR and ISR, separately. Delayed hypersensitivity will be flagged in ARR listings. Infection and malignancy will be flagged in listings for AEs.

12.2. Clinical Laboratory Evaluations

Clinical laboratory (clinical chemistry, hematology and urinalysis) 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 centrally. Additional clinical laboratory test samples will be collected if a patient experiences delayed hypersensitivity after 24 hours of study drug administration. All summaries will be based on the SI (System International) units provided by the central laboratory, no unit conversion will be done. Result of clinical laboratory parameters listed in lab specification of the central laboratory and ESR will be tabulated by treatment group for the Safety Population. All of the clinical laboratory results will be presented in listings for the ITT Population.

Actual value and change from baseline of all numeric laboratory parameters including clinical chemistry, hematology and urinalysis (if applicable) will be summarized using descriptive statistics by laboratory category, test parameter and visit. 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.

The categorized results of laboratory parameters including clinical chemistry, hematology and urinalysis (if applicable) will be summarized in a shift table from baseline to each scheduled visits. The number and percentage of patients will be displayed for post-baseline visits by treatment group, test parameter and visit.

Some numeric 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 4.03 [6] 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 2. 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 visit. Additional tables will be generated using the most severe grade after administration at Week 0 and Week 6, respectively. The most severe grade will be selected including unscheduled visits.

Clinical chemistry, hematology and urinalysis data will be presented in separate listings along with high and low flags, if applicable, to show if a value was outside the normal range and CTCAE results for applicable parameters.

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

Complement tests (C3, C4, and total hemolytic complement) will be assessed at Week 0. Additional assessment for complement (C3, C4, and total hemolytic complement) will be conducted when a patient experiences a delayed hypersensitivity reaction after 24 hours from study drug administration. All complement tests data will be presented in a listing by treatment group for the ITT Population.

12.4. Vital Signs, Weight and BMI

Vital signs (including systolic and diastolic blood pressure, heart rate, respiratory rate and body temperature), weight and BMI will be assessed at scheduled visits prior to beginning of the study drug administration. 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
- 1 hour (±10 minutes) after the end of the study drug administration

All 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.

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

Table 7. 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 and BMI 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.

12.5. 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 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.

12.6. 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, 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.

12.7. 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”. The number and percentage of patients with IGRA results will be summarized for baseline (as defined in Section 5.5) and ‘Treatment Period’ for the Safety Population. All post-baseline results of IGRA will be reported in a Treatment Period category using the following methodology:

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

12.8. Local Site Pain

Local site pain measurements using 100 mm Visual Analogue Scale (VAS) will be performed immediately (not exceeding 1 hour) after the end of the study drug administration on scheduled visits beginning at Week 6. Local site pain data (scale standardized) will be summarized using descriptive statistics by treatment group and visit for the Safety Population. All local site pain data will be listed by treatment group and visit for the ITT Population.

12.9. 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. The number and percentage of female patients who have urine pregnancy test results will be summarized by treatment group, visit and test for the Safety Population. All pregnancy test results will be listed for each patient tested by treatment group and visit for the ITT Population.

12.10. Immunogenicity

Serum sample for immunogenicity will be collected at Week 0, 6, 14, 22, 30, 38, 46, 54, and EOS. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24 hours of 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) specificity/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 specificity/confirmatory assay to determine if patients are a true positive. The test outcome for the specificity/confirmatory assay will be: {"Reactive", "Negative", and "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 specificity/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"}. For further characterization, the antibody level will be assessed by titration in samples that are "Positive" in the screening NAb assay.

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

The ADA and NAb titer values of the CT-P13 tagged assay will be transformed using a $\log_2(x/23) + 1$ and $\log_2(x/45) + 1$ transformation, respectively. If the values in the data are in forms of inequality, the sign of inequality will be removed and then the values will be transformed. Descriptive statistics of transformed ADA and NAb titer will be displayed by treatment group for the Safety Population. The actual and transformed results of ADA and NAb titer for each visit will also be presented in the listing of immunogenicity results for the ITT Population.

13. Changes in the Planned Analysis

13.1. Changes in the Protocol

1. Section 7.8 of the protocol states that a major protocol deviation that may affect the interpretation of study results of efficacy will be excluded from efficacy population. A major protocol deviation that may affect the interpretation of study results of PK will be excluded from PK population.

   In this SAP for Part 1, patients who were mis-randomized will be considered as major protocol deviation which affect the PK interpretation and will be excluded from PK population only.

2. Section 7.1.2 of the protocol states that the following secondary PK parameters for the study drug will be considered in Part 1 (between Week 22 and Week 30):

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

The BA and AUCτ/DN will not be considered as the secondary PK parameters in this analysis.

3. The formula (AUCτ [ng·h/mL]/ τobs [h]×1344 [h]) for AUCss8W was updated in the SAP from the protocol as in the following:

   - IV group: AUCτ [ng·h/mL]/ τobs [h]×1344 [h]
   - SC (A) group: mean of $\left(\frac{AUC\tau \ at \ W22}{\tau obs \ at \ W22} \ , \ \frac{AUC\tau \ at \ W26}{\tau obs \ at \ W26}\right)$×1344 [h]
   - SC (B) group: mean of $\left(\frac{AUC\tau \ at \ W24}{\tau obs \ at \ W24} \ , \ \frac{AUC\tau \ at \ W28}{\tau obs \ at \ W28}\right)$ ×1344 [h]

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15. APPENDICES

Appendix 1: Schedule of Events for Part 1

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

	Screening	Treatment Period											EOS[2]
Study Week		**0**	**2**	**6**	**8[1]**	**10[1]**	**14**	**22**	**PK Monitoring Visit[24]**	**30**	**38**	**46**	**54**	
Study Day	**–21 to –1**	**0**	**14**	**42**	**56**	**70**	**98**	**154**		**210**	**266**	**322**	**378**	
Visit Window		**N/A**	**± 3 days**							**± 3 days**	**± 5 days**			
AEs monitoring[28]	X													

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

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

17. CDAI score will be calculated once all components of the CDAI (patient's CDAI diary entries, hematocrit results, and assessments performed by site investigator) are available. For CDAI assessment at Screening and during the study period, hematocrit results from local laboratory within the 7 days prior to the CDAI assessment date will be used. Patients will complete CDAI diary at least 7 consecutive days prior to CDAI assessment date, except when CDAI assessment is performed at the same date of colonoscopy procedure. If patient is planned to have bowel preparation for colonoscopy procedure, patient should not complete CDAI diary during the day before and up to the next day of colonoscopy procedure.
18. End-of-Study assessments will only be performed if not done at Week 54.
19. All patients will assess local site pain using 100 mm Visual Analogue Scale (VAS) immediately (not exceeding 1 hour) after the end of administration of study drug.
20. Sampling and handling for calprotectin testing will be conducted only at the qualified or feasible sites.
21. Serum samples for immunogenicity testing will be drawn at the same time as the clinical laboratory tests before dosing, where applicable. Additional serum samples for immunogenicity testing may be collected if a patient experiences any delayed hypersensitivity after 24hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
22. Additional vital signs including blood pressure, heart and respiratory rates, and body temperature (prior to the beginning of the study treatment administration and 1 hour (±10 minutes) after the end of the study drug administration) to monitor for possible hypersensitivity reactions. In addition, hypersensitivity will be monitored by routine continuous clinical monitoring, including patient-reported signs and symptoms. In case of hypersensitivity, emergency equipment, such as adrenaline, antihistamines, corticosteroids, and respiratory support including inhalational therapy, oxygen, and artificial ventilation must be available and any types of ECG can be performed. In addition, delayed hypersensitivity will be monitored after 24 hours of study drug administration, including serum sickness-like reaction (myalgia with fever or rash, arthralgia, lymphadenopathy, skin eruption or edema).
23. Additional serum samples for complement (C3, C4) and total hemolytic complement will be assessed if delayed hypersensitivity occurs after 24 hours of study drug administration to determine serum sickness. Analysis will be performed at the central laboratory.
24. If the investigator deems hospitalization necessary for the blood sample collection, patients should remain in the hospital until blood samples for pharmacokinetic analysis have been collected. If the investigator deems hospitalization unnecessary and sampling can be adequately obtained without hospitalization, the patient does not have to remain hospitalized. Blood samples for pharmacokinetic analysis will be obtained at following time point;

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

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

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

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

Appendix 2: Table of CTCAE Terms and Grades

CTCAE Term	Laboratory Parameter	Level	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	Hemoglobin	Low	<LLN - 10.0 g/dL; <LLN - 100 g/L	<10.0 - 8.0 g/dL; <100 - 80g/L	<8.0 g/dL; <80 g/L;	-
Alanine aminotransferase increased	Alanine Aminotransferase (ALT)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	Alkaline phosphatase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	Aspartate Aminotransferase (AST)	High	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	Total Bilirubin	High	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
CPK increased	Creatine Phosphokinase (CPK)	High	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased	Creatinine	High	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
GGT increased	Gamma Glutamyl Transferase	High	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN

Hemoglobin increased	Hemoglobin	High	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-
Hyperkalemia	Potassium	High	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L	>7.0 mmol/L
Hypernatremia	Sodium	High	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L;	>160 mmol/L
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	-
Hypokalemia	Potassium	Low	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L #	<3.0 - 2.5 mmol/L	<2.5 mmol/L
Hyponatremia	Sodium	Low	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L
Lymphocyte count decreased	Lymphocytes	Low	<LLN - 800/mm^3; <LLN - 0.8 x $10e^9$/L	<800 - 500/mm^3; <0.8 - 0.5 x $10e^9$ /L	<500 - 200/mm^3; <0.5 - 0.2 x $10e^9$ /L	<200/mm^3; <0.2 x $10e^9$ /L
Lymphocyte count increased	Lymphocytes	High	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3	-
Neutrophil count decreased	Total Neutrophils	Low	<LLN - 1500/mm^3; <LLN - 1.5 x $10e^9$ /L	<1500 - 1000/mm^3; <1.5 - 1.0 x $10e^9$ /L	<1000 - 500/mm^3; <1.0 - 0.5 x $10e^9$ /L	<500/mm^3; <0.5 x $10e^9$ /L

Platelet count decreased	Platelet count	Low	<LLN - 75,000/mm^3; <LLN - 75.0 x $10e^9$ /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x $10e^9$ /L	<50,000 - 25,000/mm^3; <50.0 - 25.0 x $10e^9$ /L	<25,000/mm^3; <25.0 x $10e^9$ /L
White blood cell decreased	White Blood Cells	Low	<LLN - 3000/mm^3; <LLN - 3.0 x $10e^9$ /L	<3000 - 2000/mm^3; <3.0 - 2.0 x $10e^9$ /L	<2000 - 1000/mm3; <2.0 - 1.0 x $10e^9$ /L	<1000/mm^3; <1.0 x $10e^9$ /L

Note: The LLN and ULN values will be the normal ranges as provided by the central laboratory. # indicates that this grade will not be used because this grade shares the same criteria due to exclusion of clinical input.