Non-Interventional Study Protocol
Protocol C1231001

Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease (IBD) Treated with CT-P13 in Usual Clinical Practice (CONNECT-IBD)

Statistical Analysis Plan
(SAP)

Version: Amendment 4.0

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[redacted]

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Document	Version Date	Summary of Changes
Amendment 4	08 Oct 2018	• Revised subgroup definitions • Updated AESI search criteria • Added text 'in the context of standard of care (SOC) Remicade' in sections 8.2.2 • Added definition of analysis visit windows for effectiveness CCI [redacted] endpoints analyses • Added clarification that type of IBD to be used in analysis will be based on current diagnosis • Added clarification on how to analyze subjects with multiple assay assessments with different results • CCI [redacted]
Amendment 3.2	18 May 2018	• Updated AESI list and search criteria • Removed section 8.2.3 in the data to be analyzed in interim analysis since antibody analysis is now included in section 8.2.1 • Added text for the presentation of infusion related reactions and serious infections to include opportunistic infections
Amendment 3.1	26 Apr 2018	Updated AESI search criteria
Amendment 3	13 Feb 2018	The amendment has been made to align the identification of AESIs with the search criteria in CT-P13 RMP.
Amendment 2	24 Jan 2018	The amendment has been made to better define the switching group.
Amendment 1	26 Dec 2017	The amendment has been made to revise the subset for interim analysis to only include subjects who received CT-P13 any time during the observation

		period of the study.
Version 1.0	29 Nov 2017	Not applicable

2 INTRODUCTION

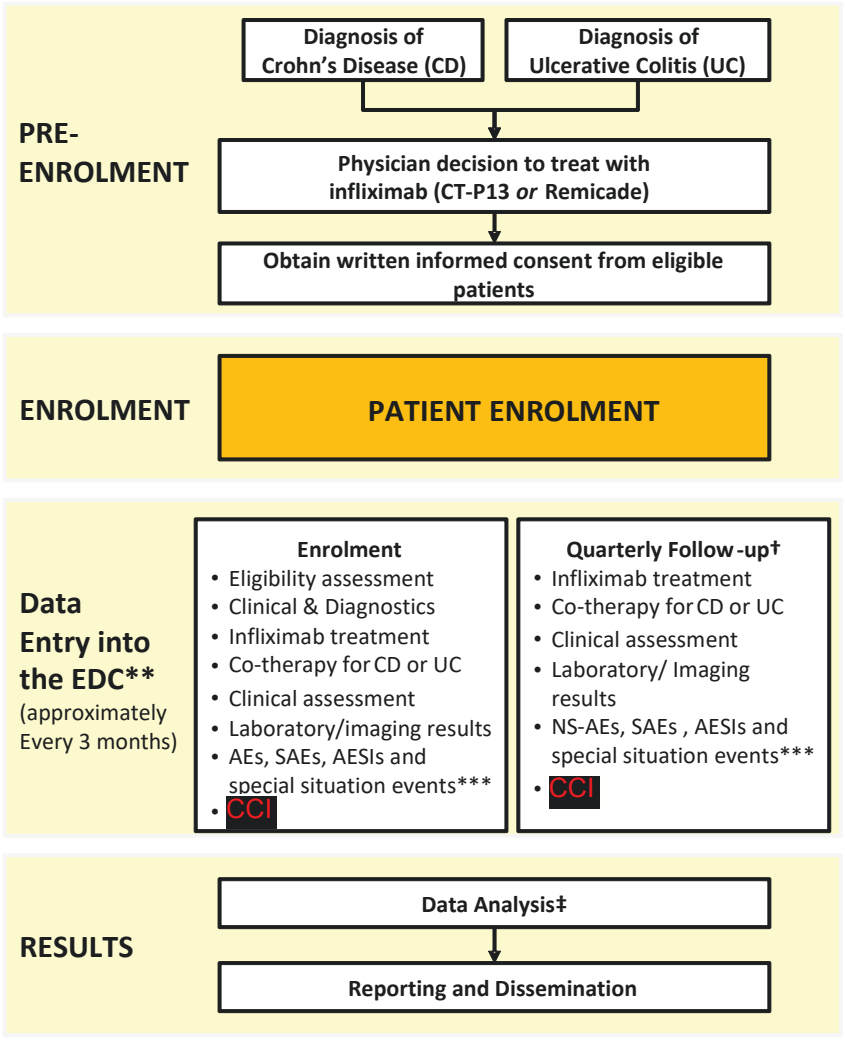
Remicade® (infliximab, Janssen Biotech, Inc.), an IgG_1 chimeric human-murine monoclonal antibody (mAb), was authorised for approval in Europe in August 1999. Since then it has been utilised in many thousands of patients for the treatment of 2 major types of inflammatory bowel disease (IBD), Crohn's Disease (CD) and ulcerative colitis (UC). In September 2013, CT-P13 (infliximab), a mAb biosimilar to reference Remicade, was approved by the European Medicines Agency (EMA) based on an extensive biosimilar comparability exercise, which demonstrated that quality, as well as the clinical efficacy, pharmacokinetics and safety profile of CT-P13 are highly comparable to that of Remicade. Marketing authorisation of CT-P13 included all approved indications for Remicade including the extrapolated indications of moderate to severe CD and UC. This study is designed to characterise the patient population currently receiving CT-P13 in the context of standard of care (SOC) utilisation of Remicade, and to document the safety and effectiveness of CT-P13, also in the context of SOC Remicade, in the treatment of patients with CD or UC in real-world clinical practice.

2.1 STUDY DESIGN

This study is a multi-national, multi-centre, observational cohort study of patients with CD or UC, who are treated with CT-P13 (or Remicade for the smaller SOC cohort). The decision to treat with CT-P13 (or Remicade) will be made at the usual care discretion of the physician independent of and before the decision to enrol patients in the study.

There will be no study visits mandated per the study protocol. Patients' visit schedules will follow local SOC, typically coinciding with the schedule of infusions of CT-P13 or Remicade, with additional visits as needed at the treating physician's discretion. Data for the study will be entered into an electronic data capture (EDC) system at enrolment and then approximately every 3 months thereafter up to a 2-year follow-up period, or until the end of the last patient 1-year follow-up period, whichever occurs first.

Figure 1: Study Design Schematic



***Updates of clinical information are recorded in patient's records during each treatment/ clinical visit; however, data entry into the EDC occurs approximately every 3 months (at a minimum),* CCI [redacted] *In order to adequately manage EDC entry, sites are encouraged to enter data in the EDC within 10 days of a patient's visit data collection date.*

**** Special situation events are detailed in Section 10. Along with SAEs and AESIs, they must be reported within 24 hours of site awareness.*

†Patient switching between CT-P13 and Remicade will be followed until end of study with the full CRF. Those who discontinue infliximab treatment, will be followed up with a simplified CRF for the remainder of the study period. Refer to Table 1 for details.

‡Data collected on patients with CD and UC may be analysed separately.

[redacted]

Study assessments will be performed as summarized in the schedule of study activities in Table 1. All screening procedures are to be performed prior to starting study drug.

Table 1. Study data collection schedule

	Once at enrolment	*Every 3 months up to a 2-year follow-up period, or until the end of the last patient 1-year follow-up period, whichever occurs first*	
	Enrolment	**Follow-up Period***	**Infliximab treatment discontinuation****
Eligibility assessment and written informed consent	X		
Relevant medical history for CD or UC • Diagnosis of CD or UC: extent, severity, duration • Prior treatments	X		
Infliximab therapy – CT-P13 or Remicade • Dose, frequency: augmentation/reduction, reasons of changes • Switch(es) or discontinuation, reasons of switch/discontinuation	X	X	
Co-therapy *(frequency, dose, augmentation/reduction, switching, reason of switch)* • Steroid use • Medication(s) relating to the treatment of CD or UC or management of the symptoms of CD or UC • Medication(s) relating to the management of SAE/AESI	X	X	X

Clinical assessment
• Data relating to Harvey-Bradshaw Index (HBI) for CD
• Data relating to Partial Mayo Scoring System for Assessment of Ulcerative Colitis Activity for UC (abbreviated version excluding endoscopy sub-score)
• Montreal classification for CD
• Montreal classification for UC:
  ○ Classification by extent
  ○ Classification by severity
• Fistula drainage assessment
• Clinical remission/relapse
	X	X	X**

Laboratory results leading to CD or UC treatment decision* **	X	X	
Imaging results leading to CD or UC treatment decision	X	X	
CCI [redacted]	X	X	
Safety outcomes • Serious adverse event (SAE) • Adverse Events of Special Interest (AESI) • Non-serious AEs • Special Situations	**Within 24 hours of awareness** for SAE, AESI and special situations. Non-serious AEs will follow standard data collection timelines	**Within 24 hours of awareness** for SAE, AESI and special situations. Non-serious AEs will follow standard data collection timelines	**Within 24 hours of awareness** for SAE, AESI and special situations. Non-serious AEs will follow standard data collection timelines

[a] *Recording of medical data into patients' charts occurs during their usual care visit. Data entry into the EDC system occurs approximately every 3 months at a minimum. However, sites are encouraged to enter all standard of care visits completed within each three month period into the EDC, and when possible conduct entry within 10 days of each patient's data collection visit date.*

[a] *Patients who discontinue infliximab treatment will be encouraged to remain in the study and be followed for the remainder* [a] *of the study period using a simplified CRF. HBI, Partial Mayo scoring, Montreal classification for CD or UC and fistula drainage assessment may not be applicable to simplified data capture depending on local SOC, but information on clinical remission or relapse will be captured to the extent possible. Clinical assessment forms are within the treatment discontinuation visit CRF.*

****For sites that conduct local practice of immunogenicity analysis, patients will have an option to provide immunogenicity results for data collection. The data collected should include the most recent test results just prior to enrolment, and for any tests performed during patient study participation. Please reference Appendix 9 (Optional Immunogenicity Data Collection) for more information.*

Study population

In order to characterise the population and drug utilisation patterns associated with the use of CT-P13 in CD and UC, as well as its safety and effectiveness in the context of contemporaneous SOC Remicade, the study plans to enrol approximately 2,500 patients in a mix of academic and community sites in approximately 13 countries where CT-P13 and Remicade are authorised for the treatment of CD or UC. In order to meaningfully describe expected subgroups in this heterogeneous patient population under treatment, approximately 1,900 of the patients enrolled will be included in the CT-P13 cohort. All patients are expected to be enrolled over an approximate 30-month period. Study participation of all ongoing patients will continue up to a 2-year follow-up period, or

[redacted]

until the end of the last patient 1-year follow-up period, whichever occurs first. Enrolled patients who permanently discontinue infliximab (CT-P13 or Remicade) treatment will be encouraged to remain in the study and be followed for the remainder of the study period using a simplified case report form (CRF).

Data source
Not applicable.

Treatment/cohort labels
CT-P13
Remicade

2.2 STUDY OBJECTIVES

Primary Study Objective

The primary study objectives of the study are to characterise the population and drug utilisation patterns of patients with CT-P13 for CD or UC and to explore the long-term safety of CT-P13 in the treatment of patients with CD or UC in the context of SOC Remicade.

Secondary Study Objective

The secondary study objective of the study is to assess effectiveness of CT-P13 in the treatment of patients with CD or UC in the context of SOC Remicade. Effectiveness is a measure of the extent to which a specific intervention, procedure, regimen, or service when deployed in the field in routine circumstances, does what it is intended to do for a specified population. 'Effectiveness' should be distinguished from 'efficacy', which is a measure of the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions.

CCI [redacted]

3 INTERIM ANALYSES

An interim analysis will be conducted for all data collected from study start through 27 December 2017 for all subjects who received CT-P13 at any time during the study. Only the safety analyses described in section 8.2.1 will be done.

4 HYPOTHESES AND DECISION RULES

Not applicable.

[redacted]

5 ANALYSIS SETS/ POPULATIONS

The set of subjects (populations) whose data are to be included in the main analyses are as follows.

5.1 FULL ANALYSIS SET

The full analysis set is defined as all patients who received at least one dose of study drug during the study observation period and have at least one post-dose assessment of any of the effectiveness endpoints (see Section 6.1). The secondary endpoints CCI [redacted] will be evaluated using this analysis population.

5.2 SAFETY ANALYSIS SET

The safety analysis set is defined as all patients who received at least one dose of study drug during the study observation period. The primary endpoints will be evaluated using this analysis population.

5.3 SUBGROUPS

Patient characteristics and study outcomes will be presented using the following subgroups:

- CT-P13: This group consists of the following subjects
  - Who are biologic naïve initiating CT-P13 and received CT-P13 continuously
  - Who are treated with CT-P13 continuously
  - Who are treated with CT-P13 then switched to other anti-TNFs (except Remicade) or non-biologic treatment during the study
  - Patients switching to CT-P13 from an alternative biologic therapy (except Remicade) due to non-responsiveness to or intolerance with existing therapy
- Remicade: This group consists of the following subjects
  - Who are biologic naïve initiating Remicade and received Remicade continuously
  - Who are treated with Remicade continuously
  - Who are treated with Remicade then switched to other anti-TNFs (except CT-P13) or non-biologic treatment during the study
  - Patients switching to Remicade from an alternative biologic therapy (e.g., adalimumab) (except CT-P13) due to non-responsiveness to or intolerance
- Switched from Remicade to CT-P13: This group consists of subjects who are treated with Remicade continuously who switched to CT-P13 once, either at enrolment or during the study

- Switched from CT-P13 to Remicade: This group consists of subjects who are treated with CT-P13 continuously who switched to Remicade once, either at enrolment or during the study
- Multiple switchers: This group consists of subjects with at least two switches between Remicade and CT-P13

6 ENDPOINTS AND COVARIATES

6.1 EFFECTIVENESS ENDPOINTS

The measures of disease activity in patients with CD or UC and laboratory and imaging results will constitute the effectiveness endpoints of the study. These are the secondary endpoints which include the following:

- Clinical assessment of disease activity
    - Data relating to Harvey Bradshaw Index (HBI) for patients with CD
    - Data relating to Partial Mayo Scoring System for Assessment of UC Activity, i.e., abbreviated version without the endoscopy sub-score
    - Data relating to the Montreal classification index for CD
    - Data relating to the Montreal classification index for UC:
        - classification by extent
        - classification by severity
    - Data relating to the fistula drainage assessment index for CD
- Laboratory results related to the treatment or assessment of CD or UC
- Imaging results related to the treatment or assessment of CD or UC

For each endpoint, baseline value will be defined as the most recent value on or before the first CT-P13 (or Remicade) treatment during the observation period of the study.

6.1.1 HBI

The Harvey-Bradshaw Index (HBI) is a simple index of Crohn's disease activity. It measures the following clinical parameters: the general well-being (ranging from 0 being very well and 4 being terrible), the abdominal pain (from 0 having none to 3 having severe), the number of liquid stools per day, the presence of abdominal mass (from 0 having none to 3 having definite and tender), and if there are any complications (ranging from 0 having no complications and 8 having abscess). The total HBI score is the sum of all the parameters. If one parameter is missing then the value of that parameter is assumed a value of 0.

The level of disease activity will be interpreted as clinical remission (HBI score < 5), mild disease (HBI score = 5-7), moderate disease (HBI score = 8-16) and severe disease (HBI score > 16).

6.1.2 Partial Mayo Scoring System

The Partial Mayo Scoring System is an assessment of Ulcerative Colitis activity. It consists of the following parameters: the stool frequency (ranging from 0 having normal number of stools for patient and 3 having 5 or more stools more than normal), the presence of rectal bleeding (from 0 having no blood seen to 3 having blood alone passes), and physician's global assessment (ranging from 0 being normal and 3 having severe disease). The total Partial Mayo score is the sum of all the parameters. The partial Mayo score is calculated if data are available for at least 1 of 3 Mayo subscores. If all 3 subscores are missing, the partial Mayo score is not calculated and is considered missing.

The level of disease activity will be interpreted as clinical remission (Partial Mayo score <2), mild disease (Partial Mayo score = 2-4), moderate disease (Partial Mayo score = 5-6) and severe disease (Partial Mayo score > 6).

6.1.3 Montreal classification index for CD

The Montreal classification index for CD is used to classify the extent of the disease activity. It consists of three parameters: age at diagnosis, location and behavior of the disease activity. There are four different disease locations: L1 is terminal ileum, L2 is colon, L3 is ileocolon and L4 is upper GI. The first three categories (L1-L3) can be combined with L4 where disease sites coexist. Also, there are four different categories of the behavior of the disease activity: B1 is nonstricturing, nonpenetrating, B2 is stricturing, B3 is penetrating and p as perianal disease. The first three categories (B1-B3) can be added with p to indicate coexisting perianal disease. Perianal disease (p) is defined as the presence of perianal abscesses or fistulae.

6.1.4 Montreal classification index for UC

The Montreal classification index for UC is used to classify the extent and severity of the disease activity. There are three subgroups of UC defined by extent: E1 is Ulcerative proctitis, E2 is Left-sided UC and E3 Extensive UC. And UC can be classified broadly into four disease activity/severity categories: S0 is UC in clinical remission, S1 is Mild UC, S2 is Moderate UC and S3 is Severe UC.

6.1.5 Fistula drainage assessment index

The fistula drainage assessment index is used to assess the improvement or remission of the disease activity of CD.

6.1.6 Laboratory

The laboratory tests related to the treatment or assessment of CD or UC are the C-reactive protein and Fecal calprotectin.

6.1.7 Imaging

Any imaging tests related to the treatment or assessment of CD or UC.

6.2 SAFETY ENDPOINTS

6.2.1 Adverse Events

Safety endpoints will include incidence of adverse events (AE), adverse events of special interest (AESI) and serious adverse events (SAE). The MedDRA dictionary (version 20.0 or later) will be used to map AE descriptions to preferred terms (PT) and system organ classes (SOC). An AE will be considered to be treatment-emergent if the event started or worsened in severity after the start of CT-P13 (or Remicade) treatment until the end of the observation period for the study.

Table 2 provides the list of AESIs for the study and the corresponding MedDRA terms and algorithms for AESI identification. Adverse events previously captured as AESIs but no longer meeting AESI criteria (due to updates to the protocol or AESI search criteria) will not be presented in the analysis tables as AESIs but will be indicated with an * (e.g. No*) in the dataset listings and explanation given as a footnote on each affected page.

In addition to excluding from the analysis those AESIs no longer meeting currently defined AESI criteria, two separate AESIs where no detailed information on infusion duration and re-induction regimen was captured in the study database, identification as AESIs of Infusion reaction associated with shortened infusion duration and Serious infusion reactions during a re-induction regimen following disease flare will not be captured as such but will be grouped and presented in the analysis tables as Infusion related reactions.

Table 2. Adverse Event of Special Interest

Adverse Event of Special Interest	MedDRA Level | MedDRA term (s)
Serious infections including sepsis (excluding opportunistic infections and tuberculosis)	Step 1: Serious Step 2: SOC Infections and Infestations Step 3: Exclude: HLT: Tuberculous infections HLGT: Chlamydial infectious disorders HLGT: Fungal infectious disorders HLGT: Helminthic disorders

	HLGT: Mycoplasmal infectious disorders HLGT: Protozoal infectious disorders HLGT: Rickettsial infectious disorders PT: Atypical pneumonia PT: BK virus infection PT: Brucellosis PT: Coccidiodomycosis PT: CSF measles antibody positive PT: Cytomegalovirus chorioretinitis PT: Cytomegalovirus colitis PT: Cytomegalovirus duodenitis PT: Cytomegalovirus enteritis PT: Cytomegalovirus enterocolitis PT: Cytomegalovirus gastritis PT: Cytomegalovirus gastroenteritis PT: Cytomegalovirus gastrointestinal infection PT: Cytomegalovirus hepatitis PT: Cytomegalovirus infection PT: Cytomegalovirus mononucleosis PT: Cytomegalovirus mucocutaneous ulcer PT: Cytomegalovirus myelomeningoradiculitis PT: Cytomegalovirus myocarditis PT: Cytomegalovirus oesophagitis PT: Cytomegalovirus pancreatitis PT: Cytomegalovirus pericarditis PT: Cytomegalovirus syndrome PT: Cytomegalovirus test positive PT: Cytomegalovirus viraemia PT: Disseminated cytomegaloviral infection PT: Encephalitis cytomegalovirus PT: Encephalitis viral PT: Epstein-Barr viraemia PT: Epstein-Barr virus infection PT: Fungaemia PT: Hepatitis infectious mononucleosis PT: Herpes oesophagitis

	PT: Herpes sepsis PT: Herpes zoster cutaneous disseminated PT: Herpes simplex visceral PT: Herpes virus infection PT: Herpes zoster PT: Herpes zoster disseminated PT: Herpes zoster infection neurological PT: Herpes zoster oticus PT: Human herpesvirus infection PT: Infective aneurysm PT: Infection in an immunocompromised host PT: Infectious mononucleosis PT: JC virus infection PT: Kaposi's sarcoma PT: Kaposi's varicelliform eruption PT: Lung infection pseudomonal PT: Lymph node tuberculosis PT: Meningoencephalitis herpetic PT: Nocardia sepsis PT: Nocardiosis PT: Opportunistic infection PT: Ophthalmic herpes zoster PT: Oral herpes PT: Pneumonia cytomegalo viral PT: Pneumonia herpes viral PT: Pneumonia primary atypical PT: Progressive multifocal leukoencephalopathy PT: Pulmonary tuberculosis PT: West Nile viral infection
Opportunistic Infection	Step 1: Serious Step 2: HLGT: Chlamydial infectious disorders HLGT: Fungal infectious disorders HLGT: Helminthic disorders HLGT: Mycoplasmal infectious disorders HLGT: Protozoal infectious disorders

	HLGT: Rickettsial infectious disorders PT: Atypical pneumonia PT: BK virus infection PT: Brucellosis PT: Coccidiodomycosis PT: CSF measles antibody positive PT: Cytomegalovirus chorioretinitis PT: Cytomegalovirus colitis PT: Cytomegalovirus duodenitis PT: Cytomegalovirus enteritis PT: Cytomegalovirus enterocolitis PT: Cytomegalovirus gastritis PT: Cytomegalovirus gastroenteritis PT: Cytomegalovirus gastrointestinal infection PT: Cytomegalovirus hepatitis PT: Cytomegalovirus infection PT: Cytomegalovirus mononucleosis PT: Cytomegalovirus mucocutaneous ulcer PT: Cytomegalovirus myelomeningoradiculitis PT: Cytomegalovirus myocarditis PT: Cytomegalovirus oesophagitis PT: Cytomegalovirus pancreatitis PT: Cytomegalovirus pericarditis PT: Cytomegalovirus syndrome PT: Cytomegalovirus test positive PT: Cytomegalovirus viraemia PT: Disseminated cytomegaloviral infection PT: Encephalitis cytomegalovirus PT: Encephalitis viral PT: Epstein-Barr viraemia PT: Epstein-Barr virus infection PT: Fungaemia PT: Hepatitis infectious mononucleosis PT: Herpes oesophagitis PT: Herpes sepsis PT: Herpes zoster cutaneous disseminated

	PT: Herpes simplex visceral PT: Herpes virus infection PT: Herpes zoster PT: Herpes zoster disseminated PT: Herpes zoster infection neurological PT: Herpes zoster oticus PT: Human herpesvirus infection PT: Infective aneurysm PT: Infection in an immunocompromised host PT: Infectious mononucleosis PT: JC virus infection PT: Kaposi's sarcoma PT: Kaposi's varicelliform eruption PT: Lung infection pseudomonal PT: Lymph node tuberculosis PT: Meningoencephalitis herpetic PT: Nocardia sepsis PT: Nocardiosis PT: Opportunistic infection PT: Ophthalmic herpes zoster PT: Oral herpes PT: Pneumonia cytomegalo viral PT: Pneumonia herpes viral PT: Pneumonia primary atypical PT: Progressive multifocal leukoencephalopathy PT: Pulmonary tuberculosis PT: West Nile viral infection
Tuberculosis	Step 1: HLT: Tuberculous infections Step 2: Exclude: PT: Latent tuberculosis
BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab	Step 1: PT: Maternal exposure during pregnancy PT: Maternal drugs affecting foetus PT: Foetal exposure during pregnancy PT: Exposure during pregnancy Step 2: Medical review to check whether BCG

	breakthrough and agranulocytosis has occurred,
Acute hypersensitivity reactions (including anaphylactic shock)	Step 1: HLGT: Allergic conditions Step 2: Serious or severe Step 3: Medical review to check if it conforms to anaphylaxis based on Sampson's et al (2006).
Infusion related reactions	AEs fulfil the following conditions. - occurred within 1 day from administration date related to study drug - SMQ narrow: Hypersensitivity - SMQ narrow: Anaphylactic reaction - PT: Pyrexia - PT: Body temperature increased - PT: Chills - PT: Eye irritation - PT: Burning sensation - PT: Non-cardiac chest pain - PT: Chest pain - PT: Upper respiratory tract congestion - PT: Procedural hypotension - PT: Hypertension - PT: Procedural hypertension - PT: Blood pressure increased - PT: Supraventricular extrasystoles - PT: Bradycardia - PT: Sinus bradycardia - PT: Tachycardia - PT: Sinus tachycardia - PT: Atrial fibrillation - PT: Vomiting - PT: Nausea - PT: Oropharyngeal pain - PT: Abdominal pain upper - PT: Abdominal pain - PT: Myalgia - PT: Arthralgia - PT: Headache

	- PT: Migraine - PT: Dizziness - PT: Hypoxia - PT: Throat irritation - PT: Hypotonia - PT: Syncope - PT: Incontinence - PT: Enlarged uvula
Serum sickness (delayed hypersensitivity reactions)	PT: Serum sickness PT: Type III immune complex mediated reaction PT: Type IV hypersensitivity reaction
Haematological reactions	Step 1: SOC Blood and lymphatic system disorders Excluding the following HLGTs: Lymphomas Hodgkin's disease, Lymphomas NEC, Lymphomas non-Hodgkin's B-cell, Lymphomas non-Hodgkin's T-cell, Lymphomas non-Hodgkin's unspecified histology Excluding the following PTs: Any PT contains 'Leukaemia' Excluding LLT: Multiple myeloma Step 2: Serious
Systemic lupus erythematosus (SLE)/lupus-like syndrome	SMQ narrow: Systemic lupus erythematosus
Lymphoma (not HSTCL)	Step 1: HLGT: Lymphomas Hodgkin's disease HLGT: Lymphomas NEC HLGT: Lymphomas non-Hodgkin's B-cell HLGT: Lymphomas non-Hodgkin's T-cell HLGT: Lymphomas non-Hodgkin's unspecified histology Step 2: Exclude PT: Hepatosplenic T-cell lymphoma
Hepatosplenic T-cell lymphoma (HSTCL)	PT: Hepatosplenic T-cell lymphoma
Leukaemia	HLGT: Leukaemias
Merkel cell carcinoma	LLT: Merkel cell carcinoma
Melanoma	HLT: Skin melanomas (excl ocular)
Cervical cancer	HLT: Cervix neoplasms

	Gender: Female
Paediatric malignancy	SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps) Age: 0-17 years
Hepatobiliary events	Step 1: Serious Step 2: PT: Alanine aminotransferase increased PT: Alanine aminotransferase abnormal PT: Aspartate aminotransferase increased PT: Aspartate aminotransferase abnormal PT: Blood alkaline phosphatase increased PT: Blood alkaline phosphatase abnormal PT: Cholecystitis acute PT: Cholecystitis chronic PT: Gamma-glutamyltransferase increased PT: Gamma-glutamyltransferase abnormal PT: Hepatic enzyme increased PT: Hepatic enzyme abnormal PT: Hepatic steatosis PT: Hepatitis PT: Hepatitis acute PT: Hepatitis toxic PT: Hepatomegaly PT: Hepatotoxicity PT: Hyperbilirubinaemia PT: Hypertransaminasaemia PT: Liver disorder PT: Liver function test abnormal PT: Transaminases increased PT: Transaminases abnormal
Hepatitis B virus (HBV) reactivation	Step 1: Medical History or in laboratory data: virus screening result PT: Hepatitis infectious PT: Hepatitis B PT: Hepatitis viral PT: Hepatitis acute PT: Hepatitis toxic PT: Hepatitis B antigen positive PT: Hepatitis B core antigen positive PT: Hepatitis B e antigen positive PT: Hepatitis B surface antigen positive

[redacted]

	PT: Hepatitis B antibody PT: Hepatitis B antibody abnormal PT: Hepatitis B antibody positive PT: Hepatitis B core antibody PT: Hepatitis B core antibody positive PT: Hepatitis B e antibody PT: Hepatitis B e antibody positive PT: Hepatitis B DNA assay PT: Hepatitis B DNA assay positive PT: Hepatitis B DNA increased Step 2: in TEAE PT: Hepatitis infectious PT: Hepatitis B PT: Hepatitis viral PT: Hepatitis acute PT: Hepatitis toxic
Congestive heart failure	PT: Cardiac failure PT: Cardiac failure chronic PT: Cardiac failure congestive LLT: Left ventricular ejection fraction decreased
Demyelinating disorders	HLGT: Demyelinating disorders
Sarcoidosis/sarcoid-like reactions	HLT: Acute and chronic sarcoidosis
Intestinal or perianal abscess (in Crohn's disease)	Step 1: Indication: Crohn's disease Step 2: AEs with HLTs: HLT: Gastric and gastroenteric infections HLT: Gastrointestinal infections, site unspecified HLT: Intestinal infections HLT: Peritoneal infections HLT: Abdominal and gastrointestinal infections
Malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma and cervical cancer)	Step 1: Age: >18 years old Step 2: SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) Step 3: Exclude PT: Hepatosplenic T-cell lymphoma HLGT: Lymphomas Hodgkin's disease HLGT: Lymphomas NEC HLGT: Lymphomas non-Hodgkin's B-cell HLGT: Lymphomas non-Hodgkin's T-cell

	HLGT: Lymphomas non-Hodgkin's unspecified histology HLT: Skin neoplasms malignant and unspecified (excl melanoma) HLT: Skin melanomas (excl ocular) HLGT: Leukaemias LLT: Merkel cell carcinoma HLT: Cervix Neoplasms Indication: UC HLGT: Gastrointestinal neoplasms malignant and unspecified
Colon carcinoma/dysplasia (in ulcerative colitis)	Step 1: Indication: Ulcerative Colitis Step 2: HLGT: Gastrointestinal neoplasms malignant and unspecified
Skin cancer (excluding melanoma, Merkel cell carcinoma)	HLT: Skin neoplasms malignant and unspecified (excl melanoma)
Pregnancy exposure	Step 1: PT: Maternal Exposure during pregnancy PT: Maternal drugs affecting foetus PT: Foetal exposure during pregnancy PT: Exposure during pregnancy Step 2: Manual review to check whether the patient has been exposed to infliximab

6.3 OTHER ENDPOINTS

6.3.1 Population Characteristics

Another primary endpoint is the evaluation of population characteristics of patients with CD or UC in terms of demographic characteristics, general medical history, disease duration and surgery status. Demographic characteristics include age, sex and race. General medical history includes whether smoker or non-smoker, had a history of cancer (including the type of cancer), whether subject had a fistulating disease and the stoma status. Disease duration is derived as the number of months from initial diagnosis of inflammatory bowel disease to the date of informed consent. Surgery status is a categorical variable defined as yes, if the patient had a prior surgical procedure for the treatment of CD or UC, and no otherwise.

6.3.2 Drug Utilisation Pattern

Included in the primary endpoints is the drug utilisation pattern. This will include the initial dose and infusion frequency (weeks) of CT-P13 in the context of standard of care (SOC) Remicade, average dose received during the observation period of the study, dose reduction or augmentation and reason for change, and concomitant medication related to the treatment of CD or UC. Also, the proportion of patients remaining in clinical remission or relapse at designated follow-up visits (see section A1.1), and proportion of patients with steroid use will be computed.

CCI

CCI [redacted]

[redacted]

7 HANDLING OF MISSING VALUES

In general, missing data will not be imputed.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

Considering the observational design of the study and its objectives, the statistical analysis will be descriptive in nature. Summary tabulations will be presented that will display the number of observations (N), mean, standard deviation (SD), median, minimum and maximum for continuous variables. For categorical variables, N and percent will be provided. Summaries will be presented by subgroups defined in Section 5.3 and by type of IBD based on final data available for analysis. The type of IBD (CD or UC) will be based on the current diagnosis upon enrolment in the study.

Subject listings of all data from the CRFs will be presented.

8.2 STATISTICAL ANALYSES

8.2.1 Primary Analyses

The primary analyses will be conducted on Safety Analysis Set and will include analysis of the following primary endpoints:

- Safety Endpoints (Adverse Events)
- Population Characteristics
- Drug Utilisation Pattern

[redacted]

Safety Endpoints

Only the treatment-emergent AE will be analyzed. However, all AEs will be presented in data listings. The number and percentage of patients with treatment-emergent AEs will be summarized according to MedDRA system organ class and preferred term. Category of AE severity and category of AE relationship to study drug will be summarized. For each subject, only the most severe category and the closest relationship will be counted. In addition, AEs leading to death, serious AEs, AEs leading to discontinuation from study and AEs leading to discontinuation of study drug will be summarised.

In order to account for the different durations of exposure, the rates for the most frequent AEs will be normalized to subject exposure so as to evaluate the incidence according to time of exposure. The most frequent AEs per 100 subject years of exposure (defined as an incidence of ≥ 2 per 100 subject years of exposure to treatment (see EAIR definition below) will be summarized by preferred term.

Subject-years are calculated per the following rule:

- For subjects with at least one incidence of the specific adverse event, the subject-year is the duration from first day study medication is taken until the first occurrence of that adverse event. Duration uses year as unit.
- For subjects without specific adverse event, the subject-year is the treatment duration with year as unit.

The Exposure-Adjusted Incidence Rate (EAIR) is the number of subjects with at least one incidence of the specific adverse event divided by total subject-years. Subjects who are exposed to study medication for a longer period of time tend to have a higher incidence of AEs. The EAIR adjusts the number of incidences by the length of exposure to study medication.

The number and percentage of subjects reporting AEs of special interest (defined in section 6.2.1) will also be summarized.

Other primary endpoints will be listed and summarized using descriptive statistics according to the method discussed in Section 8.1.

Also, antibody assay results will be listed as positive or negative for each collection time for patients included in the Safety Analysis Set. The percentages of patients with assay results will be summarized as Positive, Negative or Missing. If a subject has at least one positive assay result at any time during the study then that subject will be included in subjects with ‘Positive’ result. If a subject has no occurrence of positive assay result and with at least one negative assay result at any time during the study then that subject will

be included in subjects with 'Negative' result. Subjects will be included in "Missing' if and only if all assessments have missing results.

8.2.2 Effectiveness Analyses

To assess the effectiveness of CT-P13 in the context of standard of care (SOC) Remicade treatment in patients with CD or UC, the endpoints detailed in Section 6.1 will be listed and summarized for patients in Full Analysis Set. Changes from baseline at designated follow-up visits (see section A1.1) will be summarized using descriptive statistics. Measures of disease activity with standard categorization of disease status for HBI and Partial Mayo Scoring System will be presented using shift from baseline tables.

CCI [redacted]

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10 APPENDICES

10.1 APPENDIX 1: DATA DERIVATION DETAILS

A1.1 Definition and use of visit windows in reporting

The table below defines the analysis visit windows that will be used in reporting the effectiveness CCI [redacted] endpoints. If a patient has multiple assessments within a visit window, the assessment closest to the target study day will be used. If two

[redacted]

assessments are equally distant from a target study day, the later will be used. Study day will be calculated as follows:

- If date of assessment (QSDTC) is prior to the date of first CT-P13 (or Remicade) treatment during the observation period (RFSTDTC), then study day = QSDTC – RFSTDTC
- If date of assessment (QSDTC) is on or after the date of first CT-P13 (or Remicade) treatment during the observation period, then study day = QSDTC – RFSTDTC + 1

Visit Label	Target study day	Time in study
Baseline		Baseline visit (study day $\leq$=1)
Month 6	168	1 < study day $\leq$ 252
Month 12	336	252 < study day $\leq$ 420
Month 18	504	420 < study day $\leq$ 588
Month 24	672	588 < study day

Summaries will be presented by subgroups and by type of IBD (where applicable).