Non-Interventional Study Protocol
C1231002

Prospective Obs**E**rvational Coho**R**t **S**tudy to Assess Persistence of CT-P13™ (**I**nfliximab) in patients with Rheumatoid Diseases who are either Naive to biologics or **S**witched from s**T**able Remicade® (infliximab)

Statistical Analysis Plan
(SAP)

Version: 4

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[redacted]

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Document	Version Date	Summary of Changes
Version 4	29 Jan 2019	• Updated AESI search criteria based on the latest RMP capture rule • Added clarification on EQ-5D-3L assessment
Version 3.2	18 May 2018	• Updated AESI search criteria • Added a summary table for all infections
Version 3.1	27 Apr 2018	• Updated AESI search criteria • Revised presentation of infusion related reactions • Revised presentation of serious infections to include opportunistic infections • Excluded AESIs not applicable for the study
Version 3.0	13 Feb 2018	• Added criteria for excluding subjects for the interim analysis • Added clarification on Naïve patients • Aligned the list of AESI with the protocol and the identification of AESI with the search criteria in CT-P13 RMP • Aligned the abbreviation of Physician Global Assessment with the protocol
Version 2.0	28 Nov 2017	The following amendments have been made to reflect the changes in C1231002 Protocol Amendment 1 dated 17May2017: • Changed the name of the drug under observation to CT-P13 • Added discussion on interim analysis • Removed the exploratory study objective C CI [redacted] • Clarification of DAS28, ASDAS, HAQ-DI and PGA score computations • Included non-serious AE in safety endpoints and revised the list of adverse event of special interest according to PT • Added definition of analysis visit window

Version 1.0	16 July 2017	Not applicable

2 INTRODUCTION

Note: in this document any text taken directly from the non-interventional (NI) study protocol is ***italicised***.

Rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) are inflammatory conditions that typically cause chronic arthritis with variable localization. Timely use of disease-modifying antirheumatic drugs (DMARDs) is an essential aspect of disease management, but many patients may not respond even when conventional agents are used optimally. Widespread use of biologic disease modifying antirheumatic drugs (BDMARDs), including antitumor necrosis factor (TNF) agents, has revolutionized the treatment of these disease entities as evident by a number of randomized controlled trials in each of these indications. Remicade (infliximab, Janssen Biologics B.V.), an IgG_1 chimeric human-murine monoclonal antibody (mAb), was approved in Europe in August 1999 and has been widely used in the treatment of RA, AS, and PsA.

In September 2013, CT-P13 (infliximab), a biosimilar to the reference product Remicade (infliximab), was approved by the European Medicines Agency (EMA) based on an extensive non clinical and clinical comparability exercise between these two versions of infliximab. This rigorous comparison demonstrated similar quality, pharmacokinetics, efficacy, and safety between CT-P13 and Remicade. Marketing authorization of CT-P13 in the European Union (EU) includes all approved indications of Remicade including RA, AS and PsA; Health Canada approved CT-P13 for RA, AS, PsA, and plaque psoriasis in January of 2014.

Consistent with the basic premise of biosimilars, CT-P13 is expected to provide similar quality, efficacy, and safety as Remicade. On this basis it can be expected that CT-P13 will be considered in varied settings in RA, AS, and PsA patients including BDMARDs naive patients, and as an alternative in stable patients receiving Remicade.

This prospective observational study has therefore been designed to characterize biologic naive RA, AS, and PsA patients receiving CT-P13 or those switched to CT-P13 from stable treatment with Remicade.

2.1 STUDY DESIGN

This is a multi-national, prospective, observational study of RA, AS, and PsA patients enrolled after having already been deemed suitable by their physicians for treatment with CT-P13, either as BDMARD naive or after a switch from stable treatment with Remicade. The study will not interfere with the usual care of patients, and neither study visits nor specific diagnostic interventions will be mandated.

Refer to Table 1 in protocol for the schedule of study activities.

Study population
The study will enroll approximately 1500 patients with RA, AS, or PsA. To effectively describe the BDMARD naive and CT-P13 switch populations, approximately 650 of the patients enrolled are expected to be switched from Remicade, while the remainder are expected to be BDMARD naive. After 18 months of enrolment, enrolment for the study ended on 31st of December 2016 for futility when 351 patients had been enrolled. All patients will be followed for up to 2 years after enrolment. 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
Patient reported outcomes (PRO), clinical evaluation of disease activity and Physician's global assessment of disease activity are collected using TrialMax Slate. All other study variables are entered in a web-based EDC system (Medidata Rave).

Treatment/cohort labels
Not applicable.

2.2 STUDY OBJECTIVES

Primary study objectives:

- *To evaluate real-life drug persistence in RA, AS, and PsA patients who are initiated with CT-P13 as their first biologic, or who are switched from stable Remicade. Persistence is defined as a continuous variable to be measured in time from index until drug discontinuation.*
- *To characterise the populations and drug utilization patterns of RA, AS, and PsA patients who are initiated with CT-P13 as their first biologic, or who are switched from stable Remicade.*
- *To assess the safety of CT-P13 in RA, AS, and PsA patients who are initiated with CT-P13 as their first biologic, or who are switched from stable Remicade for up to 2 years including:*
    - *Incidence of serious adverse events (SAE)*
    - *Adverse events of special interest (AESI)*
    - *Adverse events (AE)*

Secondary study objectives:

- *To assess effectiveness of CT-P13 in the treatment of patients with RA, AS, or PsA as measured by the Disease Activity Score (DAS28) in RA and PsA patients, Ankylosing Spondylitis Disease Activity Score (ASDAS), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index for AS patients (BASFI) in AS patients over the study period*
- *To assess Patients reported Outcomes as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI) for all patients the Short Form 12-*

version 2 (SF-12v2) for all patients) the EuroQol 5-dimensions 3-levels for all patients over the study period

- *To assess the Physician Global Assessment (PGA) over the study period*

3 INTERIM ANALYSES

An interim analysis will be carried out for all data collected until 27 December 2017. The interim analysis will focus on safety assessment which will include data on subject disposition, demographic and baseline characteristics, medical history, drug utilization pattern and adverse events. Subjects with incomplete data due to follow-up visits that cannot be confirmed due to unresponsive study sites will be excluded from the interim analysis provided there are no reported adverse events for these subjects.

4 HYPOTHESES AND DECISION RULES

Not applicable.

5 ANALYSIS SETS/POPULATIONS

5.1 FULL ANALYSIS SET

The full analysis set is defined as all patients who received at least one dose of CT-P13 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 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 CT-P13 during the study observation period. The primary endpoints will be evaluated using this analysis population.

5.3 OTHER ANALYSIS SET

None.

5.4 SUBGROUPS

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

- Treatment with CT-P13 for RA, AS, or PsA
- Treatment with CT-P13 in naive patients and those who switch from Remicade
  - Naïve patients include those who received CT-P13 as the first BDMARD treatment for a rheumatoid disease
- Treatment discontinuation due to loss of efficacy
- Treatment discontinuation due to perceived harm

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

The measures of disease activity in patients with RA, PsA or AS and the patients' health status will constitute the effectiveness endpoints of the study. These are the secondary endpoints which include the following:

- DAS28 (RA and PsA only)
- BASDAI (AS only)
- ASDAS (AS only)
- BASFI (AS only)
- HAQ-DI
- EQ-5D-3L
- SF-12v2
- PGA

For each endpoint, baseline value will be defined as the most recent value measured prior to the first CT-P13 treatment during the observation period of the study.

6.1.1 DAS28

The Disease Activity Score-28 (DAS28) combines single measures into an overall, continuous measure of rheumatoid arthritis (RA) disease activity. It includes a 28 tender joint count (28TJC), a 28 swollen joint count (28SJC), erythrocyte sedimentation rate (ESR) in mm/h, and a patient's general health assessment (GH) on a visual analog scale (VAS). Both 28TJC and 28 SJC range from 0 to 28, ESR may range from 0 to 150, and GH ranges from 0 to 100.

DAS28 is calculated using the following formula:

$\mathrm{DAS28} = 0.56 \times \mathrm{sqrt}(28\mathrm{TJC}) + 0.28 \times \mathrm{sqrt}(28\mathrm{SJC}) + 0.70 \times \ln(\mathrm{ESR}) + 0.014 \times \mathrm{GH}$, if there is available patient's general health assessment or
$\mathrm{DAS28} = [0.56 \times \mathrm{sqrt}(28\mathrm{TJC}) + 0.28 \times \mathrm{sqrt}(28\mathrm{SJC}) + 0.70 \times \ln(\mathrm{ESR})] \times 1.08 + 0.16$, if there is no GH score.

The level of disease activity will be interpreted as low (DAS28 $\leq$ 3.2), moderate (3.2 < DAS28 $\leq$ 5.1) or high (DAS28 > 5.1).

In cases when there is no ESR measurement and only CRP value is available, DAS28 will be computed using the following formula:

$\mathrm{DAS28} = 0.56 \times \mathrm{sqrt}(28\mathrm{TJC}) + 0.28 \times \mathrm{sqrt}(28\mathrm{SJC}) + 0.36 \times \ln(\mathrm{CRP} + 1) + 0.014 \times \mathrm{GH} + 0.96$, if there is available patient's general health assessment or
$\mathrm{DAS28} = [0.56 \times \mathrm{sqrt}(28\mathrm{TJC}) + 0.28 \times \mathrm{sqrt}(28\mathrm{SJC}) + 0.36 \times \ln(\mathrm{CRP} + 1)] \times 1.10 + 1.15$, if there is no GH score.

The level of disease activity using DAS28 based on CRP will be interpreted as low (DAS28 $\leq$ 2.9), moderate (2.9 < DAS28 $\leq$ 4.6) or high (DAS28 > 4.6).

Although DAS28 was developed and validated only for patients with RA, the study will also use this index to measure disease activity in patients with PsA.

6.1.2 BASDAI

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is a self-reported measure of disease activity in patients with Ankylosing Spondylitis (AS). It consists of a 1-10 scale (1 being no problem and 10 being the worst problem) which is used to answer 6 questions pertaining to the 5 major symptoms of AS:

1. Fatigue
2. Spinal pain
3. Joint pain/swelling
4. Areas of localized tenderness (also called enthesitis or inflammation of tendons and ligaments)
5. Morning stiffness duration
6. Morning stiffness severity

BASDAI score is computed using the formula:

$$\text{BASDAI} = \frac{\text{Sum}(Q1, Q2, Q3, Q4) + \text{Mean}(Q5, Q6)}{5}$$

where Q1, Q2, .. , Q6 are the corresponding values for questions 1 to 6.

The level of AS disease activity will be interpreted as low (BASDAI < 4) or high (BASDAI $\geq$ 4).

6.1.3 ASDAS

The Ankylosing Spondylitis Disease Activity Score (ASDAS) was developed by the Assessment of SpondyloArthritis International Society (ASAS). The ASDAS score is calculated using the following formula:

$$\text{ASDAS} = 0.12 \times Q1 + 0.06 \times Q2 + 0.11 \times GH + 0.07 \times Q3 + 0.58 \times \ln(CRP + 1)$$

where: Q1 = Overall pain
Q2 = Duration of morning stiffness
Q3 = Pain in other joints
GH = patient's general health assessment
CRP = C-reactive Protein in mg/L

In cases when there is no CRP measurement and only ESR value is available, ASDAS will be computed using the following formula:

$$\text{ASDAS} = 0.08 \times \text{Q1} + 0.07 \times \text{Q2} + 0.11 \times \text{GH} + 0.09 \times \text{Q3} + 0.29 \times \text{sqrt(ESR)}$$

The level of AS disease activity will be interpreted as inactive disease (ASDAS < 1.3), moderate disease activity (1.3 ≤ ASDAS < 2.1), high disease activity (2.1 ≤ ASDAS ≤ 3.5) and very high disease activity (ASDAS > 3.5).

6.1.4 BASFI

The Bath Ankylosing Spondylitis Functional Index (BASFI) is a set of 10 questions designed to determine the degree of functional limitation in patients with AS. It is measured using a visual analogue scale (ranging from 0 being easy and 10 being impossible) and the questions are focused on the patient's ability to perform specific functional tasks. BASFI score is calculated as the average score of the 10 questions. BASFI score range is 0 to 10, with 0 reflecting no functional impairment and 10 reflecting maximal impairment.

6.1.5 HAQ-DI

The Health Assessment Questionnaire Disability Index (HAQ-DI) – is a reliable and valid measure of Health-related quality of life (HRQoL) that is used in a variety of diseases, particularly rheumatologic conditions. The HAQ-DI is used to evaluate 8 categories which represent a set of functional activities: dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. Each category contains at least two specific sub-category questions. *Each item is scored on 4-point scale from 0 to 3: 0 = without any difficulty; 1 = some difficulty; 2 = much difficulty; 3 = unable to do.* The highest sub-category score determines the value for each category. Dependence on equipment or physical assistance increases a lower score to the level of 2, to more accurately represent underlying disability. There must be responses in at least 6 of the 8 categories or else a HAQ-DI cannot be computed. The category scores are then averaged into an overall HAQ-DI.

6.1.6 EQ-5D-3L

EQ-5D is a standardized measure of health status developed by the EuroQol Group, in order to provide a simple generic measure of health for clinical and economic appraisal. *The EQ-5D 3 level version (EQ-5D-3L) is a measure of self-reported health outcomes. It consists of two parts: a descriptive system (Part I) and the EQ visual analogue scale (EQ-VAS) (Part II). Part I of the scale consists of 5 single-item dimensions including: mobility, self care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has a 3 point response scale designed to indicate the level of the problem. Part II uses a vertical graduated VAS to measure health status, ranging from worst imaginable health state to best imaginable health state.*

EQ-5D health states, defined by the EQ-5D descriptive system, will be converted into a single summary index using the value sets derived for Europe and Canada.
For patients enrolled in European sites, the index will be calculated as follows:

$$\text{EQ} - \text{5D index} = 1 - 0.1279 * \text{N2} - 0.2288 * \text{N3} - 0.0659 * \text{MO2} - 0.1829 * \text{MO3} - 0.1173 * \text{SC2} - 0.1559 * \text{SC3} - 0.0264 * \text{UA2} - 0.0860 * \text{UA3} - 0.0930 * \text{PD2} - 0.1637 * \text{PD3} - 0.0891 * \text{AD2} - 0.1290 * \text{AD3}$$

For patients enrolled in Canadian sites, the index will be calculated as follows:

$$\text{EQ} - \text{5D index} = 1 - 0.111 - 0.046 * \text{MO2} - 0.322 * \text{MO3} - 0.071 * \text{SC2} - 0.224 * \text{SC3} - 0.072 * \text{UA2} - 0.105 * \text{UA3} - 0.045 * \text{PD2} - 0.298 * \text{PD3} - 0.063 * \text{AD2} - 0.280 * \text{AD3}$$

where: N2 = 1 if at least one dimension has score of 2 or 3; 0 otherwise
N3 = 1 if at least one dimension has score of 3; 0 otherwise
MO2 = 1 if mobility dimension has a score of 2; 0 otherwise
MO3 = 1 if mobility dimension has a score of 3; 0 otherwise
SC2 = 1 if self care dimension has a score of 2; 0 otherwise
SC3 = 1 if self care dimension has a score of 3; 0 otherwise
UA2 = 1 if usual activities dimension has a score of 2; 0 otherwise
UA3 = 1 if usual activities dimension has a score of 3; 0 otherwise
PD2 = 1 if pain/discomfort dimension has a score of 2; 0 otherwise
PD3 = 1 if pain/discomfort dimension has a score of 3; 0 otherwise
AD2 = 1 if anxiety/depression dimension has a score of 2; 0 otherwise
AD3 = 1 if anxiety/depression dimension has a score of 3; 0 otherwise

Both EQ-5D index and EQ-VAS will be summarized as continuous variables.

6.1.7 SF-12v2

The SF-12v2 is a multipurpose short-form (SF) generic measure of health status. It consists of 12 items, which are categorized into eight domains (subscales) of functioning and well-being: physical function (PF), role limitations due to physical problems (RP), bodily pain (BP), general health perceptions (GH), energy and vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). These eight domains will be further summarized into physical component summary (PCS) and mental component summary (MCS). To score the SF-12v2, we will follow the method proposed by Ware et al. (2002).

Both PCS and MCS will be summarized as continuous variables.

6.1.8 Physician Global Assessment

Physician Global Assessment (PGA) of Disease Activity is measured on a 0 to 100 mm VAS, where 0 mm = No disease activity and 100 mm = extremely active.

6.2 SAFETY ENDPOINTS

6.2.1 Adverse Events

Safety endpoints will include incidence of adverse events (AE), AE 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. An AE will be considered to be treatment-emergent if the event started or worsened in severity after the start of CT-P13 treatment until the end of the observation period for the study.

The following table 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 data 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.Intestinal or perianal abscess (in Crohn's disease), and Colon carcinoma/dysplasia (in ulcerative colitis) are excluded from the list of AESIs since they are not applicable for the study.

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

[redacted]

	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

[redacted]

	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
Bacillus Calmette–Guérin vaccine (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: Treated with resuscitation therapy (epinephrine)* *Medical review required: Check if it

	conforms to anaphylaxis based on Sampson's et al (2006).
Infusion related reactions	AEs fulfill the following conditions: - occurred within 1 day from administration date - related to CT-P13 - SMQ narrow: Hypersensitivity OR SMQ narrow: Anaphylactic reaction OR PT terms as following: Pyrexia, Body temperature increased, Chills, Eye irritation, Burning sensation, Non-cardiac chest pain, Chest pain, Upper respiratory tract congestion, Procedural hypotension, Hypertension, Procedural hypertension, Blood pressure increased, Supraventricular extrasystoles, Bradycardia, Sinus bradycardia, Tachycardia, Sinus tachycardia, Atrial fibrillation, Vomiting, Nausea, Oropharyngeal pain, Abdominal pain upper, Abdominal pain, Myalgia, Arthralgia, Headache, Migraine, Dizziness, Hypoxia, Throat irritation, Hypotonia, Syncope, Incontinence, 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/lupus-like syndrome	SMQ narrow: Systemic lupus erythematosus
Lymphoma (not Hepatosplenic T-cell lymphoma (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 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
Malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell	Step 1: Age: ≥18 years old Step 2: SOC: Neoplasms benign, malignant

carcinoma, cervical cancer)	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
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

6.2.2 Persistence

One of the primary endpoints of the study is the treatment persistence with CT-P13 in patients with RA, PsA or AS. *Persistence (in days) is defined as a continuous variable to be measured in time from index until drug discontinuation. Drug discontinuation will be defined as either switching to another non infliximab BDMARD or elapsing of a drug free interval of 16 weeks (i.e., 2 skipped doses). For patients undergoing a switch to CT-P13 from Remicade, the index date will be considered the date from which Remicade was originally commenced and for patients who initiated treatment with CT-P13 as their first biologic, the index date will be considered the date from which CT-P13 was initiated.*

Reason for drug discontinuation will also be presented.

6.3 OTHER ENDPOINTS

6.3.1 Population Characteristics

Another primary endpoint is the evaluation of population characteristics of patients with RA, PsA or AS in terms of demographic and baseline characteristics, medical history, disease duration and surgery status. Demographic and baseline characteristics include age, sex, race, height, weight and BMI. Disease duration is derived as the number of months from initial diagnosis of rheumatoid disease to the date of informed consent. Surgery status is a categorical variable defined as 'yes', if the patient had prior surgical treatment related to the treatment of RA, PsA or AS, and as 'no' otherwise.

6.3.2 Drug Utilization Pattern

Included in the primary endpoints is the drug utilization pattern. This will include the initial dose and infusion frequency of CT-P13, average dose received during the observation period of the study, dose reduction or escalation, and concomitant medication related to the treatment of RA, PsA or AS.

6.4 COVARIATES

Not applicable.

7 HANDLING OF MISSING VALUES

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. Descriptive statistics for continuous variables will include the number of observations (N), mean, median, standard deviation (SD), minimum and maximum. For categorical variables, N and percent will be provided. Summaries will be presented overall and by subgroups discussed in section 5.4 where specified.

A Kaplan-Meier analysis will be used to assess time to drug discontinuation. The median time to drug discontinuation, together with the inter-quartile range will be estimated overall, by subgroup according the rheumatoid disease (RA, PsA or AS) and by subgroup according to patient population (BDMARD naïve or switchers from Remicade).

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:

- Persistence

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

Persistence
Descriptive statistics for persistence will be presented for the subgroups discussed in Section 5.3. A Kaplan-Meier analysis will be used to assess time to drug discontinuation, where persistence curves, quartile estimates of time to drug discontinuation and the proportion of patients who remained with their CT-P13 treatment throughout the observation period will be estimated overall, by rheumatoid disease subgroups (RA, PsA or AS) and by patient population subgroups (BDMARD naïve or switchers from Remicade). Patients will be censored if they were lost to follow up or if they were continuously treated with CT-P13 at the end of the observation period.

Safety Endpoints (Adverse Events)
All AEs collected will be presented in data listings. However, only the treatment-emergent AEs will be analyzed. The number and percentage of patients with treatment-emergent AE 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 patient, only the most severe category and the closest relationship will be counted. Summaries will be presented overall and by subgroups discussed in section 5.4.

Other primary endpoints will be listed and will be summarized overall and by subgroups discussed in section 5.4 using descriptive statistics according the method discussed in Section 8.1.

8.2.2 Effectiveness Analyses

To assess the effectiveness of CT-P13 treatment in patients with RA, PsA or AS, the endpoints detailed in Section 6.1 will be listed and summarized for patients in Full Analysis Set. Changes from baseline at each visit will be summarized using descriptive statistics. Measures of disease activity with standard categorization of disease status, including DAS28, BASDAI and ASDAS will be presented using shift from baseline tables.

The table below defines the analysis visit windows that will be used in reporting the effectiveness endpoints. If a patient has multiple assessments within a visit window, the assessment closest to the target study day will be used. If two 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 treatment during the observation period (RFSTDTC), then study day = QSDTC – RFSTDTC

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

Timepoint label	Target study day	Time in study
Baseline		Baseline visit (as indicated in PRO, or 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 overall, by rheumatoid disease subgroups (RA, PsA or AS, where applicable) and by patient population subgroups (BDMARD naïve or switchers from Remicade).

9 LIST OF TABLES AND TABLE SHELLS

A list of tables (LOT) and mock shells are available in Analysis and Reporting (A&R) Plan documents.

10 REFERENCES

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