



NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Post Authorization Safety Study (PASS) information

Title	Post-Marketing Observational Cohort Study of Patients with Inflammatory Bowel Disease (IBD) Treated with CT-P13 in Usual Clinical Practice (CONNECT-IBD)
Protocol number	C1231001 (Hospira Protocol ZOB INF 1402)
Protocol version identifier	Version 3.0
Date of last version of protocol	23 February 2015
EU Post Authorisation Study (PAS) register number	To be determined
Active substance	Infliximab
Medicinal product	CT-P13, Remicade [®]
Product reference	CT-P13: EMEA/H/C/002778 Remicade: EMEA/H/C/002576
Procedure number	Not applicable
Research question and objectives	<p>Primary study objectives:</p> <ul style="list-style-type: none"> To characterise the population and drug utilisation patterns of patients treated with CT-P13 for Crohn's Disease (CD) or Ulcerative Colitis (UC) in the context of standard of care Remicade To explore the long-term safety profile of CT-P13 in the treatment of patients with CD or UC in the context of standard of care Remicade <p>Secondary study objective:</p> <ul style="list-style-type: none"> To assess the effectiveness of CT-P13 in the treatment of patients with CD or UC in the

	context of standard of care Remicade CCI 
Author	PPD  PPD  Pfizer Inc.

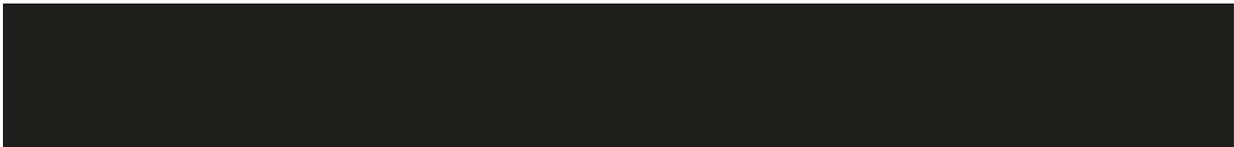


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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-Drug Antibody
AE	Adverse Event
AEM	Adverse Event Monitoring
AESI	Adverse Event of Special Interest
ARDS	Acute Respiratory Distress Syndrome
AV	Atrioventricular
CD	Crohn's Disease
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
SR	Study Report
DIC	Disseminated Intravascular Coagulation
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
EMA	European Medicines Agency
E-mail	Electronic mail
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FSFV	First Subject First Visit
GEP	Good Epidemiological Practice
GI	Gastrointestinal
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HBI	Harvey Bradshaw Index
HBV	Hepatitis B Virus
HCP	Healthcare provider
CCI	
HSTCL	Hepatosplenic T-cell Lymphoma
IBD	Inflammatory Bowel Disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
ID	Identification

Abbreviation	Definition
IEA	International Epidemiological Association
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KOL	Key Opinion Leader
LSLV	Last Subject Last Visit
mAb	Monoclonal Antibody
MAH	Marketing Authorisation Holder
NI	Non-Interventional
NIS	Non-Interventional Study
NISL	Non-Interventional Study Lead
PASS	Post Authorization Safety Study
PRCA	Pure Red Cell Aplasia
CCI	
RA	Rheumatoid Arthritis
RCT	Randomised Clinical Trial
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
CCI	
SIDS	Sudden Infant Death Syndrome
SmPC	Summary of Product Characteristics
SOC	Standard of Care
TNF	Tumour Necrosis Factor
UC	Ulcerative Colitis
CCI	

2. RESPONSIBLE PARTIES

The Pfizer Non-Interventional Study Lead (NISL) for this study protocol is PPD

The table below enlists all the National Leaders of the respective participating countries in the study.

PPD



Please refer the [Appendix 1](#) of this protocol, which indicates that a list of site Investigators are maintained in a stand-alone document.

3. ABSTRACT

Protocol Title

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

Protocol Amendment version 3.0 dated 25-Aug-2017

Rationale and Background

Remicade (infliximab, Janssen Biotech, Inc.), an IgG₁ chimeric human-murine monoclonal antibody (mAb), is a centrally authorised product approved in the European Union 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.

Research Question and Objectives

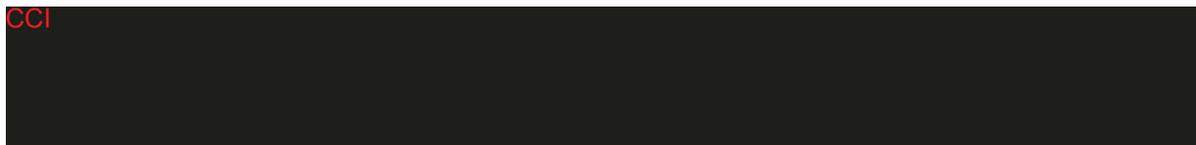
Primary study objectives:

- To characterise the population and drug utilisation patterns of patients treated with CT-P13 for CD or UC in the context of SOC Remicade.
- To explore the long-term safety profile of CT-P13 in the treatment of patients with CD or UC in the context of SOC Remicade.

Secondary study objective:

- To assess the effectiveness¹ of CT-P13 in the treatment of patients with CD or UC in the context of SOC Remicade.

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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. 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 and 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 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).

In compliance with the observational methodology of 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 (at a minimum) 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. When possible, 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. Data collection requirements for safety events, which need to be reported to Pfizer within specified timelines, are detailed in [Section 10](#).

Population

The target study population will include patients with CD or UC, who are being treated with, or initiating treatment with, CT-P13 (or Remicade for the SOC cohort) at the time of study enrolment. Below are the few examples of different treatment subgroups that can possibly be enrolled in the study:

- Biologic-naïve patients initiating CT-P13 (or Remicade).
- Patients currently being treated with CT-P13 (or Remicade).
- Patients who are considered stable by the Investigator under Remicade therapy for CD or UC, who switch to CT-P13.
- Patients switching to CT-P13 (or Remicade) from an alternative biologic therapy (eg, adalimumab) due to non-responsiveness to or intolerance.

- Patients re-initiating infliximab (CT-P13 or Remicade) after having successfully completed and exited a previous course of infliximab therapy in the past.

Patients with fistulating disease or stomas, and those receiving combination therapy will be included.

Variables

Primary variables:

- Patients' demographic characteristics.
- Clinical and diagnostic characteristics.
 - Relevant medical history of CD or UC including prior treatments.
- CT-P13 treatment.
 - CT-P13 and Remicade switches and reasons for switch.
 - Dose and frequency, augmentation/reduction and reasons of changes.
- Co-therapy(ies) related to the management of CD or UC.
- All Adverse Events (AEs), Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESIs), and events in a special situation (eg, pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure) during the patient study participation.

Secondary variables:

- Clinical assessment of disease activity.
 - Data relating to the Harvey Bradshaw Index (HBI) for patients with CD.
 - Data relating to the Partial Mayo Scoring System for Assessment of UC Activity (the abbreviated version excluding 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.

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Data Sources

CRFs will be designed to gather the data needed for the study that are collected as part of local SOC of the study patients. Clinical information recorded in the patients' medical record information will be abstracted and entered into the EDC system. As well, patients will complete the paper-based PRO questionnaires.

Study Size

The study will enrol approximately 2,500 patients with CD or UC, who are either already being treated or initiating treatment with CT-P13 or Remicade. The study is designed primarily to characterise the use of CT-P13 in patients with CD or UC.

Data Analysis

Considering this study is not designed to test specific hypotheses, the statistical analysis will be descriptive in nature. Given the expected heterogeneity of patients commonly seen in observational studies, patients will be stratified (eg, UC vs. CD, by subgroup, by country) based on final data available for analysis. Data permitting, *post hoc* inferential analysis may be used to examine the impact of risk factors or predictors on outcomes of interest, as appropriate. Detailed procedures of all analyses will be described in the Statistical Analysis Plan (SAP).

Milestones

Start of data collection (First Subject First Visit (FSFV))	22 April 2015
End of data collection (Last Subject Last Visit (LSLV))	Approximately 31 October 2018

Registration in the EU PAS register

TBD

Final Study Report

Approximately 06 February 2019

4. AMENDMENTS AND UPDATES

Amendment Number	Date	Substantial or Administrative Amendment	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	23 Feb 2015	Substantial	<u>Hospira protocol format sections:</u> 1. Throughout document. 2. List of abbreviations, References. 3. Throughout document pertaining to protocol title. 4-8. Abstract, Patient eligibility, Primary outcomes, Secondary outcomes, Exploratory outcomes, Study limitations, Study data Collection Schedule Table. 9. Secondary study objectives. 10. Figure 1. 11. Enrolment. 12. Inclusion criteria. 13. Inclusion criteria. 14. Adverse Events of Special Interest (AESI) Table 3. 15. Appendix 3. 16. Appendix 4. 17. Appendix 5. 18. Appendix 8. 19. Sponsor Signatures Page.	1. IBD specified as Crohn’s disease (CD) or Ulcerative Colitis (UC). 2. CCI [REDACTED] 3. Infliximab was added in brackets next to Inflectra. 4. Abstract: the sentence ‘Patients with fistulating disease or stomas and those receiving combination therapy will be included’ was added to population section. 5. ‘In the six months prior to enrolment for biologic naïve patients or in the 12 months prior to enrolment for biologic experienced patients’ wording was removed from study outcomes section. 6. ‘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’ were added. 7. CCI [REDACTED] 8. The wording ‘For all patients with “prevalent exposure,” data collection will include information on any AESI and SAE experienced during Inflectra or Remicade treatment prior to study enrolment, so that any AESI that occur shortly after treatment initiation will not be under-represented in the study population. A safety analysis will	1. Updated to clarify IBD indications. 2. CCI [REDACTED] 3. Updated for consistency. 4. Added to clarify that these patient types would be permitted for study enrolment. 5. Under the Legacy Hospira process, this wording was removed because SAEs and AESI prior to enrolment would not be collected. 6. Included as additional clinical assessments to the secondary outcomes section. 7. CCI [REDACTED] 8. Under the Legacy Hospira process, this wording was removed because SAEs and AESI prior to enrolment would not be collected. 9. Added to clearly define effectiveness as opposed to efficacy. 10. Updated to reflect the definition of IBD as CD or UC. 11. Updated wording to correctly describe the study enrolment process. 12. Updated wording as the first course of treatment of the adolescence population in the UK is Remicade. 13. Added wording to indicate additional

				<p>compare AESIs and SAEs experienced during Inflectra or Remicade treatment prior to enrolment with events after enrolment' was removed from study limitations section</p> <p>9. The following sentence was added "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."</p> <p>10. The study design schematic was updated.</p> <p>11. Enrolment process wording changed to 'Patients will be recruited for the study during the course of usual care at each investigative site. Patients deemed potentially eligible for the study by their physician will be invited to participate. At the time of study invitation, consenting patients may be enrolled if they are eligible to be included in either the Inflectra or the Remicade cohort and meet study inclusion and exclusion criteria.</p> <p>12. Inclusion criterion 1: 'At least 18 years of age at the time of initial confirmed diagnosis of IBD' was changed to 'at least 12 years at the time of initial confirmed diagnosis of CD and UC and at least 18 years at the time of enrolment to the study.'</p> <p>13. Inclusion criterion 2: The following sentence was added 'Patients with</p>	<p>patient subgroups included.</p> <p>14. Wording removed as requested during National Leader meeting review of protocol.</p> <p>15. Added to describe the 'Montreal Classification' of Crohn's Disease clinical assessment.</p> <p>16. Added to describe the 'Montreal Classification' of Ulcerative colitis clinical assessment.</p> <p>17. Added to describe the 'Fistula drainage assessment' of Crohn's Disease clinical assessment.</p> <p>18. Added to include a detailed description of protocol updates.</p> <p>19. Updated Sponsor contact information.</p>
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				<p>stomas or surgery/pouch will also be included” to indicate additional patient subgroups included.’</p> <p>14. ‘Infusion reaction associated with shortened infusion duration [RA [RA)’ was deleted.</p> <p>15. Added the ‘Montreal Classification’ of Crohn’s Disease clinical assessment.</p> <p>16. Added the ‘Montreal Classification’ of Ulcerative colitis clinical assessment.</p> <p>17. Added the ‘Fistula drainage assessment’ of Crohn’s Disease clinical assessment.</p> <p>18. Added descriptions of protocol updates.</p> <p>19. PPD [REDACTED] is replacing PPD [REDACTED].</p>	
2	25 Aug 2017	Substantial	All (change in template used)	<p>1. Changed from Hospira Protocol Template to Pfizer Non-Interventional Study Protocol Template.</p> <p>2. Study classification of PASS applied.</p> <p>3. Updated immunogenicity data collection so that sites that conduct immunogenicity analysis as part of their local clinical care practice will be able to offer patients the option to participate. There is no longer a central lab option.</p> <p>4. Requirement for informed consent as Inclusion criteria added.</p> <p>5. Safety reporting requirement updated including Pfizer safety reporting details.</p> <p>6. Changed number of countries participating in the study.</p> <p>7. Study population changed from 3,300 total (2,500 Inflectra and 800 Remicade) to 2,500 total</p>	<p>1. Updated to align with Pfizer’s processes.</p> <p>2. Voluntary PASS registration as per EU legislation.</p> <p>3. Updated so it is clear that only those sites who conduct immunogenicity analysis as part of their routine patient care have the option for patients to provide this data collection.</p> <p>4. Added to clarify requirement of informed consent for patient enrolment.</p> <p>5. Updated to align with Pfizer’s procedures.</p> <p>6. Updated for correct final number of participating countries.</p> <p>7. Population modified to end study early.</p> <p>8. Duration of patient participation adjusted from a 2 to 1 year follow-up period to end data collection early.</p> <p>9. Switched from trade name to molecular</p>

				<p>(1,900 CT-P13 and 600 Remicade).</p> <p>8. Wording added to indicate patient participation will complete after the last 1-year of follow-up data collection.</p> <p>9. Change to naming of drug from Inflectra to CT-P13.</p> <p>10. Study objective wording updated with regard to CT-P13 designation and change in 2 year follow-up period.</p> <p>11. Included wording that there may be an option to conduct one or more interim analyses.</p> <p>12. Removed reference to Good Clinical Practice (GCP).</p> <p>13. Updated author and MAH contact information.</p> <p>14. Included text encouraging EDC data entry within 10 days of a patient visit date.</p>	<p>name to permit either Inflectra or Remsima use.</p> <p>10. Updated for consistency with CT-P13 designation and study duration.</p> <p>11. Updated wording to allow for the option to conduct one or more interim analyses if deemed necessary.</p> <p>12. Updated to applicable ethical conduct standards (eg, Good Pharmacoevidence Practices, Good Epidemiological Practices, etc.) since this is a non-interventional study. Please reference Sections 8.8 and 9.4.</p> <p>13. New contact information provided since the previous protocol Amendment 1.</p> <p>14. Text added to recommend data entry work load.</p>
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5. MILESTONES

Milestone	Planned date
Start of data collection (FSFV)	22 April 2015
End of data collection (LSLV)	31 October 2018
Registration in the EU PAS register	<i>To be determined</i>
Final study report	06 February 2019

6. RATIONALE AND BACKGROUND

Remicade (infliximab, Janssen Biotech, Inc.), an IgG₁ 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). Infliximab was designed to bind to tumour necrosis factor- α (TNF- α), and prevent it from binding to its endogenous receptors. Since its original characterization, infliximab has been shown to act through a multitude of additional mechanisms of action beyond TNF-neutralization in inflammatory bowel disease.

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 similar to that of Remicade. CT-P13 is an IgG₁ chimeric human-murine mAb biosimilar to Remicade produced in the same type of cell-line as Remicade. In addition to extensive non-clinical comparability testing of molecular structure and function, including those mechanisms of action thought to be important in CD or UC, the approval of CT-P13 in Europe was also based on the results of 2 large, double-blind, randomised clinical trials (RCTs): a phase I-type Programme evaluating the Autoimmune disease investigational drug CT-P13 in ankylosing spondylitis (PLANETAS) in 250 patients with ankylosing spondylitis, and a Phase III-type study Programme evaluating the Autoimmune disease investigational drug CT-P13 in rheumatoid arthritis (PLANETRA) in 606 patients with rheumatoid arthritis. These 2 studies demonstrated that the pharmacokinetics and clinical efficacy of CT-P13 were equivalent based on pre-specified criteria to that of Remicade, and that the two treatments were well tolerated with comparable immunogenicity and safety profiles. Based on the totality of evidence submitted demonstrating that CT-P13 was highly similar to Remicade, the European Medicines Agency (EMA) granted licensure for CT-P13 equivalent to the license for Remicade. This marketing authorisation of CT-P13 included all approved indications for Remicade including the extrapolated indications of moderate to severe CD and UC.

A summary of key findings presented in the CT-P13 European Public Assessment Report of the non-clinical evidence supporting extrapolation to the CD or UC indications are listed below:

- Comparable binding to soluble transmembrane bound TNF- α compared to Remicade.
- Comparable binding to Fc γ RIa, Fc γ RIIa, Fc γ RIIb and FcRn, C1q compared to Remicade.
- Reduced binding (~20% by SPR vs. Remicade) to rFc γ RIIIa and rFc γ RIIIb in vitro.
 - Difference in the level of afucosylated glycans, Man5 and G0 for CT-P13: total 5.46 - 6.26% vs. Man5, G0 and G2 for Remicade: total 11.91 - 14.61%.
- Ex vivo testing in representative physiological environments, demonstrated that differences in binding to Fc γ RIIIa and in ADCC activity, were abolished in the presence of:
 - serum of a CD patient;
 - peripheral blood mononuclear cells preparations (vs. isolated NK cells);
 - whole blood.
- The EMA's interpretation was that the difference in binding affinity was overcome by competition from plasma IgGs, soluble factors, immune complexes and presence of mixed cell populations expressing multiple FcRs. At inflammatory sites, the vascular permeability is increased, which allows for many blood components to enter the extra vascular space. "A range of arguments and experiments enable to conclude with a high level of probability that the quality differences detected in the level of afucosylation and binding to Fc γ RIIIa are not clinically relevant."
- "In conclusion, by using a range of experimental models that are considered representative of the pathophysiological conditions and putative mechanisms of action of infliximab, the Applicant has provided convincing evidence that the difference detected in the amount of afucosylated species has no clinically relevant impact on the efficacy and safety of CT-P13, in particular in IBD. Additional in vitro data from human intestinal cells are further supporting extrapolation of the clinical data to IBD."

This study is designed to capture data from real-world clinical practice to characterise the population and document drug utilisation patterns. In addition, available safety data will be collected and effectiveness of CT-P13 in the context of standard of care (SOC) utilisation of Remicade, in patients with CD or UC and to document the safety and effectiveness of CT-P13.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Primary Study Objective

- To characterise the population and drug utilisation patterns of patients treated with CT-P13 for CD or UC in the context of SOC Remicade.
- To explore the long-term safety profile of CT-P13 in the treatment of patients with CD or UC in the context of SOC Remicade.

7.2. Secondary Study Objective

- To assess the effectiveness¹ 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.

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8. RESEARCH METHODS

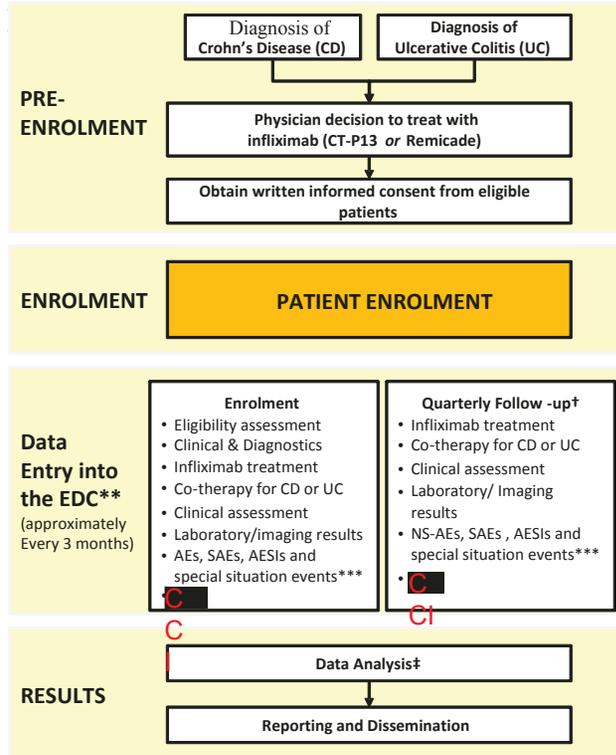
8.1. Study Design

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. 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 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 CRF.

In compliance with the observational methodology of the study, there is no study visit mandated per study protocol. Patients’ visit schedules will follow local SOC, typically coinciding with the schedule of infusions of infliximab, with any additional visits at the

treating physician's discretion. Additionally, for sites that conduct immunogenicity analysis as part of their routine clinical care, there will be an option for enrolled CT-P13 patients to provide immunogenicity profile information as part of the data collection for the study. The immunogenicity data will only be described; there will be no attempt to draw an inference on similarity. Please reference [Appendix 9](#) (Optional Immunogenicity Data Collection) for more information. Medical information will be recorded in patients' medical records during every clinic visit. Data for the study will be extracted from medical record information and entered into the EDC system at enrolment and then approximately every 3 months (at a minimum) 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. When possible, 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. The study design is presented schematically in [Figure 1](#).

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), [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.

8.2. Setting

8.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. At least 12 years of age at the time of initial confirmed diagnosis of CD or UC and at least 18 years of age at the time of enrolment to the study.
2. Patients who are prescribed CT-P13 or Remicade for the treatment of CD or UC according to the corresponding summary of product characteristics (SmPC) as determined by the Investigator. Patients with stomas or surgery/pouch will be included.
3. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

8.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Any reported contraindications for CT-P13 or Remicade, according to the SmPC/Product Label.
2. Known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients or other murine proteins, at the time of enrolment.
3. Prior history of failure to respond to Remicade or CT-P13.

8.2.3. Regions/Number of Study Sites

The study will take place in countries in which CT-P13 and Remicade are authorised for the treatment of CD and UC. A heterogeneous sample of about 150 sites is planned to be recruited in approximately 13 countries. This will include a mix of academic and community centres to ensure broad physician and patient representation. As this study is designed primarily to characterise the use of CT-P13, sites prescribing only Remicade to treat CD or UC (ie, not prescribing CT-P13 for CD or UC) will not be recruited in the study.

8.2.4. Enrolment

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. In order to assure this number of CT-P13 patients is enrolled, enrolment will be closely monitored in real time through the EDC system. It is expected that depending on local formulary regulations or institutional policies, there may be sites that prescribe either Remicade or CT-P13 but not both. Sites that only utilise Remicade will not be recruited to participate in the study.

Patients will be recruited for the study during the course of usual care at each investigative site. Patients deemed potentially eligible for the study by their physician will be invited to participate. At the time of study invitation, consenting patients may be enrolled if they are eligible to be included in either the CT-P13 or the Remicade cohort and meet study inclusion and exclusion criteria ([Sections 8.2.1](#) and [8.2.2](#)).

8.2.5. Patient Eligibility

The target study population will include patients with CD or UC, who are being treated, or initiating treatment, with CT-P13 (or Remicade for the SOC cohort) at the time of study enrolment.

Below are the few examples of different treatment subgroups that can possibly be enrolled in the study:

- Biologic-naïve patients initiating CT-P13 (or Remicade);
- Patients currently being treated with CT-P13 (or Remicade);
- Patients who are considered stable by the Investigator under Remicade therapy for CD or UC, who switch to CT-P13;
- Patients switching to CT-P13 or Remicade from an alternative biologic therapy (eg, adalimumab) due to non-responsiveness to or intolerance;
- Patients re-initiating CT-P13 or Remicade after having successfully completed and exited a previous course of infliximab therapy in the past.

Patients with fistulating disease or stomas and those receiving combination therapy will be included.

8.3. Variables

8.3.1. Primary Outcomes Variables

- Patients' demographic characteristics.
- Clinical and diagnostic characteristics.
 - Relevant medical history for CD or UC including prior treatments.
- CT-P13 treatment.
 - CT-P13 or Remicade switches and reasons for switch.
 - Dose and frequency, augmentation/reduction and reasons for changes.
- Co-therapy(ies) for the management of CD or UC.

- All adverse Events (AEs), Serious Adverse Events (SAEs) or Adverse Events of Special Interest (AESI), and events in a special situation (eg, pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure) during patient study participation.

8.3.2. Secondary Outcomes Variables

- 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, ie, abbreviated version without the endoscopy sub-score.⁶
 - 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.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.4. Data Sources

CRFs will be designed to gather the data needed for the study that are collected as part of SOC. Patients will be completing a set of CCI instruments on paper during their SOC visits at enrolment and then approximately every 3 months (based on the visit that is closest in time to 3 months after the last visit) thereafter. When possible, 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. Site research staff will enter CCI and patient-reported CCI data into the EDC system. Patients' medical record information, any relevant diagnostic reports, and

the paper-based [CCI] and patient-reported [CCI] survey are the source documents for study data collection. Clinical information recorded in patients' medical record information and/or diagnostic reports will be abstracted and entered into the EDC system, as well as the completed [CCI] and patient-reported [CCI] survey. [Table 1](#) summarises the data collection schedule of the study.

Table 1. Study Data Collection Schedule

	<i>Once at enrolment</i>	<i>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</i>	
	Enrolment	Follow-up Period*	Infliximab Treatment Discontinuation**
Eligibility assessment and written informed consent	X		
Relevant medical history for CD or UC <ul style="list-style-type: none"> • Diagnosis of CD or UC: extent, severity, duration • Prior treatments 	X		
Infliximab therapy – CT-P13 or Remicade <ul style="list-style-type: none"> • Dose, frequency: augmentation/reduction, reasons of changes • Switch(es) or discontinuation, reasons of switch/discontinuation 	X	X	
Co-therapy (<i>frequency, dose, augmentation/reduction, switching, reason of switch</i>) <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> • 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 	X	X	
Safety outcomes <ul style="list-style-type: none"> • 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
<p>* <i>Recording of medical data into patients' medical record information 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.</i></p> <p>** <i>Patients who discontinue infliximab treatment will be encouraged to remain in the study and be followed for the remainder 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.</i></p> <p>*** <i>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.</i></p>			

8.5. Study Size

The study will enrol approximately 2,500 patients with CD or UC, who are either already being treated or initiating treatment with CT-P13 or Remicade. The study is designed primarily to characterise the use of CT-P13 in patients with CD or UC. Patients being initiated or treated with Remicade will constitute a smaller although substantial SOC cohort and are expected to provide context for the CT-P13 cohort. The sample size is based on both practical and statistical considerations. The sample size must be relatively large given there are 2 diseases (CD and UC) under study with 5 population subgroups within each. Additionally, the study will seek to characterise population and drug utilisation patterns across 13 countries. 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. There is no calculation of power for this study because the objectives are descriptive rather than inferential.

In achieving one part of the primary objective of the study of documenting the safety of CT-P13 in real-world clinical practice, the simulated rates of all NS-AEs, SAEs and AESIs associated with the use of infliximab are being used to estimate the sample size of the study. The table below shows the 2-sided confidence intervals associated with observed AESI rates ranging from 0.1% to 10% in patient populations of 625 and 1875 patients. The confidence intervals are exact binomial 95% confidence intervals.

Table 2. Observed AESI Rates

Precision of Observed AESI Rates with a Sample Size of 625

(2-sided 95% confidence interval)

Observed Rate	Exact 95% Confidence Interval
0.1%	0.00, 0.59
0.5%	0.10, 1.40
1.0%	0.35, 2.08
2.0%	1.00, 3.33
5.0%	3.39, 6.97
10.0%	7.69, 12.54

Precision of Observed AESI Rates with a Sample Size of 1875

(2-sided 95% Confidence Interval)

Observed Rate	Exact 95% Confidence Interval
0.1%	0.00, 0.30
0.5%	0.22, 0.91
1.0%	0.57, 1.51
2.0%	1.39, 2.71
5.0%	4.02, 6.04
10.0%	8.65, 11.42

8.6. Data Management

8.6.1. Electronic Data Capture (EDC) System

The database will be designed using DataTrak One, a proprietary electronic data capture (EDC) system provided by DataTrak International, Inc., a third party vendor contracted by Hospira, a Pfizer company in accordance with written security policies.

8.6.2. Data Entry

All reported data from the enrolled Investigator's site will be entered via a secure web-based EDC study database. All sites will be fully trained in using the EDC system, including CRF completion guidelines. Site personnel will be provided with secure usernames and passwords in order to enter study data into the EDC system. All participating sites will only have access to view and enter the data for their own patients. A data manager will perform concurrent review during the course of the data collection period. The data manager will generate *ad-hoc* queries to sites when required, and the site management team will follow-up to request completion of such queries.

8.6.3. Statistical Software

All analyses will be performed using SAS for Microsoft Windows operating system statistical software (SAS Institute, Cary, North Carolina, USA) version 9.2 or higher, using validated implementations of each application or SAS custom programming.

8.7. Data Analysis

Considering the observational design of the study is not designed to test specific hypotheses, 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.

In keeping with one component of the primary objective of evaluating the long-term safety profile of CT-P13, for each type of SAE and AESI, both incidence rate and exposure-adjusted incidence rate will be calculated with confidence intervals. Generalised linear models will be used to examine the impact of risk factors and predictors on outcomes of interest, as appropriate.

As this is an observational study, not designed to test any *a priori* hypotheses, the sample size selected may not be sufficient to detect any statistical significance. Given the expected heterogeneity of patients commonly seen in observational studies, patients will be stratified (eg, UC vs. CD, by subgroup, by country) based on final data available for analysis. Data permitting, *post hoc* inferential analysis may be used to examine the impact of risk factors or predictors on outcomes of interest, as appropriate.

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

There is an option to conduct one or more interim analyses during the course of the study.

8.8. Quality Control

Quality Assurance representative(s) of Hospira, a Pfizer Company (or their designee) may conduct audit visits at any time during the study period. All necessary related data and documents will be made available for inspection.

8.8.1. Site Training and Initiation

Meetings will be held to train the Investigators (treating physicians) and their site staff on the study requirements and use of the EDC system. Pfizer (or their designee) will contact each site to review site initiation procedures. Ongoing site management will occur throughout the entire duration of the study. Additional outreach and training including on-site visits will occur for sites (Investigators and staff) needing remedial training and to address quality control concerns prior to analysis.

8.8.2. Site Monitoring

In-house site management or remote monitoring will be used to manage sites during the operational/maintenance phase of the programme. Site contact will be more frequent during enrolment and then decrease during the subject follow-up period due to more limited site involvement. All inbound calls from sites will be triaged immediately and all calls (inbound and outbound) will be tracked, including inquiry type, site identification (ID), query resolution and centre feedback.

8.9. Strengths and Limitations of the Research Methods

8.9.1. Lost to Follow-up

All patients will be followed for up to a 2-year follow-up period, or until the end of the last patient 1-year follow-up period, whichever occurs first. If a patient misses more than 1 usual care visit, the site will attempt to communicate with the patient and document the patient's reason for not returning. Sites should follow their normal follow-up procedures to attempt patient contacts, whether at various times of the day and evening, and on different days of the week. If the patient cannot be contacted after the due diligence process, the treating physician should consider other methods, such as an attempt to contact the patient's designated secondary contacts (including the patient's general practitioner and next of kin or out-of-household contacts) to obtain information on the patient's whereabouts and vital status. If the patient's care has been transferred to another healthcare professional (HCP), the treating physician at the enrolling site will be responsible for obtaining the required follow-up information from the new treating physician. Patients who do not return for at least 2 scheduled visits, and for whom no information is available will be considered lost to follow-up.

8.9.2. Study Limitations

Recognising that this is a non-interventional observational study, there are some limitations or potential biases inherent in this study design: survivor bias, selection bias and the risk of systematic longer follow-up period in the Remicade patient group (given the higher probability of current use). The observational study will include patients who initiated CT-P13 or Remicade prior to implementation of the study ("prevalent exposure"). One limitation of this approach is that patients who initiate treatment and discontinue shortly thereafter would not be included and could differ in demographic and clinical characteristics from those who become enrolled ("survivor bias"). A further limitation of this approach is that Remicade patients are more likely to be prevalent patients, while a higher proportion of CT-P13 patients will be biologic-naïve at the time of study entry. This may have implications on **CCI** as biologic-naïve patients may present with less advanced disease.

Given the historic availability of Remicade safety and effectiveness information, the observation groups of the study will include different numbers of patients. Therefore, the estimation of the true incidence of AEs will be supported by different statistical powers, according to those subgroup sizes. The width of the confidence intervals around the estimated incidence rates will differ between subgroups (wider with Remicade). Consequently, the findings may be difficult to compare or the comparison may not be clinically meaningful. Events may occur in the CT-P13 observation group, but the comparison groups may be too small to determine if the differences across the subgroups are significant. Historically available information for Remicade may be utilised to provide additional context. However, the findings from this study will be descriptive and not inferential in nature, due to the study nature and design.

8.10. Other aspects

8.10.1. National Leaders Committee

A National Leaders Committee (see [Section 2](#)) has been established which includes clinicians and scientists with expertise in CD or UC, epidemiology and biostatistics, with a National Leader chosen for each country involved in the study. Committee members will provide ongoing subject matter expertise for the programme. In collaboration with Hospira, a Pfizer Company, the Committee will be responsible to review the data from the study over time, to make recommendations to Pfizer regarding study conduct, and assist in study execution at the national and international levels. The Committee will be involved in case report form review and development, statistical analysis plan development and review, Study Report review, as well as publication development, if the findings from the study warrant publications in the future.

8.10.2. Concomitant Medication Use

As this is an observational study, where treatment decisions are left to the discretion of the treating physician, prescription of CT-P13 or Remicade or any other concomitant medication will not be influenced by the study protocol in any way. Therefore, the current study protocol does not impose any restriction on the prescription of concomitant medications. It is left to treating physician's discretion taking into account local standard of care and SmPC directions. With regard to co-therapy (ies), as indicated in [Table 1](#), data on the following drug usage will be extracted from medical record information and entered into the EDC system:

- Steroids.
- Medication(s) related to the treatment of CD or UC or management of the symptoms of CD or UC.
- Medication(s) related to the management of SAE or AESI.

Information on other types of concomitant medication will be recorded in the patients' medical record information as per routine practice but will not be captured as part of study data.

8.10.3. Regulatory Authorities

The approved protocol will be submitted to Regulatory Authorities in accordance with the regulations of the countries and participating sites' local clinical research regulatory requirements when applicable.

8.10.4. Protocol Modifications

Amendments to the protocol can only be made by Pfizer. All protocol amendments must be signed and dated by the Investigator physicians, and if required, submitted and approved by the Regulatory Authorities and Institutional Review Board/Independent Ethics Committees

(IRB/IEC), prior to implementation of the amendment. The National Leaders Committee may provide feedback to Pfizer on protocol modifications.

8.10.5. Compensation to Investigators

Study Investigators will be compensated for time spent in completing study requirements consistent with local prevailing conditions. This compensation schedule will be determined in accordance with national and local IRB/IEC guidelines and fair market value for the work performed.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims and/or equivalent.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The table below summarizes the requirements for recording safety events on the case report form (CRF) and for reporting safety events on the Non-interventional Study (NIS) Adverse Event Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) Serious Adverse Events (SAEs); (2) Non-serious AEs; (3) Adverse Events of Special Interest (AESIs); and (4) Special Situations - scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure. These events are defined in the section “Definitions of safety events”.

Safety event	Recorded on the CRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of Awareness
SAE	All	All
Non-serious AE	All	Adverse Events of Special Interest (AESIs). Please reference the list of AEs classified as AESIs for this study at the end of Section 10
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "[Serious Adverse Events](#)" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of CT-P13 or the time of the patient's informed consent if s/he is already exposed to CT-P13, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to CT-P13™, the SAE also must be reported to Pfizer Safety.

Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to CT-P13™, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that CT-P13™ caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether CT-P13™ caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that CT-P13™ did not cause the event, this should be clearly documented on the case report form (CRF) and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);

- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or

- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance. Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep).
- Administrative admission (eg, for yearly exam).
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery).
- Hospitalization for observation without a medical AE.
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality).
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) CT-P13™, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to CT-P13™ (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to CT-P13™ prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposures during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with CT-P13™, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to CT-P13™ in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer).
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
 - An identifiable reporter;
 - A suspect product;

- The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Adverse Events of Special Interest

Adverse Events of Special Interest (AESIs) are AEs of scientific or medical concern specific to the product for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. The following list of AEs are classified as AESIs for this study:

- Serious infections including sepsis (excluding opportunistic infections and tuberculosis);
- Opportunistic infections;
- Tuberculosis;
- BCG breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab;
- Acute hypersensitivity reactions (including anaphylactic shock)*;
- Serious infusion reactions during a re-induction regimen following disease flare;
- Serum sickness (delayed hypersensitivity reactions);
- Haematological reactions;
- Systemic lupus erythematosus/lupus-like syndrome;
- Lymphoma (not HSTCL);

- Hepatosplenic T-cell lymphoma (HSTCL);
- Leukaemia;
- Merkel cell carcinoma;
- Melanoma;
- Cervical cancer;
- Paediatric malignancy;
- Hepatobiliary events;
- HBV reactivation;
- Congestive heart failure;
- Demyelinating disorders;
- Sarcoidosis/sarcoid-like reactions;
- Intestinal or perianal abscess (in Crohn's disease);
- Malignancy (excluding lymphoma, HSTCL, paediatric malignancy, leukaemia, melanoma, Merkel cell carcinoma, cervical cancer);
- Colon carcinoma/dysplasia (in ulcerative colitis);
- Skin cancer (excluding melanoma, Merkel cell carcinoma);
- Pregnancy exposure;
- Infusion reaction associated with shortened infusion duration.

AESIs must be reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness.

10.1. Single Reference Safety Document

The EU-SmPC will serve as the single reference safety document (SRSD) during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1. Reporting to Regulatory Agencies

All reports will be submitted to the regulatory authorities by Pfizer based on country/region reporting requirements and pursuant to required timeframes.

11.2. Use of Information and Publications

All data generated from this study are the property of Pfizer. Pfizer shall have the right to publish such data and information without approval from the sites. Pfizer will establish a uniform procedure for analysing, publishing, and disseminating findings from this study. Co-authors of publications may include participating physicians, Pfizer personnel, members of the National Leaders Committee, and/or other relevant thought leaders who contribute substantially to the publication. Data from planned interim analyses will be published by Pfizer at time points deemed appropriate based on study progress. Publications will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines. Study data may not be published by participating sites without review and authorisation by Pfizer.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

12. REFERENCES

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13. LIST OF TABLES

Table 1. Study Data Collection Schedule

Table 2. Observed AESI Rates

14. LIST OF FIGURES

Figure 1. Study Design Schematic

APPENDICES

Appendix 1. Responsible Parties

A list of site Investigators is maintained in a stand-alone document and can be provided upon request.

Appendix 2. Harvey Bradshaw Simple Index

Harvey-Bradshaw Simple Index

Variable	Description	Scoring
1	General well-being	0 _ very well 1 _ slightly below par 2 _ poor 3 _ very poor 4 _ terrible
2	Abdominal pain	0 _ none 1 _ mild 2 _ moderate 3 _ severe
3	Number of liquid stools daily	1 per occurrence
4	Abdominal mass	0 _ none 1 _ dubious 2 _ definite 3 _ definite and tender
5	Complications 1 per item:	<ul style="list-style-type: none"> ● Arthralgia ● Uveitis ● Erythema nodosum ● Aphthous ulcer ● Pyoderma gangrenosum ● Anal fissure ● New fistula ● Abscess
Total score		Sum of variable scores

Appendix 3. Partial Mayo Scoring System

Mayo Scoring System for Assessment of Ulcerative Colitis Activity.*

Stool frequency†

0 = Normal no. of stools for this patient

1 = 1 to 2 stools more than normal

2 = 3 to 4 stools more than normal

3 = 5 or more stools more than normal

Subscore, 0 to 3

Rectal bleeding‡

0 = No blood seen

1 = Streaks of blood with stool less than half the time

2 = Obvious blood with stool most of the time

3 = Blood alone passes

Subscore, 0 to 3

Physician's global assessment§

0 = Normal

1 = Mild disease

2 = Moderate disease

3 = Severe disease

Subscore, 0 to 3

* The Partial Mayo score ranges from 0 to 9, with higher scores indicating more severe disease.

† Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

‡ The daily bleeding score represents the most severe bleeding of the day.

§ The physician's global assessment acknowledges the two other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

Appendix 4. Summary of revised ‘Montreal Classification’ of Crohn’s Disease

Age at diagnosis (A)			
A1	16 years or younger		
A2	17-40 years		
A3	Over 40 years		
Location (L)		Upper GI modifier (L4)	
L1	Terminal ileum	L1 + L4	Terminal ileum + Upper GI
L2	Colon	L2 + L4	Colon + Upper GI
L3	Ileocolon	L3 + L4	Ileocolon + Upper GI
L4	Upper GI	-	-
Behaviour (B)		Perianal disease modifier (p)	
B1*	Nonstricturing, nonpenetrating	B1p	Nonstricturing, nonpenetrating + perianal
B2	Stricturing	B2p	Stricturing + perianal
B3	Penetrating	B3p	Penetrating + perianal

* B1 category should be considered 'interim' until a prespecified time has elapsed from the time of diagnosis. Such a time period may vary from study to study (eg, 5-10 years is suggested) but should be defined in order for B1 behaviour to be considered 'definitive'. GI Gastrointestinal.

Appendix 5. 'Montreal Classification' of Ulcerative Colitis

Key points

- A classification system for UC is proposed that incorporates:
 - Disease extent; and
 - Disease severity of individual acute relapses.
-

Classification by extent

UC can be defined by the extent of colorectal inflammation at a radiographic, endoscopic or histological level. For the purposes of simplification, we propose that the extent of UC be defined by endoscopic appearance and by maximal extent during follow-up. The three subgroups of UC defined by extent are:

1. Ulcerative proctitis (E1): involvement limited to the rectum (ie, proximal extent of inflammation is distal to the rectosigmoid junction).
2. Left-sided UC (E2) (also known as distal UC): involvement limited to the portion of the colorectum distal to the splenic flexure.
3. Extensive UC (E3) (also known as pancolitis): involvement extends proximal to the splenic flexure.

Classification by severity

UC can be classified broadly into four disease activity/severity categories:

1. UC in clinical remission (S0): No symptoms of UC.
2. Mild UC (S1): in the classic description of disease activity by Truelove and Witts,¹ this was defined as four or fewer bloody stools daily, lack of fever, pulse of less than 90 beats/min, hemoglobin of 105 g/L or greater and erythrocyte sedimentation rate (ESR) of less than 30 mm/h. A similar definition was given in the practice guidelines for management of UC recently published by the American College of Gastroenterology (ACG)²: four or fewer stools daily (with or without blood), no systemic signs of toxicity and a normal ESR.
3. Moderate UC (S2): Truelove and Witts¹ defined this as the state between mild and severe. The ACG guidelines defined moderate disease as more than four stools daily but with minimal signs of systemic toxicity.²

4. Severe UC (S3): This was defined as the passage of at least six bloody stools daily, pulse of at least 90 beats/min, temperature of at least 37.5°C, hemoglobin of less than 105 g/L and ESR of at least 30 mm/h.¹ The ACG guidelines defined severe colitis as at least six bloody stools daily and evidence of toxicity (fever, tachycardia, anemia or elevated ESR).² The latter guidelines separated 'fulminant colitis' from 'severe'. Fulminant patients were those with at least 10 stools daily, continuous bleeding, toxicity, abdominal tenderness and distension, requirement for blood transfusion and colonic dilation on plain abdominal films.²

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Appendix 6. Simple Fistula Assessment

Fistula drainage assessment

Endpoints	Definition
Improvement	Improvement defined as a decrease from baseline in the number of open draining fistulae of \geq 50%
Remission	for at least two consecutive visits (at least 4 weeks) Remission defined as closure of all fistulae that were draining at baseline for at least two consecutive visits (at least 4 weeks)

Closure of individual fistulae defined as no fistula drainage despite gentle finger compression.

Appendix 7. CT-P13: Summary of Product Characteristics

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002778/WC500151489.pdf

Appendix 8. Remicade: Summary of Product Characteristics

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000240/WC500050888.pdf

Appendix 9. Optional Immunogenicity Data Collection

Study Population

For those sites that conduct immunogenicity analysis as part of their routine clinical care, there will be an option for enrolled CT-P13 patients to provide immunogenicity profile information as part of the data collection for the study. Sites will document patient agreement for immunogenicity data collection. The final immunogenicity analysis cohort will be a sample of the observational study population that opt to provide their immunogenicity results. Patient participation in the CONNECT-IBD study is not contingent on participating in this immunogenicity data collection. There is no pre-determined sample size for the immunogenicity analysis.

Data Collection

Following enrolment into the CONNECT-IBD study, sites that conduct immunogenicity analysis as part of their routine clinical care may offer their CT-P13 patients the option to voluntarily provide their immunogenicity results as part of the data collection into the study EDC. For CT-P13 patients who participate, data collection of immunogenicity results (including trough level as well as testing for anti-drug antibodies - ADA) of CT-P13 should be obtained from the most recent test results just prior to study enrolment, and at any time during patient study participation. The immunogenicity data will only be described; there will be no attempt to draw an inference on similarity. Since immunogenicity testing is conducted according to local routine practice, there is no specific data collection schedule.

Patients can withdraw their participation in the immunogenicity data collection at any time, and this will not affect their participation in the CONNECT-IBD study. Sites will document withdrawal of participation. However, patients who withdraw from the CONNECT-IBD study will automatically be discontinued from ongoing immunogenicity data collection. Pfizer reserves the right to terminate the optional immunogenicity analysis or the CONNECT-IBD study at any time.

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