NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	PERSIST: **P**rospective 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)
Protocol number	C1231002
Protocol version identifier	Version 2.0
Date of last version of protocol	17 May 2017
Active substance	Infliximab
Medicinal product	CT-P13™ (infliximab), Remicade® (infliximab)

Research question and objectives	Primary study objectives:
	• To evaluate real-life drug persistence in rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) patients who are either initiated with CT-P13™ as their first biologic, or who are switched from stable Remicade®
	• To characterise the patient populations and drug utilization patterns of RA, AS, and PsA patients who are either initiated with CT-P13CT-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 either initiated with CT-P13™ as their first biologic, or who are switched from stable Remicade® for up to 2 years including:
	  • 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 (BASFI) in AS patients over the study period • To assess Patients reported Outcomes as measured by the Health Assessment Questionnaire Disability Index (HAQ-DI), Short Form 12-version 2 (SF-12v2) and EuroQol 5-dimensions 3-levels (EQ-5D-3L) for all patients over the study period • To assess the Physician Global Assessment (PGA) over the study period
Author	PPD PPD Pfizer Inc.

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
AEM	Adverse event monitoring
AESI	adverse events of special interest
AS	ankylosing spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ATI	antibody to infliximab
BASDAI	Bath Ankylosing Spondylosis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BCG	Bacillus Calmette–Guérin vaccine
BDMARD	biologic disease modifying anti rheumatic drugs
BMI	body mass index
CRF	case report form
DAS	Disease Activity Score
DMARD	disease-modifying antirheumatic drugs
EDC	electronic data capture
EDP	Exposure during pregnancy
EMA	European Medicines Agency
EQ-5D-3L	EuroQol 5-dimensions 3-levels
EU	European Union
FSFV	First Subject First Visit
HAQ-DI	Health Assessment Questionnaire-Disability Index
HBV	Hepatitis B virus
HRQoL	Health Related Quality of Life
HSTCL	Hepatosplenic T-cell lymphoma
ICF	informed consent form
ID	identification number
IEC	independent ethics committee
IgG	Immunoglobulin G
IRB	institutional review board
LSLV	Last Subject Last Visit
mAb	monoclonal antibody
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
NIS	non-interventional study
PCS	Physical Component Summary
PGA	Physician Global Assessment
PI	Principal Investigator
PRO	Patient Reported Outcome
PsA	psoriatic arthritis
RA	rheumatoid arthritis
SAE	serious adverse events
SAP	statistical analysis plan
SAS	statistical analysis software
SD	standard deviation
SJC	swollen joint count
SF-12v2	Short Form-12 version 2
SmPC	Summary of Product Characteristics
SRSD	single reference safety document
TJC	tender joint count
TNF	tumor necrosis factor
VAS	Visual Analogue Scale
WIC	Written Informed Consent

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

The table below includes the list of National Leaders for the participating countries.

Name, degree(s)	Title	Affiliation	Address
PPD	Professor	PPD	PPD Bulgaria
PPD	Professor	PPD	PPD France
PPD	Professor	PPD	PPD , Germany
PPD	Professor, PHD	PPD	PPD Greece
PPD	Professor	PPD	PPD Italy
PPD	Professor	PPD	PPD Spain
PPD	Professor	PPD	PPD UK
PPD	Physician	PPD	PPD PP Canada

3. ABSTRACT

Protocol Title

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

Rationale and Background

Rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) are inflammatory conditions that typically cause chronic arthritis with variable localization.[1] 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.[2] Widespread use of biologic disease modifying anti rheumatic drugs (BDMARDs), including anti tumor 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.[3,4] Remicade® (infliximab, Janssen Biologics B.V.), an IgG_1 (Immunoglobulin G) 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.[5]

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.[6,7]

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®™.

Research Objective

Primary study objectives:

- To evaluate real-life drug persistence* in RA, AS, and PsA patients who are either initiated with CT-P13™ as their first biologic, or who are switched from stable Remicade®;

- To characterise the populations and drug utilization patterns of RA, AS, and PsA patients who are either 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 either initiated with CT-P13™ as their first biologic, or who are switched from stable Remicade® for up to 2 years including:

  - Serious adverse events (SAE);

  - Adverse events of special interest (AESI);

  - Adverse events (AE).

*Real-life drug persistence has been suggested as a simple, practically relevant, indirect approach for assessing long-term therapeutic benefit and potential harm. This suggestion is based on the assumption that when using a drug that reduces symptoms and prevents complications, patients persist with the treatment as long as they experience or perceive a benefit and they do not experience (or perceive) an unacceptable amount of harm. At present, a cure for RA, AS, and PsA is not available, long-term anti-inflammatory treatment guided by clinical activity defines current state of the art treatment options. Persistence, as one outcome of the study, is defined as a continuous variable to be measured in time from index until drug discontinuation.

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.

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.

The decision to initiate treatment with CT-P13™ or to switch from stable treatment with Remicade® to CT-P13™, as well as the decision to enrol a particular patient in the study will be the physician´s responsibility and according to the prescribing recommendation in the particular country. Only patients meeting all eligibility criteria may be invited to enrol in the study. For each eligible patient, informed consent must be obtained prior to any study related activities.

In order to meaningfully characterize the RA, AS, and PsA populations and drug utilization patterns associated with the use of CT-P13™, as well as its safety and effectiveness, the study plans to enrol approximately 1500 patients in a mix of academic and community sites in approximately 9 countries in Europe and Canada.

All patients are expected to be enrolled over an approximate 16 month period, with each patient followed for up to 2 years. However, after 18 months of enrolment, enrolment for the study ended on 31st of December 2016 for futility when 351 patients had been enrolled. 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). Due to the nature of the observation study, there will be no study visits mandated per the study protocol. Patients' visit schedules will follow local standard of care typically coinciding with the schedule of infusions of CT-P13™, 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 2-6 months thereafter up to 2 years. Additional data captured will include demographics, drug utilization patterns, safety, clinical outcomes, and patient reported outcomes (PROs).

Population

The target study population will include biologic naive RA, AS, and PsA patients receiving CT-P13™ or those switched to CT-P13™ from stable treatment with Remicade®.

The study variables to be collected include patient demographics, all clinically relevant (RA, AS, and PsA) medical history and prior treatment data, clinical assessment of disease activity, laboratory measurements and clinical outcomes, medical treatment data, PROs, and PGA of Disease activity.

Variables – include exposures, outcomes, and key co-variates

Data Sources

Case report forms will be designed to gather the data needed for the study that is collected as part of local standard of care of the study patients. Clinical information recorded in the patients' medical charts and/or diagnostic reports will be abstracted and entered into the EDC system. As well, patients will complete the PRO questionnaires.

Sample Size and Data Analysis

The study will enrol 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 will be patients enrolled are expected to be BDMARD naive. After 18 month of enrolment, enrolment for the study ended on 31st of December 2016 for futility when 351 patients had been enrolled. The study is designed to meaningfully characterize the RA, AS, and PsA populations and drug utilization patterns associated with the use of CT-P13™, as well as its safety and effectiveness. The sample size is not driven by power calculations; all analyses will be descriptive in nature.

A statistical analysis plan (SAP) will provide further level of detail to analysis planned to be applied to the data derived from the study. Given the expected heterogeneity of patients commonly seen in observational studies, patients will be stratified appropriately based on final data available for analysis.

4. AMENDMENTS AND UPDATES

Amend-ment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
01	17 March 2017	Substantial	All (change in template used)	1. Inclusion criteria for Informed Consent Form (ICF) signature added 2. Safety reporting requirement updated including Pfizer safety reporting details 3. Updated number of countries participating in the study 4. Updated to Pfizer Protocol Template language. 5. Removal of Exploratory Objective C [redacted] C 6. Changed from Hospira Protocol Template to Pfizer Protocol Template. 7. Language added to indicate enrolment has ended. 8. Switched naming of drug from Inflectra to CT-P13 9. Removal of Product Monograph as reference safety documen	1. Add to clarify requirement of ICF as a requirement for patient enrolment 2. Updated to align with Pfizer's processes 3. Updated to current numbers of countries 4. Updated to align with Pfizer's processes 5. Removed due to lack of sample size 6. Updated to align with Pfizer's processes. 7. Updated language to show total number of patients enrolled 8. Switched to molecular name 9. Switched to using a single safety reference document for the study.

[redacted]

5. MILESTONES

Milestone	Planned date
Start of data collection First Subject First Visit (FSFV)	10 September 2015
End of data collection Last Subject Last Visit (LSLV).	31 December 2018
Final study report	02 May 2019

6. RATIONALE AND BACKGROUND

Rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) are inflammatory conditions that typically cause chronic arthritis with variable localization.[1] 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.[2] Widespread use of biologic disease modifying anti rheumatic drugs (BDMARDs), including anti tumor 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.[3,4] Remicade® (infliximab, Janssen Biologics B.V.), an IgG1 (Immunoglobulin G) 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.[5]

Infliximab was designed to bind to tumour necrosis factor-α (TNF-α), and prevent it from binding to its receptors.[8] Remicade® (infliximab, Janssen Biotech, Inc.), 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.[5]

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.[6], Health Canada approved CT-P13™ for RA, AS, PsA, and plaque psoriasis in January of 2014.[7]

The approvals of CT-P13™ in Europe and Canada have added a new choice for rheumatologists in their armamentarium of biologic disease modifying anti rheumatic drugs (BDMARDs) to treat RA, AS, and PsA. CT-P13™ is now broadly available for prescription in both regions. Consistent with the basic premise of biosimilars, CT-P13™ is expected to provide the similar quality, efficacy, and safety as Remicade®. On this basis, rheumatologists have provided feedback that they would consider CT-P13™ in varied

settings in their RA, AS, and PsA patients including BDMARD naive patients, and as an alternative in stable patients receiving Remicade®.

The confirmatory clinical trial program conducted for the regulatory assessment of CT-P13™ included 2 large, double-blind, randomised clinical trials: a phase I-type Programme evaluating CT-P13™ in ankylosing spondylitis (PLANETAS) in 250 patients, and a phase III-type study Programme evaluating CT-P13™ in rheumatoid arthritis (PLANETRA) in 606 patients. These 2 studies demonstrated that the pharmacokinetics and clinical efficacy of CT-P13™ were essentially equivalent based on pre-specified criteria to that of Remicade®, and that the 2 treatments were well tolerated with comparable immunogenicity and safety profiles. Long-term extension studies followed both PLANETAS and PLANETRA in patients completing 54 weeks of study. Patients in the CT-P13™ study arms received an additional 54 weeks of open-label CT-P13™, while patients in the Remicade® treatment arms were then switched to open-label CT-P13™ for an additional year. After 54 weeks, clinical efficacy, safety, immunogenicity, and tolerability were found to be highly comparable between the patients groups who maintained CT-P13™ and those who switched from Remicade® to CT-P13™.9-11

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®.

Real-life drug persistence has been suggested as a simple, practically relevant, indirect approach for assessing long-term therapeutic benefit and potential harm. This suggestion is based on the assumption that when using a drug that reduces symptoms and prevents complications, patients persist with the treatment as long as they experience or perceive a benefit and do not experience (or perceive) an unacceptable amount of harm. This theoretical perspective on persistence seems to be applicable to TNF antagonist drugs. Historically, the primary reasons for discontinuing or switching these drugs in RA for example appears to be decreased benefit (36–67% of the discontinuations) or perceived harm (30–58%).12-22

Persistence, as one outcome of the study, 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 (ie, 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. All patients will be followed for up to 2 years after enrolment.

The real world data collection in this study will not interfere with the usual care of patients, and will not mandate specific diagnostic interventions, treatments or study visits.

Data generated from this study could be used to better define significant prognostic characteristics and guide short-term management and maintenance treatment decisions and to identify unmet medical needs, monitor the safety and impact of novel biosimilar medication, and direct future research.

7. RESEARCH QUESTION AND OBJECTIVES

7.1. Primary Study Objectives

- To evaluate real-life drug persistence in rheumatoid arthritis (RA), ankylosing spondylitis (AS), and psoriatic arthritis (PsA) patients who are either initiated with CT-P13™ as their first biologic, or who are switched from stable Remicade®;

- To characterise the populations and drug utilization patterns of RA, AS, and PsA patients who are either 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 either initiated with CT-P13™ as their first biologic or who are switched from stable Remicade® for up to 2 years including:

    - Serious adverse events (SAE);

    - Adverse events of special interest (AESI);

    - Adverse events (AE).

7.2. 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.

8. RESEARCH METHODS

8.1. 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. The decision to initiate treatment with CT-P13™ or to switch from stable treatment with Remicade® to CT-P13™, as well as the decision to enrol a particular patient in the study will be entirely the physician´s responsibility and according to the prescribing recommendation in the particular country. Only patients meeting all eligibility criteria may be invited to enrol in the study. For each eligible patient, informed consent must be obtained prior to any study related activities.

In order to meaningfully characterize the RA, AS, and PsA populations and drug utilization patterns associated with the use of CT-P13™, as well as its safety and effectiveness, the study plans to enrol approximately 1500 patients in a mix of academic and community sites in approximately 9 countries in Europe and Canada. 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 will be patients enrolled are expected to be BDMARD naive. All patients are expected to be enrolled over an approximate 16 month period, with each patient followed for up to 2 years. After 18 months of enrolment, enrolment for the study ended on 31st of December 2016 for futility when 351 patients had been enrolled. 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). There will be no study visits mandated per the study protocol. Patients' visit schedules will follow local standard of care typically coinciding with the schedule of infusions of CT-P13™, 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 2-6 months thereafter up to 2 years. Additional data captured will include demographics, drug utilization patterns, safety, clinical outcomes, and patient reported outcomes (PROs). The sample size is not driven by power calculations; all analyses will be descriptive in nature.

8.2. Setting

8.2.1. Regions/Number of Study Sites

The study will take place in countries in which CT-P13™ and Remicade® are authorized for the treatment of RA, AS, and PsA. A heterogeneous sample of approximately 100 sites is planned to be recruited in Canada and Europe. This will include a mix of academic and community centres to ensure broad physician and patient representation.

8.2.2. Enrolment

The study plans to enrol approximately 1500 patients with approximately 650 of the enrolled patients being switched to CT-P13™ from stable Remicade®. Enrolment will be closely monitored in real time through the EDC system.

All patients who meet the enrolment criteria are potentially eligible and may be invited to participate in the study. Sites will be asked to record limited, de-identified, information on all potentially eligible patients who present to the practice, whether or not they consent and are enrolled in the study. This information will include age, gender, the reason for not enrolling in the study (if applicable), and the date the patient enrolled (if applicable). This information will be used to evaluate how likely the study sample compares to the total population receiving infliximab that are screened at the participating sites.

8.2.3. Patient Eligibility

The target study population will include biologic naive RA, AS, and PsA patients receiving CT-P13™ or those switched to CT-P13™ from stable treatment with Remicade®.

8.2.3.1. Inclusion Criteria

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

1. Patients aged ≥ 18 years old at the time of enrolment.

2. Patients who are prescribed CT-P13 or Remicade for the treatment of RA, AS or PsA prescribed according to the corresponding summary of product characteristics (SmPC and Product Monograph) as determined by the investigator.

3. Patients have consented to participate in the study.

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.

8.2.3.2. Exclusion Criteria

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

1. Any reported contraindications for CT-P13 according to the SmPC.

2. Known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients or other murine proteins, at the time of enrolment.

8.3. Study Variables

8.3.1. Minimum data set (variables to be collected)

The study protocol does not mandate treatments, nor does it dictate what medical information should be entered into patient charts. Rather, each participating site provides and documents

patient care and outcomes according to usual care, physician discretion and local practice standards. Thus, study variables may not be available for all patients at all data collection time points if data are not recorded in the chart as per routine medical care.

The study variables to be collected include:

1. Patient demographics **[Enrolment]**
    - Age;
    - Gender;
    - BMI (body mass index).
2. All clinically relevant (RA, AS, PsA) medical history and prior treatment including **[Enrolment]**
    - Extra-articular manifestations
3. Clinical assessment of disease activity including **[Enrolment and over the study period]**
    - Clinician evaluation of disease activity at each routine visit–
        a. DAS 28 (eg, swollen joint count (SJC) 28/tender joint count (TJC) 28)
        b. ASDAS/BASDAI
        c. Physical function: BASFI for AS patients
    - Patient self-rated symptoms where clinician evaluation is missing
        a. Number of Tender/Swollen joints (swollen joint count [SJC]28/tender joint count [TJC]28)
        b. Spinal pain and stiffness (for axial AS)
        c. Enthesitis/dactylitis (for peripheral AS/PsA)
        d. Fatigue
        e. Pain/Discomfort
4. Laboratory Measurements and Clinical Outcomes at the Investigators discretion **[Enrolment and over the study period]**
5. Medical Treatment **[Enrolment and over the study period]**
    - Corticosteroids (oral, intravenous, or intra-articular)

- BDMARDs and non-biologic DMARDs
- Nonsteroidal anti-inflammatory drugs
- Other co-medication
- Medication(s) related to the management of SAE or AESI

6. Patient reported outcomes **[Enrolment and over the study period]**
   - EQ-5D-3L
   - SF-12v2
   - Quality of Life measured by HAQ-DI
7. Data collected after initial Diagnosis **[Enrolment and over the study period]**
   - Physician's Global Assessment of Disease activity measured on a visual analogue scale (VAS)

	Clinical evaluation of disease activity/ Functional indexes				Patient Reported Outcomes			Physician reported Outcomes	Patient self-rated symptoms where clinician evaluation is missing					
	DAS28[23]	ASDAS[24]	BASDAI*[25]	BASFI*[26]	HAQ-DI	EQ-5D-3L	SF-12	PGA	TJC-28	SJC-28	Spinal Pain and stiffness	Enthesitis/ Dactylitis	Fatigue	Pain/ Discomfort
RA	X				X	X	X	X	X	X			X	X
PsA	X				X	X	X	X	X	X		X	X	X
AS		X	X	X	X	X	X	X			X	X	X	X

*Self-reported questionnaire

RA: rheumatoid arthritis; PsA: psoriatic arthritis; AS: ankylosing spondylitis; DAS: Disease Activity Score; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; HAQ-DI: Health Assessment Questionnaire Disability Index; EQ-5D-3L: EuroQol 5-dimensions 3-levels; SF-12: Short Form 12; PGA: Physician Global Assessment; TJC: tender joint count; SJC: swollen joint count

8.3.2. Patient Reported Outcomes for assessment of Health Related Quality of Life:

The assessment of Health Related Quality of Life (HRQoL) is covered with the HAQ-DI, EQ-5D-3L and the SF-12v2. These 3 instruments all have properties that justify their inclusion. The HAQ-DI is a reliable and valid measure of functional activities and the EQ-5D-3L is preference based utility measure. With the addition of the SF-12v2 there is a comprehensive assessment of HRQoL.

The SF-12v2 is a brief self-reported tool that provides a general sense of the impact of RA on eight domains. The domains of the SF-12v2 tap into different areas affected by RA than the HAQ-DI. Thus having them both provides a more comprehensive description of the impact of RA on HRQoL. The SF-12v2 results can also be converted to produce utility scores.

Patient reported outcomes Translation Readiness:

Patient reported outcomes will be available in all target languages. List of study countries and languages are provided in Annex 6.

8.3.3. Data Sources

An EDC system will be utilized for data collection, monitoring, and quality control. Data validation will be programmed in the EDC system to automate data queries. Case report forms will be designed to gather the data needed for the study that is collected as part of local standard of care of the study patients. Clinical information recorded in the patients' medical charts and/or diagnostic reports will be abstracted and entered into the EDC system. As well, patients will complete the PRO questionnaires.

Enrolment and Data Collection

Upon provision of informed consent, clinical and socio demographic characteristics, co-morbidities, medications and PRO data will be collected. All study data required from the enrolment into the study will be collected prospectively from the date of receipt of informed consent. Upon enrolment, data will be obtained from the chart retrospectively from the date of informed consent (6 months), and prospectively from time of consent to end of study.

Follow up Period Physician Reported Data collection

Following enrolment into the study, neither sites nor patients will be prompted to visit the study site except the pre-planned visits for CT-P13™ infusions. At these visits, study site staff will collect treatment patterns and outcomes, vital status, clinical events, SAEs, and non-serious AE data from the charts of study patients followed at the participating sites. At the time of these visits patients will be requested to complete PRO questionnaires (including EQ-5D-3L) as per the data collection schedule (Table 1) as deemed appropriate by the investigator.

Clinical information recorded in patients' medical charts and/or diagnostic reports will be abstracted and entered into the EDC system, as well as the completed PROs. Table 1 summarises the data collection schedule of the study.

Drug discontinuation visit

Patients who discontinue infliximab treatment will be followed for the remainder of the study period using simplified CRF. For the drug discontinuation visit, reasons for discontinuation (free text), current co-medications (and dosage for RA drugs), SAEs, and non-serious AEs, PGA (mandatory) will be collected. Starting with this discontinuation visit, only these parameters will be collected in the study.

Table 1. Study Data Collection Schedule

Table 1. Study Data Collection Schedule

Infusion visits* over the 2-year study period)	**BV**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Additional visits as needed per standard of care**
Enrolment: (~12 months)										
Documented patient informed consent	X									
Informed consent (documented by primary caregiver)	X									
Patient/study identification number (ID)	X									
Inclusion/exclusion criteria check	X									
Demographics	X									
Diagnostics and clinical outcomes	X									
RA/AS/PsA clinical history review up to 6 months prior to study enrolment	X									
Follow-up (Over the 2-year study period)										
Co-morbidities	X									
Laboratory measurements and clinical outcomes[†]	X	***At the Investigators' discretion***								
Co-medication for RA, AS, PsA	X	X	X	X	X	X	X	X	X	X
RA, AS, PsA Diagnosis (in remission during the previous 6 months)[†]	X									
Study discontinuation (date and reason)		***Anytime during Enrolment or during the study period***								
Drug discontinuation[#]		***Anytime during the study period***								
Patient reported Outcomes§, clinical evaluation of disease activity and Physician's Global Assessment of Disease activity‡										
Physician's Global Assessment of Disease activity measured on a visual analogue scale	X	X			X			X		X
Clinical evaluation of disease activity DAS 28, BASDAI, ASDAS, BASFI	X	X			X			X		X
Patient reported outcomes (PRO) HAQ-DI, EQ-5D-3L and SF-12v2	X	X			X			X		X
Patient self-rated symptoms where clinician evaluation is missing Number of Tender/swollen Joints (SJC28/TJC28) Spinal pain and stiffness for axial AS	X	X			X			X		X

Table 1. Study Data Collection Schedule

Infusion visits* over the 2-year study period)	BV	1	2	3	4	5	6	7	8	Additional visits as needed per standard of care
Enthesitis/dactylitis (for peripheral AS/PsA)										
Fatigue										
Pain/Discomfort										
Safety Reporting										
AEs (other than AESIs)										
SAEs	***To be reported within 24 hours of becoming aware (from signed informed consent)***									
AESIs	***To be reported within 24 hours of becoming aware (from signed informed consent)***									
Special situations	***To be reported within 24 hours of becoming aware (from signed informed consent)***									

AE: adverse event; AESI: adverse event of special interest; AS: ankylosing spondylitis; ASDAS: Ankylosing Spondylitis Disease Activity Score; BASFI: bath ankylosing spondylitis functional index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BV: baseline visit; DAS 28: Disease Activity Score in 28 Joints; EQ-5D-3L: EuroQol 5-dimensions 3-levels;; HAQ-DI Health Assessment Questionnaire Disability: Index; ID: identification number; PI: principal investigator; PGA: Physician Global Assessment; PRO: Patient Reported Outcome; PsA: psoriatic arthritis, RA: rheumatoid arthritis, SAE: serious adverse event, SF-12v2: Short Form 12 version 2; SJC: swollen joint count, TJC: tender joint count; WIC: written informed consent

*eCRF at infusion and/or clinical visits (approx. at 8 weeks intervals: vital status, clinical events, resource utilization, AEs, SAEs)

‡It is recommended that the questionnaires listed in this table are completed at least once in 6 months; the parameters listed in this table are suggested procedures for each visit only

§Direct to patient reported quality of life and resource utilization (6 month intervals might be considered)

†As per investigators' discretion; should be re-done once in a period of 6 months

#Patients who discontinue infliximab treatment will be followed for the remainder of the study period using simplified CRF. For the drug discontinuation visit, reasons for discontinuation (free text), current co-medications (and dosage for RA drugs), AESIs, SAEs, non-serious-AES, PGA (mandatory) will be collected. Starting with this discontinuation visit, only these parameters will be collected in the study

8.4. Study Size

The study will enrol approximately 1,500 RA, AS, and PsA patients who are either initiated with CT-P13™ as their first biologic, or who are switched from stable Remicade®. The study is designed to characterize the RA, AS, and PsA populations and drug utilization patterns associated with the use of CT-P13™, as well as its safety and effectiveness. There is no calculation of power for this study because the objectives are descriptive rather than inferential.

A statistical analysis plan (SAP) will provide further level of detail to analysis planned to be applied to the data derived from the study.

8.5. Data Management

8.5.1. Electronic Data Capture System

The database will be designed using a secure web-based EDC study database. Hospira, a Pfizer company, will contract a third party vendor in accordance with written security policies.

8.5.2. 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 eCRF 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.

8.5.3. Statistical Software

All analyses will be performed using statistical analysis software (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.

8.6. Data Analysis

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.

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.

Patient enrolment will not be stratified by clinical subgroups, but analyses will describe patient characteristics and study outcomes for the sub populations or combinations thereof:

- Treatment with CT-P13™ for RA, AS, or PsA;
- Treatment with CT-P13™ in naive patients and those who switch from Remicade®;
- Treatment discontinuation due to loss of efficacy;
- Treatment discontinuation due to perceived harm.

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

8.6.1. Demographic and Baseline Characteristics

The demographic and baseline characteristics of patients enrolled will be summarized overall, by disease and population sub-groups.

Baseline value will be defined as the most recent value measured prior to onset of study drug infusion.

8.6.2. Study Drug Utilization

The total dose of study drug infused, and the length of infusion (minutes) will be summarized descriptively overall and by disease sub-groups.

8.6.3. Real-life Drug Persistence

Persistence is defined as the time from index until study drug discontinuation. Study drug discontinuation will be defined as either switching to another non infliximab BDMARD or elapsing of a drug free interval of 16 weeks (ie, 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.

Descriptive statistics for persistence, as a continuous variable will include N, mean, median, SD, minimum, and maximum.

8.6.4. Safety Variables

In this study, all SAEs and AEs will be collected.

8.6.4.1. Adverse Events

The number and percentage of patients with AEs will be summarized overall and by disease and population sub-groups according to Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

A data listing will be provided for all AEs including those reported within the 2 year study period.

8.6.4.2. Adverse Events of Special Interest

The MedDRA adverse event (AE) dictionary (most recent, available version at the time of study initiation) will be used to map AESI descriptions to preferred terms and system organ classes. An AESI will be considered to be treatment-emergent if the event started or worsened in severity after the start of study drug infusion up to 24 hours after discontinuation of study drug infusion. Only the treatment-emergent AESIs will be analyzed. However, all AESIs will be presented in data listings.

The number and percentage of patients with treatment-emergent AESIs will be summarized overall and by disease and population sub-groups according to MedDRA system organ class and preferred term. Category of AESI severity and category of AESI relationship to study drug will be summarized overall and by disease and population sub-groups. For each subject, only the most severe category and the closest relationship will be counted.

8.6.4.3. Serious Adverse Events

The number and percentage of patients with treatment-emergent SAEs will be summarized overall and by disease and population sub-groups according to MedDRA system organ class and preferred term. Category of SAE relationship to study drug will be summarized overall and by disease and population sub-groups.

A data listing will be provided for all SAEs including those reported within the 2 year follow-up period.

8.6.5. Effectiveness

Disease Activity Score, including change from baseline, will be summarized by visit using descriptive statistics for RA and PsA patients. On the other hand, ASDAS, BASDAI, and BASFI will be summarized for AS patients. A listing of all measures of effectiveness will be generated.

8.6.6. Patient Reported Outcomes

8.6.6.1. Health Related Quality of Life

The Health Assessment Questionnaire Disability Index scores will be summarized overall and by population sub-groups.

8.6.6.2. EuroQoL 5-dimensions 3-levels

Results of the EQ-5D-3L will be presented as a measure of overall self-rated health status. Mean, SD, median, 1st and 3rd quartiles will be presented by disease and population sub-groups.

8.6.6.3. Patient's General Health Assessment

The SF-12v2 scores will be summarized descriptively per visit assessments. Technical details of computation will be discussed in the SAP.

8.6.7. Physician's Global Assessment

Scores of PGA of Disease Activity measured on a VAS, including change from baseline will be summarized by study visit.

8.7. Quality Control and Quality Assurance

The study will be conducted following International Conference on Harmonisation guidance for industry Good Clinical Practices (E6).[27] Quality Assurance representative(s) of Hospira (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.

8.7.1. Site Training and Initiation

The Sponsor or their designee will train the investigators (treating physicians) and their site staff on the study requirements and use of the EDC system. Sponsor 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 additional training and to address quality concerns prior to analysis.

8.7.2. Site Monitoring

Monitoring of the study site via visits or remote monitoring will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or its designee (contract research organization) and by the Institutional Review Board/Independent Ethics Committees (IRB or IEC) and Regulatory authorities.

All aspects of the study and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator's binder, study medication, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

8.8. Limitations of the Research Methods

8.8.1. Lost to Follow-up

All patients will be followed for up to 2 years. 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 will be requested to attempt to contact patients 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 will 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, 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.

8.8.2. Study Limitations

Internationally, real-life data is increasingly used in the development of clear, evidence-based documentation for demonstrating value. With the diverse and growing number of stakeholders making treatment and purchasing decisions today, demonstrating product value in both clinical and economic terms is critical to achieving successful reimbursement and central to enabling the costs and benefits of competing health technologies to be quantified for funding decisions.

Collecting real-life data from various sources includes patient data, data from clinicians, hospital data, data from payers and social data. Through its use alongside traditional data sources such as clinical trials, an observational study has the potential to provide new insights into medicines and their effects in the context of different patient groups. This very much applies to use of the new infliximab biosimilar – CT-P13™ in a diverse spectrum of patients with different types of rheumatic disease.

There are a number of issues, however, which confound the collection of real-life data. In Europe, for example, there is a lack of good quality and sufficiently representative databases in many countries - very different to the United States. hose that exist are often not complete across different health care centers and may be focused on general practitioners or the hospital sector, but rarely cover all the different settings that play a role in medical treatment. The databases are also often missing data or contain poorly specified information (eg, on the severity of the condition).

Prospective data collection brings its own challenges. Even with a careful controlled design, there may be various sources of bias that can completely distort the results. One typical example applying to rheumatic disease entities is that different degrees of severity of a condition are treated with different drugs. In consequence, a treatment that is actually more effective may look less successful in an observational study, if it is administered to the very severe cases only. Besides, for patients switched from the originator product to the novel biosimilar, imposing a "six months previous stable condition under treatment with the originator" may introduce some degree of selection bias. Thorough statistical methods can control parts of these biases, however the risk of misinterpreting study results without randomized drug allocation remains high. With uncontrolled data, as in the case of the present study, there are even more sources of bias and confounding. Treatment patterns sometimes differ considerably from one country to the other so prospective research must often be conducted in a series of countries to enable a meaningful picture to be presented to the local reimbursement authorities.

8.9. Other Aspects

8.9.1. National Leaders Committee

A National Leaders Committee has been established which includes clinicians and scientists with expertise in RA, AS, and PsA, 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 program. In collaboration with Hospira, the Committee will be responsible to review the data from the study over time, to make recommendations to Hospira 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, Clinical study report review, as well as publication development, if the findings from the study warrant publications in the future.

8.9.2. 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 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), data on the following drug usage will be extracted from medical charts and entered into the EDC system:

- Corticosteroids (oral, intravenous, intra-articular);
- Non-steroidal anti-inflammatory drugs;
- BDMARDs and non-biologic DMARDs;
- Medication(s) related to the treatment of RA, AS, and PsA or management of the symptoms of RA, AS, and PsA;

- Medication(s) related to the management of SAE or AESI.

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

8.9.3. Regulatory Authorities

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

8.9.4. Protocol Modifications

Amendments to the protocol can only be made by Hospira. All protocol amendments must be signed and dated by the investigator/ physicians, and if required, submitted and approved by the Regulatory Authorities and IRB/IEC, prior to implementation of the amendment. The National Leaders Committee may provide feedback to Hospira on protocol modifications.

8.9.5. 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, Hospira 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 Hospira 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 Hospira.

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, FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets, 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 monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AESI	All	Events that are actively sought. Actively sought events are designated as Adverse Events of Special Interest (AESI) in the study
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 enrolment. In some situations, there may be a lag between the dates of informed consent and enrolment. 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 enrol 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).

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;

- Bacillus Calmette–Guérin vaccine (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 Hepatosplenic T-cell lymphoma (HSTCL));

- Hepatosplenic T-cell lymphoma (HSTCL);

- Leukaemia;

- Merkel cell carcinoma;

- Melanoma;

- Cervical cancer;

- Paediatric malignancy;

- Hepatobiliary events;
- Hepatitis B virus (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.

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 exposure 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 (eg, 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.

10.1. Single reference safety document

The 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 Hospira or designee based on country/region reporting requirements and pursuant to required timeframes.

All serious related adverse events will be expedited within 15 days of receipt and non-serious relate adverse events within 90 days of receipt in the EU.

11.2. Use of Information and Publications

All data generated from this study are the property of Hospira. Hospira shall have the right to publish such data and information without approval from the sites. Hospira will establish a uniform procedure for analysing, publishing, and disseminating findings from this study. Co-authors of publications may include participating physicians, Hospira 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 Hospira at time points deemed appropriate based on study progress. Publications will adhere to the International Committee of Medical Journal Editors guidelines. Study data may not be published by participating sites without review and authorisation by Hospira.

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 Hospira product, Hospira should be informed immediately.

In addition, the investigator will inform Hospira 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.

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13. LIST OF TABLES

Not applicable.

14. LIST OF FIGURES

Not applicable.

Appendix 1. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

CT-P13™: Summary of Product Characteristics

Remicade®: Summary of Product Characteristics

Appendix 2. ANNEX 2. HEALTH ASSESSMENT QUESTIONNAIRE DISABILITY INDEX

The Health Assessment Questionnaire Disability Index– 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 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. Overall score is computed as the sum of domain scores and divided by the number of domains answered. Total possible score range 0-3 where 0 = least difficulty and 3 = extreme difficulty.

HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: _____ Date: _____

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
DRESSING & GROOMING				
Are you able to:				
Dress yourself, including shoelaces and buttons?	☐	☐	☐	☐
Shampoo your hair?	☐	☐	☐	☐
ARISING				
Are you able to:				
Stand up from a straight chair?	☐	☐	☐	☐
Get in and out of bed?	☐	☐	☐	☐
EATING				
Are you able to:				
Cut your own meat?	☐	☐	☐	☐
Lift a full cup or glass to your mouth?	☐	☐	☐	☐
Open a new milk carton?	☐	☐	☐	☐
WALKING				
Are you able to:				
Walk outdoors on flat ground?	☐	☐	☐	☐
Climb up five steps?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Devices used for Dressing (button hook, zipper pull, etc.)
☐ Built up or special utensils
☐ Crutches
☐ Cane
☐ Wheelchair
☐ Special or built up chair
☐ Walker

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Dressing and grooming ☐ Arising ☐ Eating ☐ Walking

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
HYGIENE				
Are you able to:				
Wash and dry your body?	☐	☐	☐	☐
Take a tub bath?	☐	☐	☐	☐
Get on and off the toilet?	☐	☐	☐	☐
REACH				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	☐	☐	☐	☐
Bend down to pick up clothing from the floor?	☐	☐	☐	☐
GRIP				
Are you able to:				
Open car doors?	☐	☐	☐	☐
Open previously opened jars?	☐	☐	☐	☐
Turn faucets on and off?	☐	☐	☐	☐
ACTIVITIES				
Are you able to:				
Run errands and shop?	☐	☐	☐	☐
Get in and out of a car?	☐	☐	☐	☐
Do chores such as vacuuming or yard work?	☐	☐	☐	☐

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

☐ Raised toilet seat ☐ Bathtub bar ☐ Long-handled appliances for reach

☐ Bathtub seat ☐ Long-handled appliances in bathroom ☐ Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

☐ Hygiene ☐ Reach ☐ Gripping and opening things ☐ Errands and chores

Your ACTIVITIES: To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
☐	☐	☐	☐	☐

Your PAIN: How much pain have you had IN THE PAST WEEK?
On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

☐☐☐

Your HEALTH: Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

☐☐☐

[redacted]

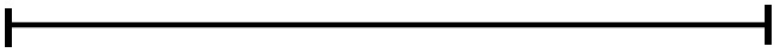
Appendix 3. ANNEX 3. PHYSICIAN GLOBAL ASSESSMENT OF DISEASE ACTIVITY

Physician Global Assessment of Disease Activity is measured on a 0 to 10 cm VAS, where 0 cm = No disease activity and 10 cm = extremely active.

Physician Global Assessment of Disease Activity

"What is your assessment of the patient's current disease activity?"

Please rate your assessment of global (overall) disease activity by drawing a vertical mark on the line below according to the following scale: left end of line = no disease activity, and right end of line = extremely active.



No disease activity Extremely active

Appendix 4. ANNEX 4. EQ-5D-3L

The EQ-5D-3L is a measure of self-reported health outcomes. It consists of two parts: a descriptive system (Part I) and a 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.

Health Questionnaire

English version for the UK

(Validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑
I have some problems in walking about ❑
I am confined to bed ❑

Self-Care

I have no problems with self-care ❑
I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

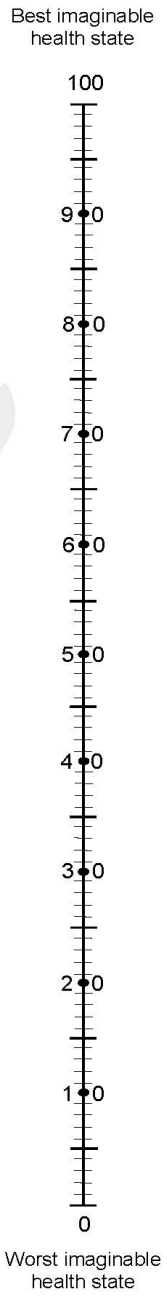
Anxiety / Depression

I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Appendix 5. ANNEX 5 SF-12v2

The SF-12v2 is a general measure of HRQoL used in a wide variety of disease states. The SF-12 includes eight subscales, as well as two summary measures: the Physical Component Summary (PCS), and the Mental Component Summary (MCS).

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
b Climbing several flights of stairs	☐ 1	☐ 2	☐ 3

3. During the past 4 weeks, how much of the time have you had any of the follov result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

Appendix 6. ANNEX 6. STUDY COUNTRIES AND LANGUAGES

[Delete highlighted blank rows below to clean up table.]

Country	Languages
Germany	German
Czech Republic & Slovakia	Czech Slovak
Belgium	Dutch French German
United Kingdom	English
Spain	Spanish
France	French
Canada	French English
Greece	Greek
Bulgaria	Bulgarian

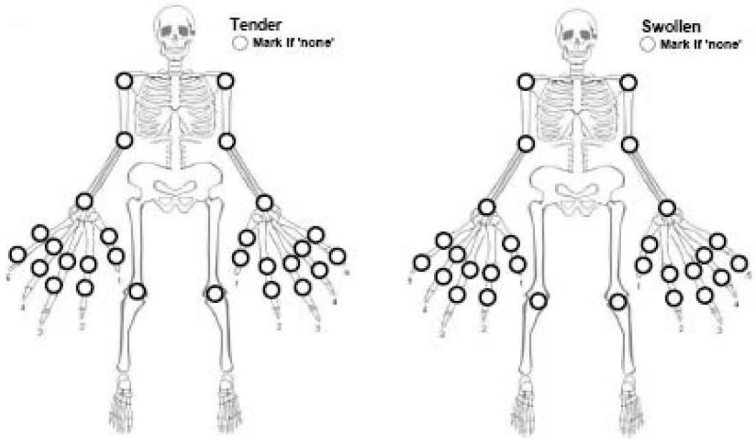
Appendix 7. ANNEX 7. DISEASE ACTIVITY SCORE IN 28 JOINTS

Disease Activity Score in 28 Joints (DAS28)

Patient global assessment
Considering all the ways in which illness and health may affect you at this time, please indicate below how you are doing:

VERY WELL ├──┤ VERY POORLY

FOR PROVIDER USE ONLY



VAS (0-100) ☐
28TJC ☐
28SJC ☐
ESR ☐
DAS28 ☐

DAS28=0.56*√(28TJC) + 0.28 * √(28SJC) + 0.70*Ln(ESR/CRP) + 0.014*VAS

How to calculate a DAS28 score:

1. Ask the patient to make a vertical mark on a 100 mm Visual Analog Scale (VAS) corresponding to their general health or global disease activity. Using a ruler, measure from the left-hand side in mm. Note: DAS28 calculations may be performed without a VAS measurement.
2. Perform a swollen and tender joint examination on your patient. Add all of the swollen and tender joints and record the totals in the appropriate boxes.
3. Erythrocyte Sedimentation Rate (ESR) should be measured (in mm/hour). Note: C-reactive protein (CRP) levels may be used as a substitute for an ESR.
4. Plug the appropriate values into the formula (many online calculators are available including http://www.das-score.nl/www.das-score.nl/dasculators.html).
5. If using CRP instead of ESR or calculating a score from only 3 variables please see http://www.reuma-nijmegen.nl/www.das-score.nl/ for the appropriate formula.

Interpretation:

- The DAS28 provides you with a number on a scale from 0 to 10 indicating current RA disease activity.
- Remission: DAS28 ≤ 2.6
- Low Disease activity: 2.6 < DAS28 ≤ 3.2
- Moderate Disease Activity: 3.2 < DAS28 ≤ 5.1
- High Disease Activity: DAS28 >5.1

Adapted from: DAS-Score.nl. Available at http://www.das-score.nl/www.das-score.nl/index.html. Accessed April 15, 2010.

Appendix 8. ANNEX 8. BATH ANKYLOSING SPONDYLITIS FUNCTIONAL INDEX

BASFI
Bath Ankylosing Spondylitis Functional Index

ASIF
ANKYLOSING SPONDYLITIS International Federation

Name: _____

Date: _____

Please draw a mark on each line below to indicate your level of ability with each of the following activities in the past 7 days:

		Evaluation by the doctor
1	**Putting on your socks or tights without help or aids (e.g. sock aid)** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
2	**Bending forward from the waist to pick up a pen from the floor without an aid** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
3	**Reaching up to a high shelf without help or aids (e.g. helping hand)** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
4	**Getting up out of an armless dining room chair without using your hands or any other help** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
5	**Getting up off the floor without help from lying on your back** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
6	**Standing unsupported for 10 minutes without discomfort** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
7	**Climbing 12–15 steps without using a handrail or walking aid, one foot on each step** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
8	**Looking over your shoulder without turning your body** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
9	**Doing physically demanding activities (e.g. physiotherapy exercises, gardening or sports)** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	
10	**Doing a full day's activities whether it be at home or at work** easy 0 1 2 3 4 5 6 7 8 9 10 impossible	

BASFI = [ ]

(sum of answers 1 to 10 divided by 10)

Ankylosing Spondylitis International Federation
World-wide network of societies of patients suffering from ankylosing spondylitis or related diseases
www.spondylitis-international.org

Appendix 9. ANNEX 9. BATH ANKYLOSING SPONDYLITIS DISEASE ACTIVITY INDEX

The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)

Please place a mark on each line below to indicate your answer to each question relating to **the past week**

1. How would you describe the overall level of **fatigue/tiredness** you have experienced?

   NONE _____ VERY SEVERE

2. How would you describe the overall level of AS **neck, back or hip pain** you have had?

   NONE _____ VERY SEVERE

3. How would you describe the overall level of pain/swelling in joints other than **neck, back, hips** you have had?

   NONE _____ VERY SEVERE

4. How would you describe the overall level of **discomfort** you have had from any areas tender to touch or pressure?

   NONE _____ VERY SEVERE

5. How would you describe the overall level of **morning stiffness** you have had **from the time you wake up?**

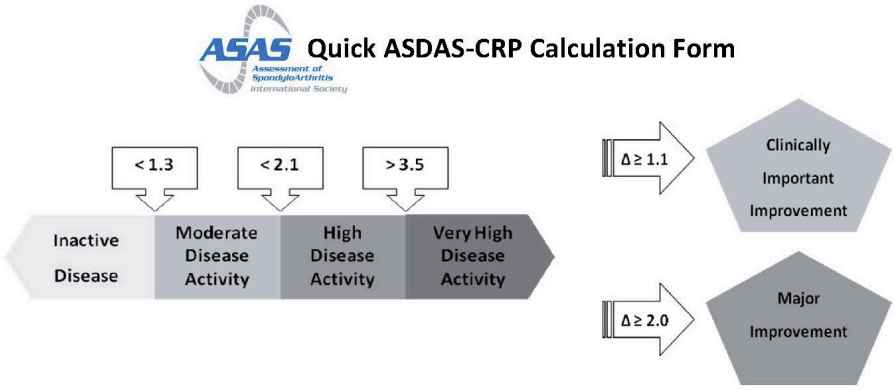
   NONE _____ VERY SEVERE

6. How long does your morning stiffness last from the time you wake up?

   _____
   0 hrs ½ 1 1½ 2 or more hours

Appendix 10. ANNEX 10. ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE

Link online ASDAS calculator:
http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html



Name : _____ **Date :** ____ /____ /_____

1) How would you describe the overall level of AS neck, back or hip pain you have had?

0 1 2 3 4 5 6 7 8 9 10

None — Very severe

2) How long does your morning stiffness last from the time you wake up?

0 1 2 3 4 5 6 7 8 9 10

0 — 1 — 2 or more hours

3) How active was your spondylitis on average during the last week?

0 1 2 3 4 5 6 7 8 9 10

Not active — Very active

4) How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0 1 2 3 4 5 6 7 8 9 10

None — Very severe

5) C-reactive protein (mg/L)?

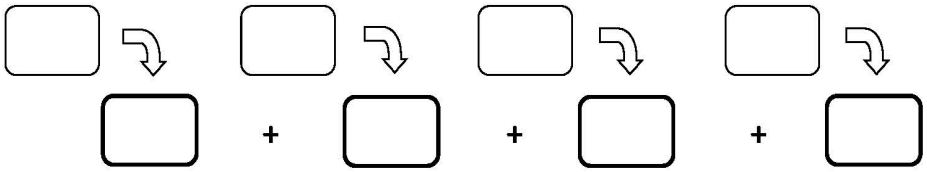
[redacted]

Back Pain	
0	**0**
1	**0,1**
2	**0,2**
3	**0,4**
4	**0,5**
5	**0,6**
6	**0,7**
7	**0,8**
8	**1,0**
9	**1,1**
10	**1,2**

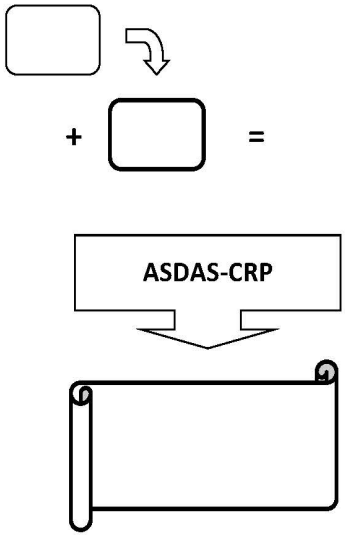
Morning Stiffness	
0	**0**
1	**0,1**
2	**0,1**
3	**0,2**
4	**0,2**
5	**0,3**
6	**0,4**
7	**0,4**
8	**0,5**
9	**0,5**
10	**0,6**

Patient Global	
0	**0**
1	**0,1**
2	**0,2**
3	**0,3**
4	**0,4**
5	**0,6**
6	**0,7**
7	**0,8**
8	**0,9**
9	**1,0**
10	**1,1**

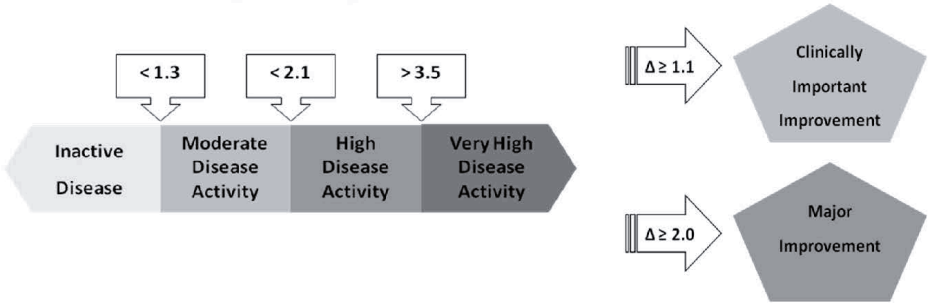
Peripheral Pain/Swelling	
0	**0**
1	**0,1**
2	**0,1**
3	**0,2**
4	**0,3**
5	**0,4**
6	**0,4**
7	**0,5**
8	**0,6**
9	**0,6**
10	**0,7**



C-Reactive Protein (mg/L)							
Note: when the conventional CRP is below the limit of detection or when the high sensitivity CRP is <2mg/L, the constant value of 2mg/L should be used to calculate ASDAS-CRP.							
≤2	**0,6**	15	**1,6**	60	**2,4**	125	**2,8**
3	**0,8**	16	**1,6**	65	**2,4**	130	**2,8**
4	**0,9**	17	**1,7**	70	**2,5**	135	**2,8**
5	**1,0**	18	**1,7**	75	**2,5**	140	**2,9**
6	**1,1**	19	**1,7**	80	**2,5**	145	**2,9**
7	**1,2**	20	**1,8**	85	**2,6**	150	**2,9**
8	**1,3**	25	**1,9**	90	**2,6**	155	**2,9**
9	**1,3**	30	**2,0**	95	**2,6**	160	**2,9**
10	**1,4**	35	**2,1**	100	**2,7**	165	**3,0**
11	**1,4**	40	**2,2**	105	**2,7**	170	**3,0**
12	**1,5**	45	**2,2**	110	**2,7**	175	**3,0**
13	**1,5**	50	**2,3**	115	**2,8**	180	**3,0**
14	**1,6**	55	**2,3**	120	**2,8**	185	**3,0**



Quick ASDAS-ESR Calculation Form



Name : _____ **Date :** ____ /____ /_____

1) How would you describe the overall level of AS neck, back or hip pain you have had?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

None — Very severe

2) How long does your morning stiffness last from the time you wake up?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

0 — 1 — 2 or more hours

3) How active was your spondylitis on average during the last week?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

Not active — Very active

4) How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

0 — 1 — 2 — 3 — 4 — 5 — 6 — 7 — 8 — 9 — 10

None — Very severe

5) Erythrocyte sedimentation rate (mm/h)?

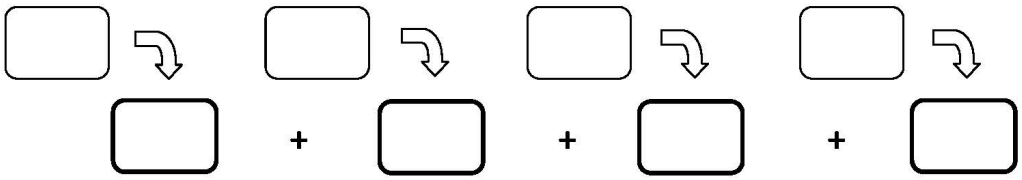
[redacted]

Back Pain	
0	0,0
1	0,1
2	0,2
3	0,2
4	0,3
5	0,4
6	0,5
7	0,6
8	0,6
9	0,7
10	0,8

Morning Stiffness	
0	0,0
1	0,1
2	0,1
3	0,2
4	0,3
5	0,4
6	0,4
7	0,5
8	0,6
9	0,6
10	0,7

Patient Global	
0	0,0
1	0,1
2	0,2
3	0,3
4	0,4
5	0,6
6	0,7
7	0,8
8	0,9
9	1,0
10	1,1

Peripheral Pain/Swelling	
0	0,0
1	0,1
2	0,2
3	0,3
4	0,4
5	0,5
6	0,5
7	0,6
8	0,7
9	0,8
10	0,9



Erythrocyte Sedimentation Rate (mm/h)							
0	0,0	14	1,1	28	1,5	70	2,4
1	0,3	15	1,1	29	1,6	75	2,5
2	0,4	16	1,2	30	1,6	80	2,6
3	0,5	17	1,2	31	1,6	85	2,7
4	0,6	18	1,2	32	1,6	90	2,8
5	0,6	19	1,3	33	1,7	95	2,8
6	0,7	20	1,3	34	1,7	100	2,9
7	0,8	21	1,3	35	1,7	105	3,0
8	0,8	22	1,4	40	1,8	110	3,0
9	0,9	23	1,4	45	1,9	115	3,1
10	0,9	24	1,4	50	2,1	120	3,2
11	1,0	25	1,5	55	2,2	125	3,2
12	1,0	26	1,5	60	2,2	130	3,3
13	1,0	27	1,5	65	2,3	135	3,4