EU Risk Management Plan
for
Remsima IV/SC and Inflectra IV (Infliximab)

RMP version to be assessed as part of this application:	
RMP version number:	18.0
Data lock point for this RMP:	11 August 2025
Date of final sign off:	30 September 2025
Rationale for submitting an updated RMP:	This RMP has been updated to add the important potential risk 'Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only) following the newly proposed presentation for IV liquid preparation.
Summary of significant changes in this RMP:	Part II – SVII: Identified and Potential Risks • Added the important potential risk 'Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)' Part II – SVIII: Summary of the safety concerns • Added the important potential risk 'Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)' Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities) • Added routine risk minimisation measures proposed for the important potential risk 'Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)' • Added additional risk minimisation measures proposed for the important potential risk 'Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)'

	Part VI: Summary of the risk management plan • Added the important potential risk 'Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)' Annex 6. • Add the contraindication regarding intravenous use of Remsima 100mg and 350mg concentrate for solution for infusion in patients with HFI in the key messages of the patient reminder card.
Other RMP versions under evaluation:	
RMP version number:	N/A
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Details of the currently approved RMP:	
Version number:	18.0
Approved with procedure:	EMEA/H/C/002576/X/0149 (For Remsima)
Date of approval (opinion date):	18 September 2025 (For Remsima)
For Remsima: QPPV name: For Inflectra (intravenous [IV] formulation)*: QPPV name:	[redacted]
QPPV oversight declaration:	The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPVs. The electronic signature is available on file.

Note: Throughout this document, symbols indicating proprietary names (®, ™) are not displayed. The appearance of product names without these symbols does not imply that these names are not protected.

**Pfizer has entered into a global licensing agreement with Celltrion, pursuant to which Pfizer holds marketing authorisations for intravenous (IV) administration infliximab of powder preparation only. A separate subcutaneous (SC) formulation and IV formulation of liquid preparation have been developed by Celltrion which is not subject to the global licensing agreement and for which Pfizer has no marketing authorisations. Data presented in this document, prepared by Celltrion relates to both the IV and SC presentations of infliximab. Pfizer has reviewed this document with reference to the IV formulation of powder preparation and agrees with its content and benefit-risk conclusion, but Pfizer has not reviewed the data or the benefit-risk conclusion pertaining to the SC presentation and IV formulation of liquid preparation.*

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List of Abbreviations

Term	Explanation
6-MP	6-Mercaptopurine
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AESI	Adverse Events of Special Interest
AGEPS	General Agency of Equipment and Health Products
AIDS	Acquired Immune Deficiency Syndrome
AIH	Autoimmune Hepatitis
ALT	Alanine Aminotransferase
ANA	Anti-Nuclear Antibody
aRMMs	Additional Risk Minimisation Measures
AS	Ankylosing Spondylitis
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASPIRE	Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset
ATC	Anatomical Therapeutic Chemical
AZA	Azathioprine
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BCC	Basal Cell Carcinoma
BCG	Bacillus Calmette–Guérin
BMWP	Biological Medicinal Products Working Party
BSRBR-RA	British Society for Rheumatology Biologics Register-Rheumatoid Arthritis
CD	Crohn's Disease
CDAI	Crohn's Disease Activity Index
CHF	Congestive Heart Failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CRP	C-Reactive Protein
CSR	Clinical Study Report

Term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
CT-P13	Marketing authorization holder's infliximab product
DAS	Disease Activity Score
DCs	Dendritic Cells
DDD	Defined Daily Dose
DMARD	Disease-Modifying Anti-Rheumatic Drug
DNA	Deoxyribonucleic Acid
EBV	Epstein-Barr Virus
EC	European Collaborative
EEA	European Economic Area
EMA/EMEA	European Medicines Agency/European Medicines Evaluation Agency
EOS	End-of-Study
EPAR	European Public Assessment Report
EQ-5D-3L	European Quality of Life Five Dimension Three Level Scale
ESI	Events of Special Interest
ESORDIG	Epidemiological Study of the Rheumatic Diseases in Greece
EU	European Union
FPFV	First Patient First Visit
GLP	Good Laboratory Practice
GPRD	General Practice Research Database
GVP	Good Pharmacovigilance Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HBc	Hepatitis B Core
HBsAG	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCPs	Healthcare Professionals
HCV	Hepatitis C Virus
HFI	Hereditary Fructose Intolerance
HIV	Human Immunodeficiency Virus
HL	Hodgkin's Lymphoma

Term	Explanation
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
HR	Hazard Ratio
HSTCL	Hepatosplenic T-Cell Lymphoma
HTLV-1	Human T-Cell Leukaemia Virus Type-1
IV	Intravenous
IBD	Inflammatory Bowel Disease
Ig	Immunoglobulin
IL	Interleukin
INN	International Non-Proprietary Name
LBW	Low Birth Weight
LPLV	Last Patient Last Visit
LVEF	Left Ventricular Ejection Fraction
mAb	Monoclonal Antibody
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MS	Multiple Sclerosis
NHL	Non-Hodgkin's Lymphoma
NYHA	New York Heart Association
OI	Opportunistic Infection
PASS	Post-authorisation safety studies
PCR	Polymerase Chain Reaction
PD	Pharmacodynamics
PK	Pharmacokinetics
PL	Package Leaflet
PLANETAS	Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Ankylosing Spondylitis
PLANETRA	Programme Evaluating the Autoimmune Disease Investigational Drug CT-P13 in Rheumatoid Arthritis
PMS	Post-Marketing Surveillance
PRAC	Pharmacovigilance Risk Assessment Committee
PROs	Patient Reported Outcomes

Term	Explanation
PsA	Psoriatic Arthritis
PSC	Primary Sclerosing Cholangitis
PUVA	Psoralen and Long-Wave Ultraviolet Radiation
PY	Patient Years
QoL	Quality of Life
RA	Rheumatoid Arthritis
RABBIT	Rheumatoid Arthritis Observation of Biologic Therapy
REACH	Randomized, Multicenter, Open-Label Study to Evaluate the Safety and Efficacy of Anti-TNF-α Chimeric Monoclonal Antibody in Paediatric Subjects with Moderate to Severe Crohn's Disease
RMP	Risk Management Plan
SAE(s)	Serious Adverse Event(s)
SC	Subcutaneous
SI	The International System of Units
SLE	Systemic Lupus Erythematosus
SmPC	Summary of Product Characteristics
SMR	Standardised Mortality Ratio
SOC	Standard of Care
SSLRs	Serum Sickness-Like Reactions
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TGF	Transforming Growth Factor
TNF	Tumour Necrosis Factor
TNF-α	Tumour Necrosis Factor Alpha
UC	Ulcerative Colitis
UK	United Kingdom
UniHA	French Hospitals Procurement Organisation
USA	United States of America
UV	Ultraviolet
WHO	World Health Organization

Part I: Product(s) Overview

Table 1: Part I.1 – Product Overview

Active substance(s) (INN or common name)	Infliximab
Pharmacotherapeutic group(s) (ATC Code)	Immunosuppressant, tumour necrosis factor alpha inhibitors (L04AB02)
Marketing Authorisation Holder	• CELLTRION Healthcare Hungary KFT. • Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	Remsima (IV and SC) Inflectra (IV)
Invented name(s) in the European Economic Area (EEA)	Remsima/Inflectra
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Infliximab is a chimeric human-murine immunoglobulin (Ig) IgG1 monoclonal antibody (mAb) directed against tumour necrosis factor alpha (TNF-α).
	Summary of mode of action: TNF-α is a cytokine with multiple actions including mediation of inflammatory responses, modulation of the immune system and the induction of apoptosis. Infliximab binds with high affinity to soluble and transmembrane forms of TNF-α and inhibits the functional activity of TNF-α. In combination with either complement or effector cells, it can induce cell lysis. *In vitro*, infliximab binds to various polymorphic variants of cell surface-expressed Fc receptors, the complement component C1q, and mediates antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity.
	Important information about its composition: Infliximab is produced in murine hybridoma cells by recombinant deoxyribonucleic acid (DNA) technology.
Hyperlink to the Product Information	Infliximab Product Information (Module 1.3.1)
Indication(s) in the EEA	*Current:* **IV formulation** Rheumatoid arthritis Remsima/Inflectra IV, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in: • adult patients with active disease when the response to disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, has been inadequate. • adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

	In these patient populations, a reduction in the rate of the progression of joint damage, as measured by X-ray, has been demonstrated. Adult Crohn's disease Remsima/Inflectra IV is indicated for: • treatment of moderately to severely active Crohn's disease (CD), in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. • treatment of fistulising, active CD, in adult patients who have not responded despite a full and adequate course of therapy to conventional treatment (including antibiotics, drainage and immunosuppressive therapy). Paediatric Crohn's disease Remsima/Inflectra IV is indicated for treatment of severe, active CD in children and adolescents aged 6 to 17 years, who have not responded to conventional therapy including a corticosteroid, an immunomodulator and primary nutrition therapy; or who are intolerant to or have contraindications for such therapies. Infliximab has been studied only in combination with conventional immunosuppressive therapy. Ulcerative colitis Remsima/Inflectra IV is indicated for treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Paediatric ulcerative colitis Remsima/Inflectra IV is indicated for treatment of severely active UC in children and adolescents aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. Ankylosing spondylitis Remsima/Inflectra IV is indicated for treatment of severe, active ankylosing spondylitis (AS), in adult patients who have responded inadequately to conventional therapy. Psoriatic arthritis Remsima/Inflectra IV is indicated for treatment of active and progressive psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy has been inadequate.

Remsima/Inflectra IV should be administered:

- in combination with methotrexate
- or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated.

Infliximab has been shown to improve physical function in patients with PsA, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease.

Psoriasis

Remsima/Inflectra IV is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen ultra-violet A (PUVA).

SC formulation

Rheumatoid arthritis

Remsima SC, in combination with methotrexate, is indicated for the reduction of signs and symptoms as well as the improvement in physical function in:

- adult patients with active disease when the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate, has been inadequate.
- adult patients with severe, active and progressive disease not previously treated with methotrexate or other DMARDs.

In these patient populations, a reduction in the rate of progression of joint damage, as measured by X-ray, has been demonstrated.

Crohn's disease

Remsima SC is indicated for:

- treatment of moderately to severely active Crohn's disease (CD), in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies.
- treatment of fistulising, active CD, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy).

Ulcerative colitis

Remsima SC is indicated for treatment of moderately to severely active ulcerative colitis (UC) in adult patients who have had an inadequate response to conventional therapy including corticosteroids

	and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. Ankylosing spondylitis Remsima SC is indicated for treatment of severe, active ankylosing spondylitis (AS), in adult patients who have responded inadequately to conventional therapy. Psoriatic arthritis Remsima SC is indicated for treatment of active and progressive psoriatic arthritis (PsA) in adult patients when the response to previous DMARD therapy has been inadequate. Remsima SC should be administered • in combination with methotrexate • or alone in patients who show intolerance to methotrexate or for whom methotrexate is contraindicated. Infliximab has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease. Psoriasis Remsima SC is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including ciclosporin, methotrexate or psoralen ultra-violet A (PUVA).
	Proposed: Not applicable.
Dosage in the EEA	*Current*: **IV formulation** *Adults (≥18 years)* Rheumatoid arthritis 3 mg/kg given as an intravenous (IV) followed by additional 3 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Moderately to severely active Crohn's disease 5 mg/kg given as an IV infusion followed by an additional 5 mg/kg infusion 2 weeks after the first infusion. If a patient does not respond after 2 doses, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion. Fistulising, active Crohn's disease

	5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusions at 2 and 6 weeks after the first infusion. If a patient does not respond after 3 doses, no additional treatment with infliximab should be given. Ulcerative colitis 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Ankylosing spondylitis 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 6 to 8 weeks. If a patient does not respond by 6 weeks (i.e., after 2 doses), no additional treatment with infliximab should be given. Psoriatic arthritis 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Psoriasis 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. If a patient shows no response after 14 weeks (i.e., after 4 doses), no additional treatment with infliximab should be given. Re-administration across indications In case maintenance therapy is interrupted, and there is a need to restart treatment, use of a re-induction regimen is not recommended. In this situation, Remsima/Inflectra IV should be re-initiated as a single dose followed by the maintenance dose recommendations described above. *Paediatric population* Crohn's disease (6 to 17 years) 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab treatment in children and adolescents not responding within the first 10 weeks of treatment. Ulcerative colitis (6 to 17 years) 5 mg/kg given as an IV infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. Available data do not support further infliximab

	treatment in paediatric patients not responding within the first 8 weeks of treatment. Method of administration Remsima/Inflectra IV should be administered IV over a 2-hour period. *Shortened infusions across adult indications* In carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of Remsima/Inflectra IV (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. **SC formulation** *Adults (≥18 years)* Rheumatoid arthritis Treatment with Remsima subcutaneous formulation should be initiated with loading doses of infliximab which may be intravenous or subcutaneous. When subcutaneous loading is used, Remsima 120 mg should be given as a subcutaneous injection followed by additional subcutaneous injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter. If intravenous loading doses of infliximab are given to initiate treatment, 2 intravenous infusions of infliximab 3 mg/kg should be given 2 weeks apart. The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the second intravenous administration. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. Remsima must be given concomitantly with methotrexate. Moderately to severely active Crohn's disease The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after loading doses of intravenous infliximab, no additional treatment with infliximab should be given. Fistulising, active Crohn's disease The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last

	administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond after loading doses of intravenous infliximab, no additional treatment with infliximab should be given. Ulcerative colitis The first treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of intravenous infusions. Before initiating treatment with Remsima subcutaneous formulation, 2 intravenous infusions of infliximab 5 mg/kg should be given at 2 weeks apart, and an additional intravenous infusion of infliximab 5 mg/kg may be given 4 weeks after the second infusion. The recommended maintenance dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. Ankylosing spondylitis Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient does not respond by 6 weeks (i.e. after 2 intravenous infusions), no additional treatment with infliximab should be given. Psoriatic arthritis Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. Psoriasis Treatment with Remsima administered subcutaneously should be initiated as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab 5 mg/kg given 2 weeks apart. The recommended dose for Remsima subcutaneous formulation is 120 mg once every 2 weeks. If a patient shows no response after 14 weeks (i.e. 2 intravenous infusions and 5 subcutaneous injections), no additional treatment with infliximab should be given.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	*Current:* **IV formulation**

	Powder for concentrate for solution for infusion. One vial contains 100 mg of infliximab. After reconstitution with 10 mL sterile water, each mL contains 10mg of infliximab. **<u>SC formulation</u>** Solution for injection (subcutaneous injection). One pre-filled syringe or pen contains 120 mg of infliximab.
	Proposed: In addition to the current IV formulation, the new presentations are added in the following: • Remsima 100 mg concentrate for solution for infusion. Each mL contains 40 mg of infliximab. Each vial contains 100 mg of infliximab. • Remsima 350 mg concentrate for solution for infusion. Each mL contains 40 mg of infliximab. Each vial contains 350 mg of infliximab.
Is/will the product be subject to additional monitoring in the EU?	No

Note: Throughout this document, Remsima IV indicates both presentations (infliximab of powder and liquid preparations) and Inflectra IV indicates only infliximab of powder preparation.

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Indication – rheumatoid arthritis (adults)

Rheumatoid arthritis (RA) is a chronic multisystem autoimmune disease of unknown cause with exacerbations and remissions of local articular and systemic extra-articular symptoms. The characteristic feature of established RA is inflammatory joint disease, which is a major cause of disability and mortality (Lipsky, 2008; Smolen & Aletaha, 2010; Van Doornum et al., 2002).

Incidence

The reported incidence rates for RA vary between regions, types of population studied, criteria used for RA diagnosis, and database and methodology used for evaluation.

The reported incidence rates for RA were between 0.008 and 0.05% (8-50 cases per 100,000) for European countries (Alamanos et al., 2006).

The median annual incidence rates of RA for the total population:

- South European countries: 0.0165% (16.5 cases per 100,000).
- North European countries: 0.029% (29 cases per 100,000).
- North American countries: 0.038% (38 cases per 100,000).
- Norway and Finland: 0.02% and 0.04%, respectively (studies based on record reviews).
- United Kingdom (UK): 0.02% (year 1990, American College of Rheumatology (ACR) 1987 criteria).
- Czech Republic: 0.31% (annual incidence: 2002-2003; two regions in Czech Republic, ACR 1987 criteria, sample: ≥16 years) (Hanova et al., 2006).
- Spain: 0.0083% (SERAP project; annual incidence of RA, ACR 1987 criteria; adults over the age of 16 years (Carbonell et al., 2008).

Prevalence

Overall, the global prevalence of RA is approximately 1% (range 0.3-2.1%) (Delabaye & DeKayser, 2010; Hsia et al., 2006; Köller et al., 2009; Lipsky, 2008).

In 2004, the global prevalence of RA was 23.7 million. The prevalence (in millions) by World Health Organization (WHO) region was reported as follows: Africa, 1.2; the Americas, 4.6; Eastern Mediterranean, 1.3; Europe, 6.2; South-East Asia, 4.4; and Western Pacific, 6.0 (WHO, 2008).

Prevalence of RA in Europe has been reported to be between 0.33% and 1.1% with higher rates in North European countries compared to South European countries (0.5% versus 0.33%) (Alamanos et al., 2006). Generally, the number of women affected by RA was higher than the number of men. The prevalence of RA increased with age. The reported prevalence rates vary between regions, types of population studied, criteria used for RA diagnosis, and database and methodology used for evaluation.

General Practice Research Database (GPRD) 1997-2002: Prevalence of RA (International classification of disease -9 code): 0.5% (500 per 100,000; mean age of individuals with RA was 58.4 years, 71.4% were female; median follow-up period was 7 years 153 days).

Sweden: 0.51% (estimated total population prevalence; subjects aged 20-75 years; two-stage population screening survey) (Symmons et al., 2002).

France: 0.31% (estimated prevalence standardised for age and sex; based on a nationwide multistage sample survey conducted in 20 counties) (Guillemin et al., 2005).

Greece, 1966-1999: 0.68% (ACR 1987 criteria); study participants (n=8,740), general population, aged 19 or older; Epidemiological Study of the Rheumatic Diseases in Greece (ESORDIG study). (Andrianakos et al., 2006). Central Greece, 2007-2008: Total 0.57% (female-male ratio: 2.3:1; mean age: 46.8 years) (Anagnostopoulos et al., 2010).

Spain: 0.5% (estimated prevalence of RA; study in 20 municipalities, n=2,998 adults); 0.6% in urban areas and 0.2% in rural areas. Extrapolating to the total population (around 40 million), there are 150,000 to 200,000 cases of RA in Spain (Carmona et al., 2002).

Italy: 0.46% (estimated prevalence of RA; MAPPING Study (prevalence of musculoskeletal conditions), sample 4000 subjects aged 18 years, time period: April 2004 to June 2004) (Salaffi et al., 2005).

Demographics of the population in the authorised indication – age, sex, racial and/or ethnic origin and risk factors of the disease

The onset of adult RA is most frequent during the fourth and fifth decades of life, with 80% of patients developing the disease between the ages of 35 and 50 years (Lipsky, 2008). RA is more common in women than in men (approximate ratio 1:3). Sex differences are diminishing in older age groups (Carbonell et al., 2008; Andrianakos et al., 2006; Lipsky, 2008; Temprano & Diamond, 2011).

Risk factors include female gender, increasing age, smoking, ethnic group, and family history of RA.

RA affects all populations, although the disease is more prevalent in some groups (e.g., 5-6% prevalence rate in some Native American groups) and less prevalent in others (e.g., black persons from the Caribbean region).

The first-degree relatives of individuals with RA are at an increased risk (2- to 3-fold) of the disease (Temprano & Diamond, 2011).

The main existing treatment options

Treatments fall into three categories – medical therapies, physical and occupational therapies for maintenance of function and management of deformity, and surgery for correction of severe joint deformity or joint replacement or tendon repair.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

RA is associated with increased mortality compared to the general population (Lipsky, 2008; Gabriel, 2008; Meune et al., 2009; Salmon & Roman, 2008; Van Doornum et al., 2002). The standardised mortality ratios (SMRs) in major studies performed in the past 50 years ranged from 0.87-3.0 (Van Doornum et al., 2002).

The median life expectancy of persons with RA is shortened by 3-7 years (Lipsky, 2008) up to 3-18 years (Van Doornum et al., 2002). The increased mortality rates seem to be limited to patients with more severe articular disease (Lipsky, 2008).

Increased mortality occurred in both men and women with RA and did not appear to decline over time, in contrast to the progressive improvement in survival of the general population (Van Doornum et al., 2002).

Increased mortality rate is considered to be largely attributed to cardiovascular causes (Chehata et al., 2001; Gabriel, 2008; Hsia et al., 2006; Lipsky, 2008; Meune et al., 2009; Salmon & Roman, 2008; Van Doornum et al., 2002).

Besides cardiovascular disease, infection (especially respiratory) and gastrointestinal bleeding, renal, gastrointestinal and pulmonary diseases as well as lymphoproliferative disorders (but not other cancers) were more prevalent in RA and seem to contribute to increased mortality rates in patients with more severe articular disease (Lipsky, 2008; Meune et al., 2009; Van Doornum et al., 2002).

Drug therapy may also play a role in the increased mortality rate of patients with RA (Lipsky, 2008).

The factors correlated with early death include disability, disease duration or severity, persistent inflammation, glucocorticoid use, age at onset and low socioeconomic or educational status (Lipsky, 2008).

Important co-morbidities

Disability: Disability (impairment in physical function/of quality of life [QoL]) due to RA is related to pain, tenderness and stiffness of the joints, and in later stages of the disease, to joint damage (erosions). Although joint damage generally begins early in the course of RA, the link between damage and disability is strongest in late disease. Joint damage accounts for approximately one quarter of disability in long-standing disease. Overall, two components in functional limitation can contribute to RA disability; those related to current disease activity (reversible) and those resulting from accrued damage (irreversible) (Smolen & Alehata, 2010).

Cardiovascular disease: Patients with RA have an increased risk for atherosclerotic cardiovascular events. Traditional cardiovascular risk factors are considered to contribute to but do not fully explain the increased risk of cardiovascular mortality (del Rincon et al., 2001; Dixon & Symmons, 2007; Gabriel, 2008; Meune et al., 2009). Chronic inflammation in RA appears to contribute to accelerated atherosclerosis and mortality (Gabriel, 2008). Prevalence of subclinical cardiovascular disease is also increased in patients with RA (Hsia et al., 2006).

Congestive heart failure (CHF): The risk of developing CHF in RA is twice the risk of developing CHF in subjects without RA. This excess risk cannot be explained by cardiovascular risk factors and/or ischaemic heart disease alone (Gabriel, 2008; Nicola et al., 2005; Voskuyl, 2006).

Malignancies and lymphoproliferative disorders (lymphoma): Generally, RA patients are at increased risk of lymphoma as compared to the general population (Askling et al., 2005; Smedby et al., 2006; Wolfe & Michaud, 2007; Wolfe & Michaud, 2004). The incidence of non-Hodgkin's lymphoma (NHL) has doubled between 1984 and 2004 (Fisher & Fisher, 2004; Smedby et al., 2006). With regard to NHL subtypes in RA, an increased proportion of diffuse large B-cell lymphoma has been described (Smedby et al., 2006).

Lymphoma rates increase with age (Wolfe & Michaud, 2004). In addition, evidence is accumulating that increased lymphoma risk in patients with RA may be due to high inflammatory activity and severity of disease, rather than to treatment (Smedby et al., 2006). An alternate explanation for the association between RA and lymphoma risk is the existence of shared genetic and/or environmental risk factors for both conditions.

Overall, treatment of RA with DMARDs, including methotrexate, AZA, and other immunosuppressive substances, has been repeatedly suggested as a risk factor for RA-associated lymphomas. However, the role of immunosuppressive therapy seems to be limited (Smedby et al., 2006).

Indication – ankylosing spondylitis

Incidence

Reported incidence rates for AS vary between regions, types of population studied, criteria used for AS diagnosis, and databases and methodologies used for evaluation.

The incidence of AS is between 0.5 and 14 of 100,000 people (0.0005% to 0.014%) per year in studies from different countries. Several factors contribute to these differences: (1) selection of the target populations; (2) selection of screening criteria (e.g., back pain, diagnostic criteria to confirm the diagnosis); (3) prevalence of Human leukocyte antigen (HLA) B27 and the distribution of its subtypes, which may differ in populations with different ethnic background. There is a rough correlation between the prevalence of HLA B27 and the incidence and prevalence of AS in any given population (Braun & Sieper, 2007).

Prevalence

About 8% of the general population of Western European and 10-16% of some of the Scandinavian and Eastern European populations express HLA-B27 (Akkoc & Khan, 2005).

Approximately 90% of white patients with AS express HLA-B27, whereas AS associated with HLA-B27 is nearly absent in both American blacks and Japanese people (where the prevalence of B27 is less than 1%) (Olivieri et al., 2002).

Europe: Few incidence data of AS have been reported in the published literature in contrast to prevalence data of AS.

Czech Republic: The age-standardised annual incidence of AS in adults was 6.4/100,000 (95% Confidence interval (CI) 3.3-11.3) and the male to female ratio was 3.3:1 (Hanova et al., 2010).

Finland: Studies on the incidence of AS have given figures of 6 to 10 per 100,000 people in Finland (Savolainen et al., 2003). An age-adjusted incidence rate of 6.3 per 100,000 (95% CI 4.9-7.9) people (0.0063%) aged ≥16 years was reported in a Finnish study (Olivieri et al., 2002).

Norway: Incidence and prevalence of AS in Northern Norway were determined by (Bakland et al., 2005) in a cohort study of all patients registered with a diagnosis of AS between 1960 and 1993. Annual incidence of AS was 8.71 of 100,000 (0.0087%).

Worldwide: Among whites, the estimated prevalence of AS defined by the (modified) New York criteria ranges from 67.7/100,000 population over 20 years of age in the Netherlands to 197/100,000 in the United States of America (USA) (Olivieri et al., 2002).

Europe: Overall, the prevalence of AS is between 0.1% and 1.4% (Braun & Sieper, 2007).

In population-based surveys of the prevalence of AS in some European populations, prevalence rates ranging from 0.15% to 1.8% were reported (Akkoc & Khan, 2005).

Czech Republic: The age-standardised prevalence of AS was 94.2/100,000 (95% CI 80.8-109.2). The prevalence of AS for children younger than 16 years was 6.2/100,000 (95% CI 0.7-22.4/100,000). The male to female ratio was 4.6:1 (Hanova et al., 2010).

France: The estimated prevalence rate of AS in 2001 was 0.14% (Saraux et al., 2003).

Finland: The prevalence of AS in Finland was 0.15% (Olivieri et al., 2002).

Germany: In the German RA Population survey, the age-specific prevalence of self-reported doctor-diagnosed AS was reported as follows: 18-44 years: 0.6%; 45-64 years: 1.6%; 65-74 years: 1.9%; 75-79 years: 1.4%; total 1.1% (Westhoff et al., 2009).

Braun et al., 1998 investigated the prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors in Berlin, who agreed to have magnetic resonance imaging of the sacroiliac joints in addition to physical examination. The calculated prevalence of AS was 0.86% in this population (Olivieri et al., 2002).

Greece: A prospective 2-step population based cross-sectional survey conducted from April 2007 to June 2008 in Central Greece reported a prevalence of 0.29% (95% CI 0.29-0.94). The female to male ratio was 1:4 (Anagnostopoulos et al., 2010).

In the ESORDIG epidemiological study conducted in northern, central and southern mainland Greece (1996-1999), the age and sex adjusted prevalence of AS was 0.24% (Andrianakos et al., 2006).

Italy: A regional community-based study on the prevalence of musculoskeletal conditions (the MAPPING study) including 2155 subjects was conducted in Italy. The estimated rate of AS prevalence was 0.37% (95% CI 0.23-0.49), (i.e., 370 per 100,000 population) (Salaffi et al., 2005).

Norway: In Northern Norway, estimated point prevalence of AS rose from 0.043% (43 in 100,000) in 1970 to 0.26% (260 in 100,000) in 1990 (Bakland et al., 2005).

Sweden: In Southern Sweden, the prevalence of AS was 0.12% (CI 0.11% to 0.124%), (i.e., 120 per 100,000 population, during 2003 to 2007) (Haglund et al., 2011).

Netherlands: The prevalence of AS in the Netherlands was reported to be 67.7 per 100,000 population (Olivieri et al., 2002).

Demographics of the population in the authorised indication – age, sex, racial and/or ethnic origin and risk factors of the disease

AS patients generally present at around 26 years of age. About 80% develop the first symptoms at an age <30 years, and less than 5% present at >45 years (Braun & Sieper, 2007).

Men are more often affected than are women, with a ratio of roughly 2 to 1.

Risk factors include male gender; and being positive for the HLA-B27.

The main existing treatment options

Treatments fall into three categories – medical therapies, physical and occupational therapies for maintenance of function and management of spinal deformity, and surgery for correction of severe joint deformity or joint replacement.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Mortality attributable to AS is largely the result of spinal trauma, aortic insufficiency, respiratory failure, amyloid nephropathy, or complications of therapy such as upper gastrointestinal haemorrhage (Taurog, 2008).

Mortality in AS patients was low in a cohort study in Northern Norway including 534 patients. In this study, SMR indicated lower death rates in all age and sex subgroups of patients with AS compared with controls (Bakland et al., 2005).

Most patients remain gainfully employed. Some studies of survival have suggested that AS shortens life span, as compared with the general population (Taurog, 2008).

Important co-morbidities

In patients with AS, bone mineral density is diminished in the spine and proximal femur early in the course of the disease. The most serious complication of AS is fracture of the rigid osteoporotic spine, most commonly involving the lower cervical spine. These fractures may cause spinal cord injury. A recent survey suggested a >10% lifetime risk of fracture (Taurog, 2008).

Acute anterior uveitis is the most common extra-articular manifestation of AS occurring in 40% of patients. Attacks tend to be recurrent, often involving the opposite eye. Cataract and secondary glaucoma are common complications (Taurog, 2008).

Up to 60% of patients develop inflammation in the colon or ileum. This is usually asymptomatic, but frank inflammatory bowel disease (IBD) occurs in 5-10% of patients with AS (Taurog, 2008).

About 10% of AS patients also have psoriasis.

Aortic insufficiency, sometimes producing symptoms of CHF, occurs in a small proportion of patients. Third-degree heart block may occur alone or together with aortic insufficiency.

Restrictive pulmonary disease may occur due to severe kyphosis in advanced AS.

Cauda equina syndrome and upper pulmonary lobe fibrosis are rare and late complications. Retroperitoneal fibrosis is a rare associated condition. Prostatitis has been reported to have an increased prevalence. Amyloidosis is a rare late complication of long-standing disease (Taurog, 2008).

Indication – Crohn's disease (adults)

Incidence

General observations in Northern Europe and the USA suggest that the incidence of CD has been rising since the mid-1990s (Gismera & Aladrén, 2008).

Worldwide, there is an apparent gradient with more polar latitudes (north or south) having higher incidences than more equatorial regions.

The incidence rate of CD varies between 0.1-16 per 100,000 inhabitants worldwide. (Lakatos, 2006).

Europe: In Europe, incidence ranges from 0.7-9.8 per 100,000 (Friedman & Blumberg, 2008).

The highest incidence rates of CD and UC have been reported from the UK, Scandinavia, with lower rates reported in Central and Southern Europe. The European geographic gradient is exemplified by an incidence (per 100,000 population) of 5.3 for Crohn's disease in Western Norway, 2.7 in Italy, and 0.9 in Spain.

A multicentre European Collaborative (EC) Study on IBD reported incidence rates between 3.9 and 7.0 cases per 100,000 person-years for CD. These figures produce estimates of between 23,000 and 41,000 new cases of CD diagnosed annually throughout Europe.

The incidence of CD per 100,000 population (corrected for age and sex) was reported as follows: UK Caucasians, 3.8; UK immigrants, 5.6; the Netherlands, 9.2; Germany, 4.4; France, 9.2; Italy, 3.3; Portugal (north), 4.2; Spain, 5.2; Portugal (south), 2.6; Greece, 0.9 (Keighley & Stockbrugger, 2003).

Denmark: In a Danish study, the mean incidence reported for CD was 4.6 (5.4 for women and 3.7 for men) per 100,000 per year, with a peak incidence in younger women. The incidence increased with age with the highest incidence in older women (Fonager et al., 1997).

France: A study was conducted in Northern France with more than 5,000,000 inhabitants. All cases with a diagnosis of definite or probable IBD from the EPIMAD population registry between January 1988 and December 2007 were included. The CD incidence rate increased significantly, from 5.2 cases per 100,000 person-years in the time period from 1988 to1990 to 6.7 in 2006-2007 (Chouraki et al., 2011).

Hungary: In Western Hungary, mean incidence rate was 8.87 cases per 100,000 inhabitants. Incidence rate increased from 6.95 in 2002 to 11.25 in 2006. The peak age of onset in CD patients was between 20 and 30 years with an incidence rate of 21.4 per 100,000 inhabitants (Laszlo et al., 2009).

Italy: A nationwide population-based study was carried out in eight Italian cities. From 1989 to 1992, an age-adjusted incidence rate (per 100,000 per year) of 2.3 was reported for CD. The rate computed after correcting underestimation was 2.8. The highest age-specific incidence rates were between 20 and 29 years (Tragnone et al., 1996).

Spain: The incidence of CD in Navarra, Northern Spain, was assessed in a prospective population-based study including 569,628 inhabitants. The crude rate of CD was 5.96 cases/100,000 inhabitants/year (Arin-Letamendia et al., 2008).

Sweden: Incidence of CD in Stockholm County was assessed for the time-period of 1955-1989. Incidence has stabilised at 4.6/100,000 over the last two decades (Lapidus et al., 1997).

UK: The incidence of CD in the UK white population (3.8) is lower than the European average (5.5), but UK immigrants have similar incidence (5.6). Several regional British studies have reported incidence rates of about 6 or 7 per 100,000, although substantially higher rates of 11 to 15 have been reported for northern regions such as north Tees and the North East of Scotland.

Prevalence

In Western Countries, the prevalence of CD has increased in the past 50 years. The prevalence of CD in North America ranges from 44 to 201/100,000; in Europe, CD prevalence ranges from 8 to 214/100,000 (Cosnes et al., 2011; Friedman & Blumberg, 2008).

Denmark: The prevalence of CD in 1987 was reported to be 54 per 100,000 inhabitants in Denmark; 45 per 100,000 in males and 63 per 100,000 females.

Spain: In central Spain, CD annual prevalence was 19.8/100,000 in the time-period of 1981 to 1988 (Mate-Jimenez et al., 1994).

UK: The prevalence of CD was 37.5 per 10,000 (375 per 100,000) subjects born in 1970 at 30 years of age; 21.1 per 10,000 subjects born in 1958 at 30 years of age, and 32.5 per 10,000 subjects born in 1958 at 42 years of age. There was no significant association between social class at birth or sex and CD (Ehlin et al., 2003).

For the whole British population, the point prevalence of 144.8 per 100,000 can be derived from a survey of 135,723 general practice clinical records in the North of England on 01 January 1995.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The peak age of onset of CD (and UC) is between 15 and 30 years. A second peak occurs between the ages of 60 to 80. The male to female ratio for CD is 1:1.8 (Friedman & Blumberg, 2008).

The CD is associated with being Caucasian, and under the age of 30 years. Other risk factors include Ashkenazi Jewish extraction; having a first-degree relation with the disease, urban residence; and cigarette smoking.

CD has a two- to four-fold increased frequency in Jewish populations in the USA, Europe and South Africa.

Smoking is associated with a two-fold increased risk of CD. Oral contraceptives are also linked to CD; the odds ratio of CD for oral contraceptive users is about 1.4. Appendectomy increases the risk of CD (Friedman & Blumberg, 2008).

UC (and CD) is associated with Turner's syndrome. Immunodeficiency disorders, such as hypogammaglobulinaemia, selective IgA deficiency, and hereditary angioedema, also exhibit an increased association with IBD (Friedman & Blumberg, 2008).

In twin studies, 58% of monozygotic twins are concordant for CD, whereas 4% of dizygotic twins are concordant for CD (Friedman & Blumberg, 2008).

The main existing treatment options

CD is usually treated with dietary measures, nutritional supplements, and medicines. Surgery may be required to treat intestinal obstruction, fistulae, and abscesses.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

The life expectancy of patients with CD is slightly reduced (Baumgart & Sandborn, 2007).

Overall and disease-related mortality was investigated 10 years after diagnosis in a prospectively assembled, uniformly diagnosed European population-based inception cohort of 380 CD patients diagnosed between 1991 and 1993 (Wolters et al., 2006). Thirty-seven deaths were observed in the entire cohort whereas 21.5 deaths were expected. The SMR was 1.85 (95% CI 1.30-2.55). Mortality risk was significantly increased in both females (SMR 1.93 [95% CI 1.10-3.14]) and males (SMR 1.79 [95% CI 1.11-2.73]). Patients from northern European centres had a significant overall increased mortality risk (SMR 2.04 [95% CI 1.32-3.01]) whereas a tendency towards increased overall mortality risk was also observed in the south (SMR 1.55 [95% CI 0.80-2.70]). Mortality risk was increased in patients with colonic disease location and with inflammatory disease behaviour at diagnosis. Mortality risk was also increased in the age group above 40 years at diagnosis for both total and CD related causes. Excess mortality was mainly due to gastrointestinal causes that were related to CD. This European multinational population-based study revealed an increased overall mortality risk in CD patients 10 years after diagnosis, and age above 40 years at diagnosis was found to be the sole factor associated with increased mortality risk (Wolters et al., 2006).

Denmark: A population-based cohort comprising 374 patients with CD diagnosed in Copenhagen County between 1962 and 1987 was observed until 1997 for mortality and causes of death. SMR was 1.3 (95% CI 1.01-1.56). Increased mortality was observed late in the disease course that was most pronounced among women younger than 50 years at diagnosis and was attributed to death associated with severe CD (Jess et al., 2002).

Italy: Long-term follow up (median 15 years) was completed to re-evaluate mortality in a Mediterranean cohort (Florence IBD study). Among CD patients, mortality was strongly increased for gastrointestinal diseases (SMR 4.49 [95% CI 1.80-9.25]), all cancers (SMR 2.10 [95% CI 1.22-3.36]), and lung cancer (SMR 4.00 [95% CI 1.60-8.24]), leading to a significant 50% excess total mortality (Masala et al., 2004).

Sweden: In a Swedish population study, the SMR for CD was 1.51 (Friedman & Blumberg, 2008).

UK: Mortality rates are not increased in IBD as compared with the general population. Low mortality rates in patients with UC and CD, respectively, were reported in three British district general hospital practices. Five hundred fifty-two patients with IBD were evaluated. The overall SMR for CD patients was 94 (95% CI: 59-140) (Farrokhyar et al., 2001).

Important co-morbidities

CD patients have an impaired QoL in all six categories of the IBD questionnaire. The most frequent concerns of CD patients are the uncertain nature of the disease, impaired energy level, effects of medication, the need for surgery, and having a stoma (Friedman & Blumberg, 2008).

Because CD is a transmural process, serosal adhesions develop that provide direct pathways for fistula formation. Perforation occurs in 1-2% of patients. The peritonitis of free perforation, especially colonic, may be fatal (Friedman & Blumberg, 2008).

Intra-abdominal and pelvic abscess occur in 10-30% of patients at some time in the course of their illness. Systemic glucocorticoid therapy increases the risk of intra-abdominal and pelvic abscesses in CD patients who have never had an operation (Friedman & Blumberg, 2008).

Surgery is an option only when medical treatment has failed or complications indicate their necessity. Patients with small bowel disease have an 80% chance of requiring surgery. Those with colitis alone have a 50% chance (Friedman & Blumberg, 2008). As per the study, after 20 years most patients with CD will require surgery (Baumgart & Sandborn, 2007).

Risk factors for developing cancer in Crohn's colitis are long-duration and extensive disease, bypassed colon segments, colon strictures, primary sclerosing cholangitis (PSC), and family history of colon cancer. In patients with extensive Crohn's colitis, 22% developed dysplasia or cancer by the fourth surveillance examination after a negative screening colonoscopy (Friedman & Blumberg, 2008).

Indication – Crohn's disease (children) (IV only)

Incidence

The incidence of CD in children and adolescents is about 3 per 100,000 and has risen during the past decade. In about 25% of all patients, the disease presents before the age of 18 years, and even in very young children (<2 years of age), the CD is becoming more common (Caprilli et al., 2006).

Prevalence

Estimates of prevalence rates for UC and CD in paediatric populations are limited. Incidence rates are consistently lower among children than among adolescents.

Denmark: A study was conducted in Western Denmark calculating the incidence and prevalence for UC, CD and indeterminate colitis per 100,000 children with <15 years of age (Jakobsen et al., 2008) in the time periods from 1998-2000 and 2002-2004. The incidence of CD was 2.3 and 3.1, respectively, for the two periods.

Finland: In Finland, in 2003, the incidence of CD in children <18 years of age was 2.6 per 100,000 (Turunen et al., 2006).

France: During the 1988-2007 period, the incidence rate of CD was 6.4. Incidence rates in the 0-19 age group increased steadily over the entire study period, from 3.4 cases per 100,000 person-years in 1988-1990 to 5.9 in 2006-2007. Further analyses showed that the 10 to 19-year-old age group was mainly responsible for this increase, since the incidence rates increased continuously, from

6.5 cases per 100,000 person-years in 1988-1990 to 11.1 in 2006-2007, whereas the incidence rates in the 0 to 9-year-old age group increased only slightly during the same period (Chouraki et al., 2011).

Iceland: A nation-wide study from Iceland described an incidence rate of 8.5 per 100,000 for CD among adolescents (Turunen et al., 2006).

UK: Increases in the incidence of paediatric CD have been reported in the UK. In Scotland, there was a 3-fold increase in paediatric incidence from 1968 to 1983, a further 50% increase from 1981-83 to 1990-92, and a 100% increase in North East Scotland from 1980-89 to 1990-99. In South Glamorgan, there was a 140% increase in the incidence of paediatric disease from 1983-88 to 1989-93. A recent comparison of two national British birth cohorts indicates that the prevalence of CD has increased in younger people, although the prevalence of UC has remained stable.

UK and Ireland: A study prospectively identified cases of IBD among children 1 to 16 years-of-age for 13 months (1998-1999), via the British Paediatric Surveillance Unit. The overall incidence of IBD was 5.2 per 100,000 children per year. The incidence for CD was 3.1 in UK and England, 4.2 in Scotland, 3.2 in Wales, 2.4 in Northern Ireland, and 2.3 in the Republic of Ireland (Sawczenko et al., 2001).

Sweden: The incidence of paediatric CD in Sweden was reported to be 1.3 per 100,000 between 1993 and 1995 (Kim & Ferry, 2004).

Based on varying results from population-based studies, it can be stated that paediatric IBD accounts for 7% to 20% of all IBD cases. Paediatric prevalence rates of 10 per 100,000 to 100 per 100,000 have been estimated.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

A study published by Turunen et al., 2006 characterised the incidence and clinical pattern of IBD from 1987 to 2003 on the basis of 2 large university hospital databases covering more than 50% of the child population in Finland (N=619,340). A total of 604 cases with IBD were diagnosed. The mean annual incidence rate of IBD increased from 3.9 in 1987 to 7.0 per 100,000 in 2003 with no predominance of CD. The majority of cases were for 12 to <15-year-old (33%, n=200); 5.1% were <3-year-old and 14% were <6-year-old age groups. UC was the most prevalent disease in all of the age groups. CD was infrequent in children <6 years of age.

The CD is associated with being Caucasian, and under the age of 30 years. Other risk factors include Ashkenazi Jewish extraction; having a first degree relative with the disease; urban residence; Turner's syndrome; immunodeficiency disorders, such as hypogammaglobulinaemia, selective IgA deficiency, and hereditary angioedema (Friedman & Blumberg, 2008).

The main existing treatment options

The treatment options for paediatric CD are the same as those described for adults.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

No data pertaining to the mortality of CD in children and adolescents have been identified in the literature.

Important co-morbidities

While many aspects of CD are encountered in both adult and paediatric patients, some features are unique to paediatric CD. Important features specific for paediatric CD are growth failure (decreased

growth velocity, short stature, delayed bone age) and developmental retardation including delayed sexual maturation, which are present at diagnosis in 10-40% of affected children as a result of chronic inflammatory activity, disease-related poor nutritional status, but also prolonged treatment with systemically acting steroids (Caprilli et al., 2006; Shamir et al., 2007; Kim & Ferry, 2004; Griffiths et al., 1993; Hildebrand et al., 1994; Markowitz et al., 1993; Motil et al., 1993). These factors may also significantly impair normal bone mineral accretion in children and adolescents (Gokhale et al., 1998; Boot et al., 1998; Kim & Ferry, 2004).

Systemic steroids are effective in inducing symptomatic and clinical remission in children (Escher et al., 2003), but entail a multitude of side effects with cosmetic disfigurements, bone demineralisation and growth and developmental retardation being of particular concern for this population (Boot et al., 1998; Gokhale et al., 1998). Although the inflammation process itself is known to impair growth (Shamir et al., 2007; Motil et al., 1993), treatment with systemically acting steroids has been shown to further impact growth and development in children (Allen 1996; Cezard et al., 2002; Hyams & Markowitz, 2005). Furthermore, the risk of resistance to steroid treatment and of steroid dependency in paediatric Crohn's patients is as high as in adults (Tung et al., 2006; Carvalho & Hyams, 2007).

Indication – Ulcerative colitis (adults)

Incidence

The highest incidences of CD and UC have been reported in northern Europe, the UK, and North America. In countries that are becoming industrialised, the incidence of UC increases first, followed later by CD. The peak age for UC is 30-40 years. UC occurs slightly more frequently in men (60%) (Cosnes et al., 2011). Worldwide, the incidence of UC varies greatly between 0.5 and 24.5 per 100,000 (Lakatos, 2006).

The incidence of UC is approximately 10-20 per 100,000 per year with a reported prevalence of 100-200 per 100,000.

In Europe, incidence rates range from 1.5 to 20.3 cases per 100,000 person-years for UC. The multicentre EC-IBD reported incidence rates between 8.7 and 11.8 cases per 100,000 person-years for UC. In the EC-IBD, the incidence of UC including proctitis (per 100,000) for ages 15 and older was reported as 11.4 in all northern centres, 8.0 in all southern centres, and 9.8 in all centres combined (Shivananda et al., 1996).

The incidence of UC per 100,000 population (corrected for age and sex) was reported as follows: UK Caucasians, 10; UK immigrants, 15.3; Germany, 4.1; France, 6.7; Italy, 8.7; Portugal, 6.6; Spain, 9.8; Greece, 9.3; and Finland, 4.8. (Keighley & Stockbrugger, 2003).

Denmark: In a Danish study based on the National Registry of Patients, the mean incidence reported for UC was 13.2 (13.4 for women and 13.0 for men) per 100,000 per year, with the highest incidence on older men. A decreasing tendency in incidence was present in most age groups (Fonager et al., 1997).

France: A study was conducted in northern France with more than 5,000,000 inhabitants. All cases with a diagnosis of definite or probable IBD from the EPIMAD population registry between 1988 and 1999 were included. During the total period, UC incidence rate was 4.1 per 100,000 person-years and was significantly higher in men (4.7) than in women (3.6) (Moliniè, 2004).

Spain: The crude incidence rate of UC was 10.29 cases/100,000 inhabitants/year in Navarra, northern Spain (children aged 0-14 years were included) (Arin-Letamendia et al., 2008). In central

Spain, UC annual incidence was 3.16/100,000 in the time-period from 1981 to 1988 (Mate-Jimenez et al., 1994).

UK: The incidence of UC among the UK white population (10.0 per 100,000) is similar to the average of all European countries reported (9.4), but UK immigrants have a substantially higher rate.

Prevalence

The global prevalence of UC is 100-200 per 100,000 (Carter et al., 2004).

In Western countries, the prevalence of IBD has increased in the past 50 years, up to 120-200 per 100,000 persons for UC. The prevalence of UC in North America varies from 37.5 to 238/100,000; and in Europe, UC prevalence varies from 21 to 294/100,000 (Cosnes et al., 2011).

UK: The prevalence of UC in the UK is currently about 160-240 per 100,000. Patients with an emergency hospital admission of three or more consecutive days were included in a UK study on prevalence and mortality of UC and CD conducted from 1999 to 2007 in Wales. The overall hospitalised prevalence rate per 100,000 population was 50.6 for UC. The hospitalised prevalence of UC increased with age and was highest in patients aged over 65 years and similar in males and females (Button et al., 2010).

The prevalence of UC was 30.3 per 10,000 (375 per 100,000) subjects born in 1970 at 30 years of age; 27.3 per 10,000 subjects born in 1958 at 30 years of age, and 58.9 per 10,000 subjects born in 1958 at 42 years of age (Ehlin et al., 2003).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The peak age of onset of UC (and CD) is between 15 and 30 years. A second peak occurs between the ages of 60 and 80. The male to female ratio for UC is 1:1. UC (and CD) has two- to four-fold increased frequency in Jewish populations in the USA, Europe and South Africa. The risk of UC in smokers is 40% when compare to non-smokers. Additionally, former smokers have a 1.7-fold higher risk for UC than people who have never smoked. Appendectomy is protective against UC. UC (as for CD) is associated with Turner's syndrome and immunodeficiency disorders, such as hypogammaglobulinaemia, selective IgA deficiency, and hereditary angioedema. In twin studies, 6% of monozygotic twins are concordant for UC, whereas none of the dizygotic twins are concordant for UC (Friedman & Blumberg, 2008).

The UC is associated with being Caucasian, and under the age of 30 years or over 60 years. Other risk factors include Ashkenazi Jewish extraction; having a family history of the disease; Turner's syndrome; immunodeficiency disorders, such as hypogammaglobulinaemia, selective IgA deficiency, hereditary angioedema, and Hermansky-Pudlak syndrome (Friedman & Blumberg, 2008).

The main existing treatment options

UC is usually treated with dietary measures, nutritional supplements, and medicines. Surgery may be required to treat intestinal complications including bleeding, perforation, and toxic megacolon. A colectomy may be necessary to prevent or treat colon cancer.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Sweden: The highest mortality is during the first years of disease and in long-standing disease due to the risk of colon cancer. In a Swedish population study, the SMR for UC was 1.37 (Friedman & Blumberg, 2008).

UK: Mortality rates are not increased in IBD compared with the general population. Low mortality rates in patients with UC and CD, respectively, were reported in three British district general hospital practices. Five hundred fifty-two patients with IBD were evaluated. The overall SMRs was 103 (95% CI: 79-140) for UC patients (Farrokhyar et al., 2001).

In a study conducted in Wales, including 1482 UC patients hospitalised as emergencies for three or more days, mortality was 9.2% and 20.8% after 1 and 5 years follow-up (Button et al., 2010).

Italy: Long-term follow-up (median 15 years) was completed to evaluate mortality in a Mediterranean cohort (Florence IBD study). UC patients showed a significantly reduced total mortality because of lower cardiovascular (SMR 0.67 [95% CI 0.45-0.95]) and lung cancer (SMR 0.32 [95% CI 0.07-0.95]) mortality. No significant excess for colorectal cancer mortality was evident (Masala et al., 2004).

Important co-morbidities

Severe gastrointestinal haemorrhage may occur with flares of UC in 1% of patients. Toxic megacolon occurs in about 5% of attacks and can be triggered by electrolyte abnormalities or narcotics. About 50% of acute dilatations will resolve with medical therapy alone, but urgent colectomy is required for those who do not improve. Perforation is the most dangerous of the local complications. The mortality rate of perforation complicating toxic megacolon is about 15%. Strictures occur in 5-10% of patients with UC and are a concern because of the possibility of underlying neoplasia. UC patients occasionally develop anal fissures, perianal abscess, or haemorrhoids, but the occurrence of extensive perianal lesions is more often associated with CD. Patients with long-standing UC are at increased risk for developing colonic epithelial dysplasia and carcinoma. The risk of neoplasia in chronic UC increases with duration and extent of disease. The risk of cancer rises by 0.1-1.0% per year after 8-10 years of disease in patients with pancolitis. A prospective surveillance study reported a rate of cancer of 2.5% at 20 years of disease, 7.6% at 30 years, and 10.8% at 40 years (Friedman & Blumberg, 2008).

Indication – Ulcerative colitis (children) (IV only)

Incidence

Scotland: The incidence of juvenile-onset of IBD between 1981 and 1995 was investigated in a retrospective population-based study using a Scottish hospital discharge database. A total of 1,002 patients less than 19-year-old who were coded as having IBD between 1981 and 1997. During the 15-year period of 1981-1995, 227 incident cases of UC were identified, giving standardised incidences of 1.3/100,000 population per year for UC (Armitage et al., 2001). The crude prevalence rates for paediatric UC were 9.2 cases per 100,000 population.

Denmark: In a population-based cohort study conducted from 1998 to 2000 in a total of 421,898 children, and from 2002 to 2004 in a total of 439,443 children, the incidence of UC in patients <15 years of age was 1.8/100,000 during 1998 to 2000 and 2.6/100,000 during 2000 to 2004, respectively (Jakobsen et al., 2008). In a subsequent population-based study conducted by Jakobsen et al., 2011 during 2007 to 2009, in a paediatric population of 668,056 patients with <15 years of age, 62 patients were diagnosed with UC. Mean incidence rates for UC were 3.1/100,000.

USA: In a population-based retrospective study, using a community-based health-care delivery system, the average annual incidence of UC in patients aged 0 to 17 years was 3.2/100,000 (95% CI, 2.8 to 3.6) during 1996-2006. During the 11-year study period, the annual incidence per 100,000 increased from 1.8 to 4.9 ($p<0.001$). In this population, the incidence of UC increases significantly by 2.7-fold over the study period (Abramson et al., 2010).

Prevalence

The average length of enrolment during the 11-year study period (1996 to 2006) exceed 8 years resulting in a point prevalence in 2006 of 19.5/100,000 (95% CI, 16.2 to 22.6).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The peak age of onset is in late adolescence. There is a higher incidence of UC in male paediatric patients compared to females (ratio approximately 4:1) (Kelsen & Baldassano, 2008; Benchimol et al., 2011).

The UC is associated with being Caucasian, and under the age of 30 years or over 60 years. Other risk factors include Ashkenazi Jewish extraction; having a family history of the disease; Turner's syndrome; immunodeficiency disorders, such as hypogammaglobulinaemia, selective IgA deficiency, hereditary angioedema, and Hermansky-Pudlak syndrome (Friedman & Blumberg, 2008).

The main existing treatment options

UC is usually treated with dietary measures, nutritional supplements, and medicines. Surgery may be required to treat intestinal complications including bleeding, perforation, and toxic megacolon. A colectomy may be necessary to prevent or treat colon cancer.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

No mortality data available.

Important co-morbidities

Children with UC tend to have more extensive disease than adults. Children with UC are at particular risk for extraintestinal manifestations of the disease and can include growth failure, weight loss, anaemia, joint symptoms, and delayed puberty (Benchimol et al., 2011; Kelsen & Baldassano, 2008). The juvenile onset of UC is associated with an increased risk to develop colorectal cancer (Langholz et al., 1997). The duration of the disease and the presence of pancolitis are recognised risk factors for the development of malignancy, with the risk of cancer increasing over that of the general population after 10 years of disease (Kelsen & Baldassano, 2008).

Indication – psoriasis

Incidence

In an US study, average annual sex and age-adjusted (1980 US white population) incidence rate was 60.4 per 100,000. Most of the cases of psoriasis, (i.e., 58%), were mild, defined as less than 10% body surface area (Neimann et al., 2006).

Based on data from the GPRD, the overall incidence of psoriasis in the UK was 14 per 10,000 person-years.

Prevalence

Prevalence studies indicate that psoriasis is a common disease and its frequency varies based on age, ethnicity and geography. Epidemiological studies from around the world have estimated the prevalence of psoriasis to be anywhere from 0.6 to 4.8% (Neimann et al., 2006).

In Caucasian population, psoriasis is estimated to have a prevalence of 1-3% (Taurog, 2008).

In the USA, the prevalence of psoriasis was estimated to be around 4.6%, while in Canada it was 4.7%. Data for Europe show little variation which is as follows: UK, 1.6%; Norway, 1.4%; Croatia, 1.55%; Germany, 2.60%; Belgium, 2.00%; Switzerland, 0.60%; Spain, 1.80%; Italy, 1.00%; Portugal, 0.40%; France, 2.39%; total, 1.46%.

Denmark: The prevalence of psoriasis was 2.72 per 100,000 in the year 2005 in Denmark (Eaton et al., 2010).

France: In 2003, the self-reported and dermatologist-reported prevalence rates of psoriasis in adults were 4.8% and 6.4%, respectively.

Germany: In Germany, the prevalence of psoriasis in 2005 was 2.5% (Augustin et al., 2010).

Spain: The prevalence of psoriasis in Spain was estimated to be 1.17-1.4%. The highest prevalence was among 20 to 50-year-old subjects (Ferrandiz et al., 2001).

The overall prevalence of psoriasis, similar in men (1.46%) and women (1.40%), was 1.43% in the study sample consisting of more than 12,000 subjects.

UK: The overall prevalence of psoriasis in the GPRD from 1987 to 2002 was reported to be 1.5%.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The age of onset of psoriasis has a bimodal distribution, peaking in early adult life (late teens to 20s) and again in later adult life (50s and 60s). Patients with onset of psoriasis before the age of 40 years (thought to account for more than 75% of cases) tend to have more severe disease. Most studies suggest that psoriasis may be slightly more prevalent among males as compared to females, however, in young patients (<20 years) the prevalence of psoriasis is greater in females than in males (Neimann et al., 2006).

Family history is the strongest risk factor for the development of psoriasis. Certain bacterial and viral infections are also strongly associated with psoriasis, especially human immunodeficiency virus (HIV) and Streptococcal pharyngitis.

The main existing treatment options

Psoriasis treatment aims to reduce the turnover of skin cells and reduce inflammation. Treatments fall into three categories: topical therapies, systemic therapies, and phototherapy. Topical therapies are usually tried first and are most successful for milder forms of the disease.

Topical therapy includes glucocorticosteroids, anthralin, retinoids, calcineurin inhibitors, salicylic acid, coal tar, and simple moisturisers.

Phototherapy involves exposure to ultra-violet (UV) light. It is usually used in combination with psoralens (PUVA).

Systemic therapies may be administered orally or parenterally. These include retinoids, hydroxyurea, and immunosuppressants such as methotrexate, AZA, cicloporine, leflunomide, TNF-α inhibitors, and thioguanine.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Severe psoriasis is associated with an increased risk of death. In a population-based study conducted in the UK, patients with severe psoriasis showed an increased overall mortality risk (hazard ratio [HR] 1.5; 95% CI 1.3-1.7). The association between severe psoriasis with mortality persisted after adjustment for risk factors for mortality (HR 1.4; 95% CI 1.3-1.6) and after exclusion of patients with inflammatory arthropathy (HR 1.5; 95% CI 1.3-1.8) (Gelfand et al., 2007).

An association between cardiovascular mortality and severe psoriasis measured as repeated hospital admissions with a diagnosis of psoriasis was reported. The SMR among outpatients with psoriasis was 0.94 (95% CI 0.89-0.99), whereas the SMR among patients admitted at least once for psoriasis was increased by 50% (SMR 1.52, 95% CI 1.44-1.6) (Neimann et al., 2006).

Important co-morbidities

Approximately, 15-20% of psoriasis patients have extensive skin involvement or severe disease requiring systemic therapy.

Psoriasis causes significant disability in many individuals, especially women and young patients. About 80% of patients with psoriasis report that the disease has negative impact on their lives for a variety of reasons including physical symptoms, embarrassing physical appearance (particularly because it begins at <30 years of age in 60% of cases), helplessness, frustration, anger, anxiety, depression and increased use of alcohol (Friedewald et al., 2008).

The literature suggests that psoriasis is associated with multiple other diseases including cancer, diabetes mellitus, cardiovascular disease, autoimmune and psychiatric disease. It is unclear if these associations are due to the pathophysiology of psoriasis, the treatment of psoriasis or psoriasis-associated behaviours (e.g., smoking, alcohol) (Neimann et al., 2006; Friedewald et al., 2008).

A large population-based cohort study using the GPRD showed that psoriasis is associated with an increased risk of lymphoma. The association is strongest for Hodgkin's lymphoma (HL) and cutaneous T-cell lymphoma. The excess risk of lymphoma attributed to psoriasis was 7.9/100,000 psoriasis patients per year (Gelfand et al., 2006b).

Patients with psoriasis had an increased adjusted relative risk for myocardial infarction that varied by age. The risk ratio was greatest in young patients with severe psoriasis (Gelfand et al., 2006a).

Psoriasis is associated with metabolic syndrome, and its components, such as obesity, diabetes, and hypertension. Obesity is an independent risk factor for developing psoriasis. Increasing body mass index is associated with greater degrees of psoriasis severity. In a large, population-based, cross-sectional study in the UK, the increased prevalence of diabetes in patients with psoriasis was independent of traditional diabetes risk factors such as obesity and dyslipidaemia (Azfar & Gelfand, 2008).

Metabolic syndrome was 2.9-fold more frequent in psoriasis patients as compared with controls (Augustin et al., 2010).

Cardiovascular risk factors that are key components of the metabolic syndrome are more strongly associated with severe psoriasis than with mild psoriasis (Neimann et al., 2006).

Population based studies, which are broadly representative of all patients with psoriasis, have reported the prevalence of PsA in patients with psoriasis to be 6.25-30% (Kurd et al., 2007). The PsA precedes skin manifestation in 10% of cases (Friedewald et al., 2008).

Indication – psoriatic arthritis

Incidence

Europe: In a cross-sectional observational study conducted in the UK, Spain, France, Italy and Germany in 2006 (Adelphi Psoriasis Disease Specific Program), the incidence of PsA in the population of patients with psoriasis (n=2,962) remained relatively constant, largely below 1% per year during the 30 years examined (74 per 1,000 person-years).

There is a wide variation in reported annual incidence of PsA (median 6.4, range 0.1 to 23.1 cases per 100,000 inhabitants) (Alamanos et al., 2008).

Czech Republic: The total annual incidence of PsA in adults aged ≥16 years was 3.6/100, 000 (95% CI 1.4-7.6) and the prevalence of PsA was 49.1/100,000 (95% CI 39.5-60.4/100,000) (Hanova et al., 2010).

Finland: A Finnish study reported the incidence of joint inflammation in patients with psoriasis (excluding patients with seropositive peripheral polyarthritis) to be 8 per 100,000 in men and 6 per 100,000 in women.

Prevalence

Prevalence estimates for PsA varied from 1 case per 100,000 population in Japan to 420 cases per 100,000 population in Italy (Alamanos et al., 2008).

Estimates of the prevalence of PsA in the psoriatic population vary widely, from 5% to 40% (Taurog, 2008). In 60-70% of cases, psoriasis precedes joint disease. In 15-20% of cases, the two manifestations appear within one year of each other. In about 15-20% of cases, arthritis precedes the onset of psoriasis (Taurog, 2008).

Population based studies, which are broadly representative of all patients with psoriasis, have reported the prevalence of PsA in patients with psoriasis to be 6.25-30% (Kurd et al., 2007).

Czech Republic: The prevalence of PsA in adults aged ≥16 years was 49.1/100,000 (95% CI 39.5-60.4) (Hanova et al., 2010).

Germany: The prevalence of PsA among patients attending a dermatologist for plaque-type psoriasis was 20.6%.

Of 2,009 patients with psoriasis from 13 dermatological hospitals and 129 dermatological private practices and outpatient clinics in Germany, 19% had PsA (Radtke et al., 2009).

Italy: In a cross-sectional, population-based epidemiological study (the MAPPING study), the prevalence of PsA was estimated as 0.42% (Salaffi et al., 2005).

Norway: In a geographically defined population in Western Norway, the estimated prevalence of PsA was 1.95 per 1,000 adults (Madland et al., 2005).

UK: People with psoriasis were identified from the computerised morbidity indices of 2 large UK general practices. The estimated prevalence of PsA in this population was 13.8% (Ibrahim et al., 2009).

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease

The frequency of PsA in men and women is almost equal, although the frequency of disease patterns differs somewhat in the two sexes. The disease can start in childhood or late in life but typically begins in the fourth or fifth decade, at an average age of 37 years (Taurog, 2008).

Psoriasis (especially in those with ungual lesions) is the single greatest risk factor for the development of PsA. Age between 30 and 50 years and family history are also associated with a greater risk of development of PsA.

The main existing treatment options

Treatments fall into three categories – medical therapies, physical and occupational therapies for maintenance of function and management of deformity, and surgery for correction of severe joint deformity or joint replacement or tendon repair.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

In some large published series, mortality was found to be significantly increased as compared with the general population (Taurog, 2008).

Studies including patients with more severe PsA have shown a higher risk of mortality for patients with PsA compared with the expected rates in the community, and higher overall frequencies of destructive joint changes. An increased rate of myocardial infarction, pulmonary emboli, and pulmonary infarcts as a cause of death was reported in patients with PsA (Neimann et al., 2006).

Important co-morbidities

Co-morbidities in patients with PsA include nail changes, arthritis mutilans, eye involvement (uveitis), and cardiovascular disease (Neimann et al., 2006; Taurog, 2008).

Nail changes in the fingers or toes occur in 80-90% of patients with PsA, as compared with 40-46% of psoriatic patients without arthritis (Neimann et al., 2006; Taurog, 2008).

About 5% of PsA patients have arthritis mutilans, in which there can be a widespread shortening of digits (“telescoping”), sometimes coexisting with ankylosis and contractures in other digits.

Eye involvement, either conjunctivitis or uveitis, is reported in 7-33% of PsA patients (Taurog, 2008).

Cardiovascular disease: An increased rate of myocardial infarction, pulmonary emboli and pulmonary infarcts as a cause of death was reported in patients with PsA (Neimann et al., 2006).

Aortic valve insufficiency has been reported in <4% of patients, usually after long-standing disease (Taurog, 2008).

Part II: Module SII - Non-clinical part of the safety specification

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety findings (from non-clinical studies)	Relevance to human usage
CT-P13 IV	
Toxicity	
Acute or repeat-dose toxicity studies *Rat (Sprague Dawley): IV, 10 animals/sex/group+TK satellite animals Good Laboratory Practice (GLP) compliant, doses of CT-P13 and Remicade at 0, 10 and 40 mg/kg on day 1 and day 8 (Study No. 8214158). (TK immunogenicity evaluation was conducted with 9/sex for both 10 and 40 mg/kg/dose active dose groups and 3/sex for the 0 mg/kg control group)* <u>Increase in absolute reticulocyte count in males at 40 mg/kg CT-P13 or Remicade</u> The main finding related to this 2-week repeat dose study was an increase in absolute reticulocyte count. This increase was seen at the 40 mg/kg dose level of both CT-P13 and Remicade; and was restricted to male animals only. Despite being the main finding and being statistically significant (P≤0.05), the magnitude of the response to CT-P13 and Remicade exposure at 40 mg/kg was low and consequently not reported as adverse by the Study Director. The elevation of reticulocytes at 40 mg/kg in males only is not accompanied by a similar rise in other haematology parameters that might indicate a more serious toxic response to CT-P13 and Remicade exposure. Furthermore, microscopic analysis of the sternum and femur bone marrow did not uncover any remarkable findings that might also be indicative of a pronounced toxic response to both CT-P13 and Remicade. <u>Minimal Kupffer Cell hyperplasia</u> Test item-related changes were observed following microscopic analysis of the livers of some test animals. Kupffer cell hyperplasia was reported in 7/10 male and 6/10 female rats which were given 40 mg/kg CT-P13 and in 7/10 males and females who were exposed to 40 mg/kg Remicade. Kupffer cell hyperplasia was also observed in 2/10 males and females who were given 10 mg/kg CT-P13 and	These findings are considered to be of little relevance to human usage. Reticulocyte count elevation is not accompanied by significant alterations in other haematological or pathological parameters. Furthermore, this specific alteration is restricted to males at the top dose level and so is not considered adverse. Remicade has been used safely in the clinic since 1999. Since these reticulocyte findings are comparable between Remicade and CT-P13, it is reasonable to suggest that they are of little clinical relevance. Liver changes reported in this study are described as minimal and thus not adverse in nature. On the basis of the magnitude of the response, the changes are not considered adverse and are thus of no relevance to human usage. The comparative nature of the Kupffer Cell hyperplasic response between CT-P13 and Remicade is further evidence that this reported finding has little clinical relevance. Remicade has

Key Safety findings (from non-clinical studies)	Relevance to human usage
4/10 males and 3/10 females who were exposed to 10 mg/kg Remicade.	been used extensively in the clinic for many years without reported issues related to Kupffer Cell hyperplasia.
<u>Minimal lymphocyte necrosis</u> Minimally increased individual lymphocyte necrosis was present in the thymus of a few males and/or females given CT-P13 or Remicade at both 10 and 40 mg/kg. This finding was not evident in control animals. However, low incidences and minimal severity coupled with a lack of clear dose response indicate that this effect is unlikely to be treatment-related.	The relevance of this finding to humans is unclear. However, the previously highlighted low incidence and minimal severity indicate that this finding is unlikely to pose a safety concern and may very well be a result of biological variation. Extensive clinical experience with Remicade has not highlighted findings in humans including lymphocyte necrosis, and so we can safely assume that this finding has no clinical relevance now.
Rat (Sprague Dawley): IV, 10 animals/sex/group, GLP compliant, doses of CT-P13 and Remicade at 0, 10 and 50 mg/kg on day 1 and day 8 (Study No. G09197).	
<u>Transient subdued behaviour</u> Subdued behaviour was reported in all animals exposed to 50 mg/kg Remicade or CT-P13. This was a transient finding and only reported on the day of dosing. The transient nature of this finding is perhaps evidence that the response is in fact a reaction to the dosing protocol and a heavy protein load, particularly as it is not reported in either control animals or at the low 10 mg/kg dose.	Although treatment-related, subdued behaviour in animals at the top dose level is of no concern to human usage. It is important to appreciate the large doses (50 mg/kg) received by animals in the top dose group. It is possible that the high protein load animals receive at the top dose level may explain the transient subdued behaviour. As this finding is consistently reported for both CT-P13 and its marketed comparator, Remicade, and as indicated above, Remicade has a history of extensive and long–standing, safe clinical use.
<u>Decrease in food consumption</u> At the top dose of 50 mg/kg for both Remicade and CT-P13, decreases in food consumption were reported in this study. Although identified as being treatment–related, the decreases were of a low magnitude and not associated with decrease in body	Of importance in relation to this finding is the fact that the decrease in food consumption was reported for both Remicade and CT-P13. This is further evidence of the comparability of both products. As Remicade has an extensive and well-defined clinical

Key Safety findings (from non-clinical studies)	Relevance to human usage
weight. Consequently, these treatment-related changes are not viewed as adverse findings.	safety profile, it is reasonable therefore to assume that this finding has no relevance to human usage.
Reproductive/developmental toxicity Comparative reproductive studies between CT-P13 and Remicade have not been performed in line with the European Union (EU) guidance on biosimilar products (Committee for Medicinal Products for Human Use [CHMP]) 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues'(EMEA/CHMP/BMWP/42832/2005 Rev1). This guidance states that routine toxicological studies, such as reproduction and developmental toxicology, are not required.	CT-P13 (infliximab) has been developed as a similar biological medicinal product to Remicade. Consequently, the reproductive/ developmental toxicity package developed for Remicade should be considered when considering this type of toxicity.
Genotoxicity Genotoxicity studies were not conducted as they are not applicable to biotechnology-derived pharmaceuticals.	None
Carcinogenicity Carcinogenicity studies were not conducted as they are not applicable to biotechnology-derived pharmaceuticals.	None
Safety pharmacology	
Safety pharmacology studies were not performed in line with the EMEA/CHMP/BMWP 'Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues', February 2006 and draft CHMP 'Guideline on similar biological medicinal products containing monoclonal antibodies' (EMEA/CHMP/BMWP/403543/2010, 18 November 2010).	None
Drug Interactions	
On the basis of the specificity of infliximab and the extensive clinical experience with the reference product, no nonclinical studies pertinent to drug interaction were conducted.	None
Other toxicity-related information or data	

Key Safety findings (from non-clinical studies)	Relevance to human usage
Cardiotoxicity There is no evidence of cardiotoxicity in any of the repeat dose studies performed as part of the nonclinical study package. Consequently, no cardiotoxicity studies have been conducted in support of the safety profile of CT-P13.	None
Juvenile Toxicity Studies Juvenile toxicity studies were not performed in line with the EMEA/CHMP/BMWP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues, February 2006 and draft CHMP 'Guideline on similar biological medicinal products containing monoclonal antibodies' (EMEA/CHMP/BMWP/403543/2010, 18 November 2010).	None
CT-P13 SC	
Local tolerance *Rabbit (New Zealand White rabbit): SC, 10 animals/male/group Good Laboratory Practice (GLP) compliant, doses of CT-P13 SC at 0, 80.4 mg (120 mg/mL), single dose (Study No. B15613)* <u>Leukocyte infiltration</u> Mild leukocyte infiltration was evident in one animal and minimal leukocyte infiltration in another animal. Leukocyte infiltration was confirmed only in the 1st necropsy group (day 1). In the 2nd necropsy group (day 7), no abnormal signs were evident at the subcutaneous injection sites of the test substance in any animals. Since the MTS (mean tolerance score) of the test substance was '0.3', which is below '1', the degree of local tolerance was classified to be 'None' according to the Tolerance Index. Based on the result of this study, CT-P13 SC was well tolerable in New Zealand White rabbits at the actual concentration of 120 mg/mL intended for human use.	The relevance of this finding to human is not clear. However, this finding is unlikely to pose a safety concern. Because no abnormal signs were observed except minimal or mild leukocyte infiltration in two animals respectively, which was temporary sign in the CT-P13 SC group. Macroscopic examination at the injection sites was clinically insignificant and comparable between negative control (physiological saline) and CT-P13 SC treated animals.

Part II: Module SIII - Clinical trial exposure

The clinical safety of CT-P13 has been evaluated in 12 clinical studies (8 with CT-P13 IV and 4 with CT-P13 SC). The studies compared CT-P13 IV and Remicade in the following controlled studies; CT-P13 IV 1.1, CT-P13 IV 1.2 (Treatment Phase I), CT-P13 IV 3.1, CT-P13 IV 3.3 and B1P13101 and in the extension studies; CT-P13 IV 1.3, CT-P13 IV 3.2, CT-P13 IV 1.2 (Treatment Phase II) and B2P13111. One study CT-P13 IV 1.2 had further 2 treatment phases as Phase I and Phase II. The clinical safety data base consists of the information from 5 clinical trials up to 54 weeks of treatment with CT-P13 IV or the reference product Remicade, and 4 extension studies, which included CT-P13 IV 1.2 Phase II, studies up to 102 weeks-158 weeks of treatment with CT-P13 IV.

The clinical safety of CT-P13 SC has been evaluated in 4 clinical studies. Studies CT-P13 SC 3.5 and CT-P13 SC 1.6 compared multidoses of CT-P13 SC and CT-P13 IV. Studies CT-P13 SC 3.7 and CT-P13 SC 3.8 evaluated safety of CT-P13 SC over placebo SC. A total of 1265 patients received at least 1 dose of CT-P13 SC.

Safety data for CT-P13 IV and Remicade are available from 5 double-blind, active-controlled, parallel-group studies and 3 open-label controlled studies. A total of 732 patients were exposed to CT-P13 IV and 493 to Remicade (safety population): a total of 446 patients received at least one dose of CT-P13 IV in studies 1.1, 3.1, 3.3 and 1.2; a total of 235 patients received at least one dose of CT-P13 IV in the extension studies 1.3 and 3.2, and in the extension study 1.2; and a total of 51 patients received CT-P13 IV in study B1P13101 and 71 patients (33 of which were switched from Remicade in study B1P13101) received CT-P13 IV in study B2P13111.

A Japanese study (B1P13101) in RA patients and its extension study (B2P13111) were conducted by Celltrion’s business partner, Nippon Kayaku Co. Ltd. who holds proprietary rights for both studies. The safety data for these studies have not been integrated into Celltrion’s safety database. B2P13111 trial clinical study report (CSR) was finalised on 06 July 2015. A total of 72 patients were enrolled in this study. Among 72 patients who had completed 54-week administration of CT-P13 IV or Remicade in the B1P13101 and enrolled in the extension study, the efficacy and safety were assessed in 71 patients who were administered with CT-P13 IV.

The following tables summarise exposure to CT-P13 IV and CT-P13 SC for patients included in completed clinical trials and extension studies in patients with RA [studies CT-P13 IV 3.1, CT-P13 IV 3.2, CT-P13 IV 3.3, CT-P13 IV 1.2 and CT-P13 SC 3.5 (Part 1 and Part 2)], patients with AS (studies CT-P13 IV 1.1 and CT-P13 IV 1.3), and patients with CD or UC (CT-P13 SC 1.6; Part 1 CD only, Part 2 CD & UC, CT-P13 SC 3.7; UC only, and CT-P13 SC 3.8; CD only). The longest total exposure for individual patients that was planned in the IV and SC study protocols for the studies that have been included in the summary of exposure was 102 weeks.

Table 2: SIII.1: Duration of exposure

Duration of exposure for CT-P13 IV studies

Cumulative for all indications (person time)				
	CT-P13 IV		**Remicade**	
Duration of exposure (at least)	**Patients**	**Person time (days)**	**Patients**	**Person time (days)**
≥14 weeks	414	230033	412	220775
≥30 weeks	388	226595	387	217735
≥54 weeks	360	219001	341	205396
≥62 weeks	256**	179385	235*	164868
≥78 weeks	244	173727	228*	161580
≥102 weeks	231	165810	209*	150161
Total	446	230977	440	221532
Source: Studies CT-P13 3.1, CT-P13 3.2, CT-P13 3.3, CT-P13 1.2, CT-P13 1.1 and CT-P13 1.3 *After week 54, patients received CT-P13 in the extension study period from studies CT-P13 1.2 (Treatment Phase II), CT-P13 3.2 and CT-P13 1.3. These patients have not been counted as patients treated with CT-P13. ** One patient did not receive CT-P13 in the extension study period (CT-P13 3.2). So, this patient was not included in '62 weeks' dose.				
Rheumatoid Arthritis				
	CT-P13 IV 3 mg/kg		**Remicade 3 mg/kg**	
Duration of exposure	**Patients**	**Person time (days)**	**Patients**	**Person time (days)**
≥14 weeks	293	156572	293	151216
≥30 weeks	271	153687	274	148884
≥54 weeks	251	148284	237	138834
≥62 weeks	166**	115873	151*	105909
≥78 weeks	155	110708	147*	103998
≥102 weeks	147	105709	133*	95603
Total	318	157308	318	151901
Source: Studies CT-P13 3.1, CT-P13 3.2, CT-P13 3.3 and CT-P13 1.2 * After week 54, patients received CT-P13 in the extension study period from studies CT-P13 1.2 (Treatment Phase II) and CT-P13 3.2. ** One patient did not receive CT-P13 in the extension study period (CT-P13 3.2). So, this patient was not included in '62 weeks' dose.				
Ankylosing Spondylitis				
	CT-P13 IV 5 mg/kg		**Remicade 5 mg/kg**	
Duration of exposure (at least)	**Patients**	**Person time (days)**	**Patients**	**Person time (days)**
≥14 weeks	121	73461	119	69559
≥30 weeks	117	72908	113	68851
≥54 weeks	109	70717	104	66562
≥62 weeks	90	63512	84*	58959

≥78 weeks	89	63019	81*	57582
≥102 weeks	84	60101	76*	54558
Total	128	73669	122	69631

Source: Studies CT-P13 1.1 and CT-P13 1.3

*After week 54, patients received CT-P13 in the extension study period from study CT-P13 1.3. These patients have not been counted as patients treated with CT-P13.

Duration of exposure for CT-P13 SC studies

Cumulative for all indications

	CT-P13 IV		CT-P13 SC	
Duration of exposure	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
≥ 14 weeks	247	32759	1195	502470
≥ 30 weeks	23	7525	1010	472571
≥ 54 weeks	0	0	580	341160
≥ 62 weeks	0	0	483	301659
≥ 78 weeks	0	0	445	282774
≥ 102 weeks	0	0	3	2180
Total	267	33713	1265	505125

Protocol Number: CT-P13 1.6 (Part 1 and Part 2), CT-P13 3.5 (Part 1 and Part 2), CT-P13 3.7 and CT-P13 3.8

Note: Only exposures on randomization at Week 6 (CT-P13 1.6 and 3.5) or Week 10 (CT-P13 3.7 and 3.8) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6 and 3.5) or Week 10 (CT-P13 3.7 and 3.8) with exceptions as follows;

- For CT-P13 1.6 Part 2 and 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

Person time (days) = (date of the last exposure - date of the first exposure +1), Duration of exposure (weeks) = (person time in days)/7.

Rheumatoid Arthritis

	CT-P13 IV		CT-P13 SC	
Duration of exposure	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
≥ 14 weeks	179	22974	347	100485
≥ 30 weeks	13	4288	269	87583
≥ 54 weeks	0	0	83	33791
Total	189	23478	363	101025

Protocol Number: CT-P13 3.5 (Part 1 and Part 2)

Note: Only exposures on randomization at Week 6 (CT-P13 3.5) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 3.5) with exceptions as follows; For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.

Person time (days) = (date of the last exposure - date of the first exposure +1), Duration of exposure (weeks) = (person time in days)/7.

Crohn's Disease

	CT-P13 IV		CT-P13 SC	
Duration of exposure	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
≥ 14 weeks	32	5720	383	183187
≥ 30 weeks	10	3237	342	176527
≥ 54 weeks	0	0	222	138167
≥ 62 weeks	0	0	217	136146
≥ 78 weeks	0	0	204	129752
≥ 102 weeks	0	0	2	1449
Total	38	5998	404	184045

Protocol Number: CT-P13 1.6 (Part 1 and Part 2) and CT-P13 3.8

Note: Only exposures on randomization at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.8) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6) or Week 10 for CT-P13 3.8) with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

Person time (days) = (date of the last exposure - date of the first exposure +1), Duration of exposure (weeks) = (person time in days)/7.

Ulcerative Colitis

	CT-P13 IV		CT-P13 SC	
Duration of exposure	**Patients (n)**	**Person time (days)**	**Patients (n)**	**Person time (days)**
≥ 14 weeks	36	4065	465	218798
≥ 30 weeks	0	0	399	208461
≥ 54 weeks	0	0	275	169202
≥ 62 weeks	0	0	266	165513
≥ 78 weeks	0	0	241	153022
≥ 102 weeks	0	0	1	731
Total	40	4237	498	220055

Protocol Number: CT-P13 1.6 (Part 2) and CT-P13 3.7

Note: Only exposures on randomization at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.7) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.7) with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.7, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

Person time (days) = (date of the last exposure - date of the first exposure +1), Duration of exposure (weeks) = (person time in days)/7.

Table 3: SIII.2: Age group and gender (totals)

Age group and gender (totals) for CT-P13 IV studies

Total population: All Indications								
	CT-P13 IV				**Remicade**			
	Person (n)		**Person time (days)**		**Person (n)**		**Person time (days)**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	112	150	62125	80553	111	158	64216	77689
51 to 64	43	114	21435	56464	34	115	16807	54240
65 to 74	6	19	3665	6520	4	18	1123	7457
≥75	0	2	0	215	0	0	0	0
Total	161	285	87225	143752	149	291	82146	139386
Source: Studies CT-P13 3.1, 3.2, 3.3, 1.2, 1.1, and 1.3								
Rheumatoid Arthritis								
	CT-P13 IV 3 mg/kg				**Remicade 3 mg/kg**			
	Person (n)		**Person time (days)**		**Person (n)**		**Person time (days)**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	28	132	14110	68743	28	140	14660	68434
51 to 64	27	106	12599	52883	19	111	8600	52278
65 to 74	4	19	2238	6520	2	18	472	7457
≥75	0	2	0	215	0	0	0	0
Total	59	259	28947	128361	49	269	23732	128169
Source: Studies CT-P13 3.1, 3.2, 3.3, and 1.2								
Ankylosing Spondylitis								
	CT-P13 IV 5 mg/kg				**Remicade 5 mg/kg**			
	Person (n)		**Person time (days)**		**Person (n)**		**Person time (days)**	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	84	18	48015	11810	83	18	49556	9255
51 to 64	16	8	8836	3581	15	4	8207	1962
65 to 74	2	0	1427	0	2	0	651	0
≥75	0	0	0	0	0	0	0	0
Total	102	26	58278	15391	100	22	58414	11217
Source: Studies CT-P13 1.1 and 1.3								

Age group and gender (totals) for CT-P13 SC studies

Total population: All Indications

	CT-P13 IV				CT-P13 SC			
	Patients (n)		Person time (days)		Patients (n)		Person time (days)	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	44	103	5651	14142	464	437	209349	171760
51 to 64	23	62	2469	7502	105	180	39543	60947
65 to 74	11	24	1249	2700	26	51	7613	14732
≥ 75	0	0	0	0	1	1	536	645
Total	78	189	9369	24344	596	669	257041	248084

Protocol Number: CT-P13 1.6 (Part 1 and Part 2), CT-P13 3.5 (Part 1 and Part 2), CT-P13 3.7 and CT-P13 3.8

Note: Only exposures on randomization at Week 6 (CT-P13 1.6 and 3.5) or Week 10 (CT-P13 3.7 and 3.8) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6 and 3.5) or Week 10 (CT-P13 3.7 and 3.8) with exceptions as follows;

- For CT-P13 1.6 Part 2 and 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Rheumatoid Arthritis

	CT-P13 IV				CT-P13 SC			
	Patients (n)		Person time (days)		Patients (n)		Person time (days)	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	13	73	1750	9907	28	133	7804	36649
51 to 64	18	56	1963	6477	38	114	10865	32015
65 to 74	8	21	911	2470	13	37	3308	10384
Total	39	150	4624	18854	79	284	21977	79048

Protocol Number: CT-P13 3.5 (Part 1 and Part 2)

Note: Only exposures on randomization at Week 6 (CT-P13 3.5) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 3.5) with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Crohn's Disease

	CT-P13 IV				CT-P13 SC			
	Patients (n)		Person time (days)		Patients (n)		Person time (days)	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	14	18	2039	2934	212	133	100212	59169
51 to 64	1	5	115	910	21	27	8434	11736
65 to 74	0	0	0	0	4	6	1116	2733
≥ 75	0	0	0	0	0	1	0	645
Total	15	23	2154	3844	237	167	109762	74283

Protocol Number: CT-P13 1.6 (Part 1 and Part 2) and CT-P13 3.8

Note: Only exposures on randomization at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.8) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.8) with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Ulcerative Colitis

	CT-P13 IV				CT-P13 SC			
	Patients (n)		Person time (days)		Patients (n)		Person time (days)	
Age group	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
18 to 50	17	12	1862	1301	224	171	101333	75942
51 to 64	4	1	391	115	46	39	20244	17196
65 to 74	3	3	338	230	9	8	3189	1615
≥ 75	0	0	0	0	1	0	536	0
Total	24	16	2591	1646	280	218	125302	94753

Protocol Number: CT-P13 1.6 (Part 2) and CT-P13 3.7

Note: Only exposures on randomization at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.7) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.7) with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.7, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Table 4: SIII.3: Ethnic origin

Ethnic origin for CT-P13 IV studies

Total population: All Indications				
	CT-P13 IV		**Remicade**	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	324	170195	319	159715
Black	2	920	1	582
Asian	60	30956	58	28523
Other	60	28906	62	32712
Total	446	230977	440	221532
Source: Studies CT-P13 3.1, 3.2, 3.3, 1.2, 1.1, and 1.3				
Rheumatoid Arthritis				
	CT-P13 IV 3 mg/kg		**Remicade 3 mg/kg**	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	226	112648	228	108378
Black	2	920	1	582
Asian	44	22642	45	20323
Other	46	21098	44	22618
Total	318	157308	318	151901
Source: Studies CT-P13 3.1, 3.2, 3.3, and 1.2				
Ankylosing Spondylitis				
	CT-P13 IV 5 mg/kg		**Remicade 5 mg/kg**	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	98	57547	91	51337
Black	0	0	0	0
Asian	16	8314	13	8200
Other	14	7808	18	10094
Total	128	73669	122	69631
Source: Studies CT-P13 1.1 and 1.3				

Ethnic origin for CT-P13 SC studies

Total population: All Indications				
	CT-P13 IV		**CT-P13 SC**	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	235	30120	1160	468367
Black	0	0	1	645
Asian	8	964	32	12163
Other	24	2629	72	23950
Total	267	33713	1265	505125

Protocol Number: CT-P13 1.6 (Part 1 and Part 2), CT-P13 3.5 (Part 1 and Part 2), CT-P13 3.7 and CT-P13 3.8

Note: Only exposures on randomization at Week 6 (CT-P13 1.6 and 3.5) or Week 10 (CT-P13 3.7 and 3.8) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6 and 3.5) or Week 10 (CT-P13 3.7 and 3.8) with exceptions as follows;

- For CT-P13 1.6 Part 2 and 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

American Indian or Alaska Native patients in CT-P13 3.7 and 3.8 were categorized within the 'other' ethnic origin subgroup.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Rheumatoid Arthritis				
	CT-P13 IV		**CT-P13 SC**	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	164	20736	314	89408
Asian	2	228	5	1222
Other	23	2514	44	10395
Total	189	23478	363	101025

Source: Study CT-P13 3.5 (Part 1 and Part 2)

Note: Only exposures on randomization at Week 6 (CT-P13 3.5) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 3.5) with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Crohn's Disease

	CT-P13 IV		CT-P13 SC	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	32	5260	360	164397
Black	0	0	1	645
Asian	5	623	26	10773
Other	1	115	17	8230
Total	38	5998	404	184045

Source: Study CT-P13 1.6 (Part 1 and Part 2) and CT-P13 3.8

Note: Only exposures on randomization at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.8) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.8) with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

American Indian or Alaska Native patients in CT-P13 3.8 were categorized within the 'other' ethnic origin subgroup.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Ulcerative Colitis

	CT-P13 IV		CT-P13 SC	
Ethnic Origin	**Persons (n)**	**Person time (days)**	**Persons (n)**	**Person time (days)**
White	39	4124	486	214562
Asian	1	113	1	168
Other	0	0	11	5325
Total	40	4237	498	220055

Source: Study CT-P13 1.6 (Part 2) and CT-P13 3.7

Note: Only exposures on randomization at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.7) after the IV induction were considered.

Treatment groups were categorized based on the treatment they were randomized to at Week 6 (CT-P13 1.6) or Week 10 (CT-P13 3.7) with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The exposures before switching were included in IV treatment group and the exposures on or after switching were included in SC treatment group separately.
- For CT-P13 3.7, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only exposures on or after having CT-P13 SC were included in SC treatment group.

American Indian or Alaska Native patients in CT-P13 3.7 were categorized within the 'other' ethnic origin subgroup.

Person time (days) = (date of the last exposure - date of the first exposure +1)

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Hypersensitivity to infliximab, excipients, or murine proteins

Reason for exclusion: Patients with a history of hypersensitivity to infliximab or its excipients or murine proteins were excluded from the clinical development programme for safety reasons. Patients with a known hypersensitivity would be at a higher risk of subsequent serious systemic hypersensitivity reactions with re-exposure.

Is it considered to be included as missing information?: No

Rationale: Similar to all medicinal products, patients with a known hypersensitivity to the active substance (infliximab) or to any of the excipients or to other murine proteins are contraindicated and therefore it is unlikely that Remsima IV/SC and Inflectra IV will be used in this population (Remsima IV/SC and Inflectra IV Summary of Product Characteristics [SmPC]).

Tuberculosis or other serious infections

Reason for exclusion: Anti-TNF-α agents have been associated with an increased risk of serious infection including tuberculosis (TB), bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections (OIs); these infections are considered a class effect of anti-TNF-α agents. Risk of development of TB or other serious infections during the study would be increased leading to increased risk of dropout from the study, therefore patients with TB or other serious infections were excluded from the clinical development programme.

Is it considered to be included as missing information?: No

Rationale: The available evidence from the use of infliximab is already sufficient to contraindicate its use in the patients with TB or other serious infections. This advice is included in section 4.3 ‘Contraindications’ in the Remsima IV/SC and Inflectra IV SmPC. The risk has been included in the RMP as an important identified risk.

Moderate to severe heart failure

Reason for exclusion: This was an ethical and precautionary position applied to clinical trial subjects when the drug was not widely used in humans. Also, CHF is considered a class effect for anti-TNF-α agents. Therefore, patients with moderate to severe heart failure were excluded from the clinical development programme.

Is it considered to be included as missing information?: No

Rationale: The available evidence from the use of infliximab is already sufficient to contraindicate its use in the patients with moderate to severe heart failure. This advice is included in section 4.3 ‘Contraindications’ in the Remsima IV/SC and Inflectra IV SmPC.

Previous administration of a biological agent

Reason for exclusion: To reduce the risk of adverse events, the previous use of biological agents was prohibited or required a washout period as it may complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: Clinical experience from post-authorisation exposure and exposure to the reference product indicates that infliximab may be administered safely to subjects previously exposed to biologicals, with appropriate monitoring.

Recent exposure to persons with active TB, or a positive/indeterminate result to the screening test for latent TB

Reason for exclusion: Risk of development of TB during the study would be increased leading to increased risk of dropout from the study.

Is it considered to be included as missing information?: No

Rationale: The available evidence from the use of infliximab is already sufficient to contraindicate its use in the patients with TB or other serious infections. This advice is included in section 4.3 'Contraindications' in the Remsima IV/SC and Inflectra IV SmPC.

Presence of an infection or recurrent infections

Reason for exclusion: Risk of worsening infection during the study would be increased leading to increased risk of dropout from the study.

Is it considered to be included as missing information?: No

Rationale: Adding an immunosuppressing agent to an infectious process can potentially lead to worsening infection. There is sufficient evidence from clinical trials that the risk of infection may be increased with the treatment of TNF inhibitors.

Current or past history of drug or alcohol abuse

Reason for exclusion: Risk of non-compliance with requirements of the study. These subjects may not have been able to comply with the requirements of a clinical trial and were not appropriate for enrolment.

Is it considered to be included as missing information?: No

Rationale: No signal of an increased risk in these patients has been observed with Remsima IV/SC and Inflectra IV or the reference product.

Obesity, bone marrow hypoplasia, unstable diabetes mellitus, uncontrolled hypertension, other inflammatory or rheumatic diseases, history of any malignancy, history of lymphoma or lymphoproliferative disease, organ transplantation, severe physical incapacitation, demyelinating disorders, including multiple sclerosis and Guillain-Barré syndrome, any conditions significantly affecting the nervous system, chronic obstructive pulmonary disease, any other serious acute or chronic medical or psychiatric condition

Reason for exclusion: Risk of hospitalisation during the study may increase, which may lead to dropout from the study. This would impact the study analysis, as the medicinal product may not be the reason for the dropout.

Is it considered to be included as missing information?: No

Rationale: These exclusions were based on a known increased risk of occurrence with TNF inhibitors or were simply excluded because of the risk of premature discontinuation, and the effect this would have had on the integrity of the study.

Corticosteroids, except oral glucocorticoids, of maximum equivalent daily dose of 10 mg of prednisolone

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with study efficacy endpoints and therefore no associated safety issues are expected.

Disease-modifying anti-rheumatic drugs (DMARDS), other than methotrexate

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Alkylating agents

Reason for exclusion: May increase the risk of development of cardiac failure during the study.

Is it considered to be included as missing information?: No

Rationale: This was done as a precaution to maintain the integrity of the studies by minimising the potential risk of premature discontinuation. It is not considered an important risk in itself but the risk of cardiac failure is already considered as the important identified risk.

Live or live-attenuated vaccine

Reason for exclusion: Live vaccines should not be administered during treatment with TNF-inhibitors because of the risk of infection with live vaccine.

Is it considered to be included as missing information?: No

Rationale: There is sufficient evidence that immunosuppression due to inhibition of TNF may increase the risk of complications associated with live vaccines.

Participation in a study with an investigational drug

Reason for exclusion: May complicate the interpretation of safety and efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: This consideration would not be expected to apply to use of the commercial product.

Pregnant or breast-feeding, or were planning to become pregnant or breast-feed

Reason for exclusion: Infliximab is not recommended during pregnancy and breast-feeding.

Is it considered to be included as missing information?: No

Rationale: ‘Pregnancy exposure’ is no longer considered as important potential risk following the reference product.

Patients with total ankylosis of the spine

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Current or past history of chronic infection with hepatitis C or human immunodeficiency virus (HIV)-1 or -2 or current infection with hepatitis B (SC only)

Reason for exclusion: Anti-TNF α agents have been associated with an increased risk of serious infection including tuberculosis (TB), bacterial infections, including sepsis and pneumonia, invasive fungal, viral, and other opportunistic infections (OIs); these infections are considered a class effect of anti-TNF α agents. Risk of development of serious infections during the study would be increased leading to increased risk of dropout from the study, therefore patients with hepatitis C or HIV-1 or -2 were excluded from the clinical development programme.

Is it considered to be included as missing information?: No

Rationale: Adding immunosuppressive drugs such as infliximab in patients with infectious diseases can potentially lead to worsening of the infection. There is sufficient evidence from clinical trials that the risk of infection may be increased with the treatment of TNF inhibitors.

Antibiotics for the treatment of Crohn's disease or ulcerative colitis (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Use of thalidomide, tacrolimus, or ciclosporin within 3 months prior to the first administration of the study drug (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Abdominal surgery, including but not limited to, for active gastrointestinal bleeding, peritonitis, intestinal obstruction, gastrointestinal resection or intra-abdominal or pancreatic abscess requiring surgical drainage within 6 months prior to the first administration of the study drug (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Any surgical procedure, including bone or joint surgery or synovectomy (including joint fusion or replacement) within 12 weeks prior to the first administration of the study drug or planned within 6 months after the first administration of the study drug (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Subtotal and total colectomy prior to the first administration of the study drug (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

Use of parenteral nutrition within a month prior to the first administration of the study drug (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab a

Use of exclusive enteral nutrition for more than 3 consecutive days within a month or any single day of exclusive enteral nutrition within 2 weeks prior to the first administration of the study drug (SC only)

Reason for exclusion: May complicate the interpretation of efficacy endpoints.

Is it considered to be included as missing information?: No

Rationale: It was excluded to prevent interference with efficacy study endpoints. It has no impact on the safety of infliximab.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

Seven hundred and thirty-two (732) subjects were exposed to CT-P13 IV and 1265 subjects were exposed to CT-P13 SC during the clinical development programme. ADRs with a true frequency lower than approximately 1 in 250 would not be expected to be quantifiable with a data set of this size even if they may be observed. Subjects have been treated with CT-P13 IV for a maximum of 158 weeks and CT-P13 SC for a maximum of 102 weeks in the clinical development programme. Adverse reactions which require more than 158 weeks to manifest after the first dose are unlikely to be detected in the clinical trials conducted.

Adverse reactions due to cumulative effects are unlikely as the animal and human pharmacokinetics (PK) data suggest that accumulation of infliximab is unlikely. The PK of infliximab has been shown to be similar to that of the reference product.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 5: SIV.1: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Pregnant women were not included in the clinical development programme. The SmPC indicates that the available clinical experience is too limited to exclude a risk, and administration of infliximab is therefore not recommended during pregnancy. It also indicates that women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for 6 months after the last CT-P13 treatment. Infliximab crosses the placenta and has been detected in the serum of infants up to 12 months following birth. After *in utero* exposure to infliximab, infants may be at increased risk of serious disseminated infection. Fatal outcome due to disseminated Bacillus Calmette–Guérin (BCG) (vaccine) infection has been reported following administration of the BCG vaccine in infants exposed *in utero* to Remicade. Cases of agranulocytosis in infants exposed *in utero* have also been reported with Remicade. The SmPC indicates that administration of live vaccines (e.g. BCG, rota virus, and oral polio virus vaccines) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth. If infant infliximab serum levels are undetectable or infliximab administration was limited to the first trimester of pregnancy, administration of a live vaccine might be considered at an earlier timepoint if there is a clear clinical benefit for the individual infant. BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab is considered an important identified risk (Remicade RMP) (Remicade SmPC).
Breast-feeding women	Breast-feeding women were not included in the clinical development programme. Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding. The SmPC indicates that women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for 6 months after the last CT-P13 treatment, because human Igs are excreted in milk.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with hepatic impairment were not included in the clinical development programme.
• Patients with renal impairment	Patients with renal impairment were not included in the clinical development programme.

Type of special population	Exposure
• Patients with cardiovascular impairment	Patients with cardiovascular impairment such as NYHA class III or IV heart failure, uncontrolled hypertension, severe cardiac disease were not included in the clinical development programme.
• Immuno-compromised patients	Immunocompromised patients were not included in the clinical development programme.
• Patients with a disease severity different from the inclusion criteria in the clinical trial population	In accordance with the indications authorised for the reference product Remicade, the efficacy and safety of CT-P13 in male or female patients, who had been diagnosed with RA according to the revised 1987 ACR classification criteria (Arnett et al., 1988) for at least 1 year prior to screening have been evaluated in the clinical studies CT-P13 1.2 and 3.1. Active disease was defined by the presence of 6 or more swollen joints, 6 or more tender joints, and at least 2 of the following: morning stiffness lasting at least 45 min, an erythrocyte sedimentation rate greater than 28 mm/h, and a serum C-reactive protein (CRP) concentration greater than 2.0 mg/dL. Patients with early RA or milder symptoms were not included in the clinical development programme. The reference product Remicade is authorised for the treatment of severe, active AS, in adult patients who have responded inadequately to conventional therapy. Accordingly, patients with AS according to the 1984 modified New York classification criteria (van der Linden et al., 1984) for at least 3 months prior to the screening were included in the clinical study CT-P13 1.1. The patients had to have active disease as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 (range 0 to 10) at screening in spite of following conventional treatment for AS for at least 3 months prior to the screening, and a visual analogue scale score for spinal pain of ≥4 (range 0 to 10).
Population with relevant different ethnic origin	Table 4 shows the numbers of patients treated with CT-P13 in the clinical trial development programme studies by ethnicity (studies CT-P13 3.1, CT-P13 3.2, CT-P13 3.3, CT-P13 1.2, CT-P13 1.1, CT-P13 1.3, CT-P13 1.6, CT-P13 3.5, CT-P13 3.7, and CT-P13 3.8). Of a total of 1711 patients (446 patients received at least one dose of CT-P13 IV in CT-P13 IV studies and 1265 patients received at least one dose of CT-P13 SC in CT-P13 SC studies), the majority of patients treated were white 1484 (87%); 92 patients were of Asian (5%). Only 3 black patients were treated (<1%).
Subpopulations carrying relevant genetic polymorphisms	Patients with genetic polymorphism were not included in the clinical development programme. Matsukura et al., 2008 investigated whether genetic polymorphisms of tumour necrosis factor receptor superfamily 1A and 1B affect the response to infliximab in the Japanese population. The results of the study suggest that tumour necrosis factor receptor genotypes may be involved in the different responses to infliximab in Japanese patients with CD. Several meta-analyses have been conducted to evaluate the association of TNF-α 308 G/A polymorphism and responsiveness to TNF-α blockade therapy. While O'Rielly et al., 2009 found some evidence indicating that the 308(A) variant

Type of special population	Exposure
	predicts poor response to TNF-α inhibitors, the meta-analysis performed by Pavy et al., 2010 could not determine the TNF-α 308 polymorphism as a predictor of clinical response. An association between the FcγRIIIA-158F/F polymorphic form (also known as FcγRIIIA 176F/F [van Sorge et al., 2003; Tomita et al., 2010]) and enhanced clinical response to TNF inhibitors, including infliximab, in arthritis patients has been reported by Tutuncu et al., 2005 (35 patients with RA or PsA treated with infliximab, etanercept, or adalimumab) and Canete et al., 2009 (91 patients with RA treated with infliximab). However, this association has not been confirmed in the larger clinical studies of Kastbom et al., 2007 (282 patients with RA treated with infliximab or etanercept), Criswell et al., 2004 (457 patients with RA, 301 of whom treated with etanercept), Miceli-Richard et al., 2006 (289 patients with RA treated with adalimumab), and Rooryck et al., 2008 (78 patients with RA treated with infliximab). Considering currently available data, there is no robust evidence for an association between FcγRIIIA polymorphism and a better clinical response to TNF inhibitors in RA patients. Tomita et al., 2010 evaluated the association between TNF-α and Fcγ receptor polymorphisms with infliximab treatment of CD. TNF-α and Fcγ receptor polymorphisms were determined by the Polymerase chain reaction (PCR) based restriction fragment length polymorphism method in 41 CD patients. Patients were given infliximab 5 mg/kg IV and were followed prospectively for 8 weeks. The distribution of TNF-α, FcγRIIA, and FcγRIIIA genotypes were not significantly different between responders and non-responders 8 weeks after the treatment. The distribution of FcγRIIIB genotypes significantly differed between responders and non-responders after 8 weeks ($P<0.05$). The study showed that FcγRIIIB polymorphisms may be an important factor for clinical response to infliximab treatment in CD. No significant association between clinical response to infliximab and FcγRIIIA polymorphism has been observed in the studies of Louis and Papamichael (Louis et al., 2004; Louis et al., 2006; Papamichael et al., 2011) in patients with CD. A trend towards a better clinical response in FcγRIIIA-158V/V patients versus 158V/F and 158F/F patients has been observed by Louis et al., 2004 in a subgroup of CD patients with elevated baseline CRP, but the difference was not statistically significant. It appears that FcγRIIIA polymorphism influences the CRP response to infliximab in CD patients. FcγRIIIA-158V/V homozygotes have a better CRP response (decrease) to infliximab, as compared to 158F/F patients. The differences in CRP response between patients carrying different FcγRIIIA polymorphic forms was statistically significant in one study (Louis et al., 2004), and showed a non-significant trend in two other studies (Louis et al., 2006; Papamichael et al., 2011). Currently available data suggest a possible association between the FcγRIIIA-158V/V polymorphic form and a CRP response (decrease) to infliximab in patients with CD; however, further studies would be necessary to confirm this association, and to assess its clinical relevance. Okuyama et al., 2011 prospectively examined the possible factors including Fcγ receptor polymorphism associated with the development of infusion reactions in

Type of special population	Exposure
	patients with RA receiving infliximab. Ninety-six patients received infliximab at a dose of 3 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter. Genetic polymorphisms for Fcγ receptor were examined in FCGR3A 176F/V and FCGR3B NA1/2 alleles by allele specific PCR analysis. FCGR3B NA1/NA1 genotype, use of glucocorticoids and the presence of anti-infliximab antibody accounted for nearly all patients with RA who developed infusion reactions.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

The estimate of the cumulative patient exposure since launch was calculated based on the sales volumes of active ingredient in milligram and the defined daily dose (DDD) provided by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo. Sales data include data from Celltrion and data from Celltrion's business partners. The postmarketing exposure for Remsima IV/SC and Inflectra IV have been updated from first lauch date to 31 December 2022.

The DDD for infliximab for IV and SC use is 3.75 mg.

Patient exposure (patient-days)=Number of dosage forms sold x dosage form strength in mg/DDD in mg

Patient exposure (patient-years)=Patient exposure (patient-days)/ 365.25

SV.1.2 Exposure

Table 6: SV.1: Non-study post-authorisation exposure – cumulative exposure from first launch date to 31 December 2022 for Remsima IV Exposure

Region	Sales of finished product (mg)*	Patient-days	Patient-years
[redacted]			

Region	Sales of finished product (mg)*	Patient-days	Patient-years
[redacted]			

Region	Sales of finished product (mg)*	Patient-days	Patient-years
[redacted]			
Remsima IV Total	[redacted]	914,035,587	2,502,493

*The number represents the total number of vials shipped out from storage.

[redacted]

Note: Rounding errors may be introduced in the total figure.

Table 7: SV.1: Non-study post-authorisation exposure – cumulative exposure from first launch date to 31 December 2022 for Inflectra IV Exposure

Region	Sales of finished product (mg)	Patient-days	Patient-years
[redacted]			

Region	Sales of finished product (mg)	Patient-days	Patient-years
[redacted]			
Inflectra IV Total	[redacted]	440,774,901	1,206,779

Table 8: SV.1: Non-study post-authorisation exposure – cumulative exposure from first launch date to 31 December 2022 for Remsima SC Exposure

Region	Sales of finished product (mg)*	Patient-days	Patient-years
[redacted]			

*The number represents the total number of vials shipped out from storage.
Note: Rounding errors may be introduced in the total figure.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Abuse is unlikely since Remsima/Inflectra IV is administered by IV infusion by healthcare professionals (HCPs) and has no psycho-stimulating effects. Based on the mechanism of action, there is no reason to expect potential abuse or dependence. There have been no reports of misuse of infliximab in the clinical development programme and there is no evidence of potential for abuse or misuse of infliximab for illegal purposes.

The potential for misuse of Remsima SC for illegal purposes is not considered to be a significant risk. Infliximab does not produce positive psychoactive effects, such as sedation, euphoria, perceptual and other cognitive distortions, hallucinations, and mood changes. No cases of psychic or physical dependence, leading to the disorder of addiction have been reported in the scientific literature.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

This RMP section should contain the initial identification of safety concerns and is expected to be populated with the initial submission of an RMP. As this application does not involve a new marketing authorisation and this is not the first RMP to be submitted for this product this section is not applicable.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Following the addition of the newly proposed IV liquid formulation which contains sorbitol (EMEA/H/C/002576/X/0149), PRAC requested to add the risk of serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only) as the important potential risk. Further details on the safety concerns should be provided in section SVII.3.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important identified risk: Serious infections including sepsis

Potential mechanisms:

Immunosuppression

Evidence source(s) and strength of evidence:

A USA incidence cohort showed that RA patients were at risk of developing infections as compared with non-RA patients. The hazard ratios for objectively confirmed infections, infections requiring hospitalisation and any documented infection in patients with RA were 1.70 (95% CI 1.42-2.03), 1.83 (95% CI 1.52-2.21), and 1.45 (95% CI 1.29-1.64), respectively, after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus (Doran et al., 2002). Since RA patients are treated with immunosuppressive drugs, it is not clear whether this is related to the underlying disease or the treatment. Before the methotrexate and anti-TNF era, studies showed a general increase in mortality due to infection in RA patients (Gabriel & Michaud, 2009). RA appears to increase the risk for bacterial, tubercular, fungal, opportunistic, and viral infections, with all infections being more common in more active and severe RA. TNF acts to regulate and enhance appropriate inflammatory, innate and adaptive immune responses to pathogenic organisms, and hence inhibition of TNF by Remsima IV/SC and Inflectra IV may suppress these beneficial activities of TNF and increase the potential for serious infections. Sepsis constitutes a systemic

response to infection which is characterised by both a pro-inflammatory response mediated by cytokines such as TNF and interleukin (IL) and an anti-inflammatory indicated by the expression of IL-10 and transforming growth factor (TGF)-beta.

Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP, and hence the strength of the evidence is good.

Characterisation of the risk:

Frequency

CT-P13 IV Clinical studies:

Important Identified Risk – Serious infections including sepsis **Indication – Rheumatoid arthritis**				
	Studies 1.2+1.2Ext+3.1+3.2+3.3 (N=636)			
Treatment	**CT-P13 IV only (N=318)**	**Switched from Remicade (N=151)**	**Total (N=469)**	**Remicade (N=318)**
N (%) Patients with TEAEs [1]	18 (5.7%)	4 (2.6%)	22 (4.7%)	7 (2.2%)
Total N of TEAEs	21	4	25	8
Number of Patients with TEAEs per 100 PY	3.780	3.058	3.624	2.103
95% CI for Number of Patients with TEAEs per 100PY	(2.240, 5.974)	(0.833, 7.831)	(2.271, 5.487)	(0.845, 4.332)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrence.

Note: Only TEAEs are included. Durations (years) are calculated as [date of last visit – date of first administration+1]/365.25. PY = Patient Years.

Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 15.1

Important Identified Risk – Serious infections including sepsis **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) **(N=250)**			
Treatment	**CT-P13 IV only** **(N=128)**	**Switched from Remicade** **(N=84)**	**Total** **(N=212)**	**Remicade** **(N=122)**
N (%) Patients with TEAEs [1]	4 (3.1%)	1 (1.2%)	5 (2.4%)	3 (2.5%)
Total N of TEAEs	4	1	5	4
Number of Patients with TEAEs per 100 PY	1.806	1.356	1.694	2.208
95% CI for Number of Patients with TEAEs per 100PY	(0.492, 4.625)	(0.034, 7.554)	(0.550, 3.953)	(0.455, 6.453)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrence.

Note: Only TEAEs are included. Durations (years) are calculated as [date of last visit – date of first administration+1]/365.25. PY = Patient Years.

MedDRA dictionary, version 15.1

CT-P13 SC Clinical studies:

Important Identified Risk – Serious infections including sepsis **Indication – Rheumatoid arthritis**			
	Study CT-P13 3.5 (Part 1+Part 2) **(N=391)**		
Treatment	**CT-P13 IV** **(N=188)**	**CT-P13 SC** **(N=363)**	**Total** **(N=391)**
N (%) Patients with TEAEs[1]	2 (1.1%)	5 (1.4%)	7 (1.8%)
Total N of TEAEs	2	5	7
Number of Patients with TEAEs per 100 PY	2.148	1.673	1.786
95% CI for Number of Patients with TEAEs per 100PY	(0.260, 7.758)	(0.543, 3.904)	(0.718, 3.680)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

Note: Only TEAEs occurred from maintenance phase are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

Durations (years) are calculated as [date of last visit (or the day before switching from IV to SC) - date of first administration of each treatment in maintenance phase +1]/365.25. PY = Patient Years.

Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 20.0 for Study 3.5 (Part 1 and Part 2)

Important Identified Risk – Serious infections including sepsis **Indication – Crohn's Disease and Ulcerative Colitis**			
	Study CT-P13 1.6 (Part 1+Part 2), 3.7 and 3.8 (N=924)		
Treatment	**CT-P13 IV (N=78)**	**CT-P13 SC (N=902)**	**Total (N=924)**
N (%) Patients with TEAEs[1]	2 (2.6%)	30 (3.3%)	32 (3.5%)
Total N of TEAEs	2	35	37
Number of Patients with TEAEs per 100 PY	5.115	2.532	2.614
95% CI for Number of Patients with TEAEs per 100PY	(0.619, 18.477)	(1.708, 3.614)	(1.788, 3.691)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

Note: Only TEAEs occurred from maintenance phase (including extension phase in CT-P13 3.7 and 3.8) are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only events on or after having CT-P13 SC were included in SC treatment group.

Durations (years) are calculated as [date of last visit (or the day before switching from IV to SC) - date of first administration of each treatment in maintenance phase +1]/365.25. PY = Patient Years.

Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 20.0 for Study 1.6 (Part 1), version 20.1 for Study 1.6 (Part 2) and version 25.0 for Study 3.7 and Study 3.8

Seriousness/outcomes

CT-P13 IV Clinical studies:

Important Identified Risk – Serious infections including sepsis **Indication – Rheumatoid arthritis**				
	Studies 1.2+1.2Ext+3.1+3.2+3.3 (N=636)			
Treatment	**CT-P13 IV only (N=318)**	**Switched from Remicade (N=151)**	**Total (N=469)**	**Remicade (N=318)**
N (%) Patients with TEAEs [1]	18 (5.7%)	4 (2.6%)	22 (4.7%)	7 (2.2%)
Serious [2]	18 (5.7%)	4 (2.6%)	22 (4.7%)	7 (2.2%)
Outcomes [3]				
Missing	0	0	0	0
Recovered	17 (5.3%)	4 (2.6%)	21 (4.5%)	7 (2.2%)
Recovering	0	0	0	0
Did not recover	1 (0.3%)	0	1 (0.2%)	0
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious>Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal>Not Recovered/Not Resolved> Recovering/Resolving>Recovered/Resolved, Recovered/Resolved with Sequelae>Unknown+Missing

Important Identified Risk – Serious infections including sepsis **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) **(N=250)**			
Treatment	**CT-P13 IV only** **(N=128)**	**Switched from Remicade** **(N=84)**	**Total** **(N=212)**	**Remicade** **(N=122)**
N (%) Patients with TEAEs [1]	4 (3.1%)	1 (1.2%)	5 (2.4%)	3 (2.5%)
Serious [2]	4 (3.1%)	1 (1.2%)	5 (2.4%)	3 (2.5%)
Outcomes [3]				
Missing	0	0	0	0
Recovered	2 (1.6%)	1 (1.2%)	3 (1.4%)	3 (2.5%)
Recovering	2 (1.6%)	0	2 (0.9%)	0
Did not recover	0	0	0	0
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious>Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal>Not Recovered/Not Resolved> Recovering/Resolving>Recovered/Resolved, Recovered/Resolved with Sequelae>Unknown+Missing

CT-P13 SC Clinical Studies:

Important Identified Risk – Serious infections including sepsis **Indication – Rheumatoid arthritis**			
	Study CT-P13 3.5 (Part 1+Part 2) **(N=391)**		
Treatment	**CT-P13 IV** **(N=188)**	**CT-P13 SC** **(N=363)**	**Total** **(N=391)**
N (%) Patients with TEAEs[1]	2 (1.1%)	5 (1.4%)	7 (1.8%)
Serious [2]	2 (1.1%)	5 (1.4%)	7 (1.8%)
Outcomes [3]			
Missing	0	1 (0.3%)	1 (0.3%)
Recovered/Resolved	2 (1.1%)	3 (0.8%)	5 (1.3%)
Recovering/Resolving	0	0	0
Not Recovered/Not Resolved	0	1 (0.3%)	1 (0.3%)
Fatal	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrence.

[2] Only the most serious event is counted - Seriousness: Serious/Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown, Missing

Note: Only TEAEs occurred from maintenance phase are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

Important Identified Risk – Serious infections including sepsis **Indication – Crohn's Disease and Ulcerative Colitis**			
	Study CT-P13 1.6 (Part 1+Part 2), 3.7 and 3.8 (N=924)		
Treatment	**CT-P13 IV (N=78)**	**CT-P13 SC (N=902)**	**Total (N=924)**
N (%) Patients with TEAEs[1]	2 (2.6%)	30 (3.3%)	32 (3.5%)
Serious [2]	2 (2.6%)	30 (3.3%)	32 (3.5%)
Outcomes [3]			
Missing	0	0	0
Recovered/Resolved	2 (2.6%)	30 (3.3%)	32 (3.5%)
Recovering/Resolving	0	0	0
Not recovered/Not resolved	0	0	0
Fatal	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most serious event is counted - Seriousness: Serious/Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown, Missing

Note: Only TEAEs occurred from maintenance phase (including extension phase in CT-P13 3.7 and 3.8) are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only events on or after having CT-P13 SC were included in SC treatment group.

Severity and nature of risk

CT-P13 IV Clinical studies:

Important Identified Risk – Serious infections including sepsis **Indication – Rheumatoid arthritis**				
	Studies 1.2+1.2Ext+3.1+3.2+3.3 (N=636)			
Treatment	**CT-P13 IV only (N=318)**	**Switched from Remicade (N=151)**	**Total (N=469)**	**Remicade (N=318)**
N (%) Patients with TEAEs [1]	18 (5.7%)	4 (2.6%)	22 (4.7%)	7 (2.2%)
Severity [2]				
Missing	0	0	0	0
Grade 1	1 (0.3%)	1 (0.7%)	2 (0.4%)	0
Grade 2	9 (2.8%)	0	9 (1.9%)	1 (0.3%)
Grade 3	8 (2.5%)	3 (2.0%)	11 (2.3%)	6 (1.9%)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most severe event is counted - Severity: Grade 3>Grade 2>Grade 1>Missing

Important Identified Risk – Serious infections including sepsis **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) (N=250)			
Treatment	**CT-P13 IV only (N=128)**	**Switched from Remicade (N=84)**	**Total (N=212)**	**Remicade (N=122)**
N (%) Patients with TEAEs [1]	4 (3.1%)	1 (1.2%)	5 (2.4%)	3 (2.5%)
Severity [2]				
Missing	0	0	0	0
Grade 1	0	0	0	2 (1.6%)
Grade 2	3 (2.3%)	0	3 (1.4%)	0
Grade 3	1 (0.8%)	1 (1.2%)	2 (0.9%)	1 (0.8%)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most severe event is counted - Severity: Grade 3>Grade 2>Grade 1>Missing

CT-P13 SC Clinical studies:

Important Identified Risk – Serious infections including sepsis **Indication – Rheumatoid arthritis**			
	Study CT-P13 3.5 (Part 1+Part 2) **(N=391)**		
Treatment	**CT-P13 IV** **(N=188)**	**CT-P13 SC** **(N=363)**	**Total** **(N=391)**
N (%) Patients with TEAEs[1]	2 (1.1%)	5 (1.4%)	7 (1.8%)
Severity [2]			
Grade 1	0	0	0
Grade 2	1 (0.5%)	1 (0.3%)	2 (0.5%)
Grade 3	1 (0.5%)	4 (1.1%)	5 (1.3%)
Grade 4	0	0	0
Grade 5	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1

Note: Only TEAEs occurred from maintenance phase are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

Important Identified Risk – Serious infections including sepsis **Indication – Crohn's Disease and Ulcerative Colitis**			
	Study CT-P13 1.6 (Part 1+Part 2), 3.7 and 3.8 (N=924)		
Treatment	**CT-P13 IV (N=78)**	**CT-P13 SC (N=902)**	**Total (N=924)**
N (%) Patients with TEAEs[1]	2 (2.6%)	30 (3.3%)	32 (3.5%)
Severity [2]			
Grade 1	0	0	0
Grade 2	0	4 (0.4%)	4 (0.4%)
Grade 3	2 (2.6%)	19 (2.1%)	21 (2.3%)
Grade 4	0	7 (0.8%)	7 (0.8%)
Grade 5	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1

Note: Only TEAEs occurred from maintenance phase (including extension phase in CT-P13 3.7 and 3.8) are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only events on or after having CT-P13 SC were included in SC treatment group.

Post-marketing experience:

As of 31 March 2023, 5,679 cases (7,537 events) of Serious infections including sepsis were reported from post-marketing data from the pooled data of Remsima IV/SC and Inflectra IV across all indications. 3,074 events were reported as recovered or recovering; 4,255 events were not recovered or unknown and 208 events were fatal. Based on the review of the data, no new safety information was identified.

In pooled analysis on Adverse Events of Special Interest (AESI), 4,393 subjects were treated with at least one dose of CT-P13 across the six post-marketing, non-interventional observational studies for the authorised indication. Overall, 109 (2.48%) subjects in total treatment group, 94 subjects (2.56%) in CT-P13 and 15 subjects (2.09%) in Remicade to CT-P13 experienced at least 1 treatment-emergent serious adverse events (TESAEs) of infection including TB across all indications and all treatment groups. Of the 109 subjects, there were 27 subjects (4.03%) with RA, 17 subjects (2.08%) with AS, 1 subject (1.11%) with PsA/PS, 24 subjects (2.40%) with UC and 40 subjects (2.21%) with CD.

Overall, 96 (2.19%) subjects in total treatment group, 82 subjects (2.23%) in CT-P13 group and 14 subjects (1.96%) in Remicade to CT-P13 group experienced at least a TESAE of infection excluding TB across all indications and all treatment groups. Of the 96 subjects, there were 24

subjects (3.58%) with RA, 12 subjects (1.47%) with AS, 1 (1.11%) subject with PsA/PS, 23 subjects (2.30%) with UC and 36 subjects (1.98%) with CD.

Incidence rate per 100 PY of serious infection excluding TB was 2.99 in total treatment group across all indications.

Incidence rate per 100 PY of Active TB was 0.44 in total treatment group across all indications. No notable differences were found in each indication. (RA=0.58, AS=0.88, PsA/PS=0, UC=0.28, CD=0.30).

Opportunistic infections could not be systematically identified in isolation from other infections using the variables available in the data catalogue in the pooled data set. This is because opportunistic infections are dependent on the presence of host factors, such as immunodeficiency, and no inclusive algorithm could be designed to reliably identify such subjects.

Impact on the quality of life

Sepsis carries a high risk of death and serious potentially irreversible morbidity.

Risk factors and risk groups:

- very young people and elderly people
- immunosuppressive medications (such as transplant recipients), including steroids
- treatment with chemotherapy drugs or radiation
- splenectomy
- long-standing diabetes, acquired immune deficiency syndrome (AIDS), or cirrhosis
- large burns or severe trauma
- infections such as pneumonia, meningitis, cellulitis, urinary tract infection

Preventability:

Remsima IV/SC and Inflectra IV is contraindicated in patients with TB or other severe infections, such as sepsis, abscesses, and OIs ('Contraindications' section of the SmPC).

Remsima IV/SC and Inflectra IV should not be given to patients with a clinically important, active infection ('Special Warnings and Precautions for Use' section of the SmPC). The SmPC indicates that caution should be exercised when considering the use of Remsima IV/SC and Inflectra IV in patients with chronic infection or a history of recurrent infections, including concomitant immunosuppressive therapy. Patients should be advised of and avoid exposure to potential risk factors for infections, as appropriate. Early recognition of atypical clinical presentations of serious infections is critical in order to minimise delays in diagnosis and treatment.

Additional risk minimisation measures for this risk have been discussed in detail in Section V.2.

Impact on the risk-benefit balance of the product:

Remsima IV/SC and Inflectra IV are similar to the reference product Remicade that is already authorised in the EU. Remsima IV/SC and Inflectra IV and the reference product Remicade contain the same active substance. In accordance with the EU requirements, Remsima IV/SC and Inflectra IV has been shown to have a comparable quality, safety and efficacy profile to Remicade. Therefore, as for Remicade, the benefit of an effective treatment of RA, CD, UC, AS, PsA, and psoriasis outweighs the identified risk of serious infections including sepsis.

Public health impact:

In post-marketing spontaneous reporting of the reference product Remicade, infections are the most common serious adverse event in patients treated with infliximab. Some of the cases have resulted in a fatal outcome. Nearly 50% of reported deaths have been associated with infection.

MedDRA terms:

SOC: Infections and infestations.

Important identified risk: BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab

Potential mechanisms:

BCG Breakthrough infection in infants with in utero exposure to infliximab

TNF acts to regulate and enhance appropriate inflammatory, innate and adaptive immune responses to pathogenic organisms (Hehlgans and Pfeffer, 2005), and hence inhibition of TNF by infliximab may suppress these beneficial activities of TNF and increase the potential for infection. Infliximab crosses the placenta and has been detected up to 12 months in the serum of infants born to women treated with infliximab during pregnancy.

Agranulocytosis in infants with in utero exposure to infliximab

The causal relationship between TNF inhibitors and agranulocytosis is poorly understood. Bone marrow suppression has been reported, albeit rarely, in patients after treatment with etanercept (Hyrich KL et al., 2004). TNF up-regulates the expression of proinflammatory cytokines involved in the differentiation and maturation of haemopoietic stem cells, it is thus possible that its blockade could mediate bone marrow failure by inhibiting stem cell differentiation (Keystone EC et al., 2001). Infliximab crosses the placenta and has been detected up to 12 months in the serum of infants born to women treated with infliximab during pregnancy.

Evidence source(s) and strength of evidence:

In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth.
Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP as well as limited post-marketing data from Remsima/Inflectra.

Characterisation of the risk:

Frequency

Clinical Studies:

BCG Breakthrough infection and Agranulocytosis in infants with in utero exposure to infliximab

No cases involving infants of women who participated in CT-P13 clinical trials have been reported. Women who were pregnant, nursing, or planning a pregnancy were excluded from CT-P13 clinical trials. In addition, if a woman became pregnant while participating in a clinical trial, the study agent was discontinued.

Seriousness/outcomes
See above.

Severity and nature of risk
See above.

Post-marketing experience:

BCG Breakthrough infection and agranulocytosis in infants with in utero exposure to infliximab

As of 31 March 2023, 2 adverse drug events (2 cases) of BCG breakthrough infection were reported from post-marketing data from the pooled data of Remsima IV/SC and Inflectra IV and the

outcomes of these events were fatal. In one case from spontaneous report, the infant was given a BCG vaccine in the first few weeks of birth and developed disseminated tuberculosis. The infant's mother received infliximab at unspecified dose for an unspecified indication. The infant died on an unspecified date. In other case from literature source, the infant was BCG-vaccinated at 3 months old and experienced tuberculosis granuloma. The infant's mother received infliximab during pregnancy at unspecified dose for Crohn's disease. The patient died at 4.5 months. Relevant medical history and concomitant medications were not reported in both cases. Based on the known safety profile of this medicinal product and plausible temporal relationship, a possible contributory role of the suspect drug cannot be excluded in the reported event.

Impact on the Individual Patient
The impact of this risk on an infant exposed to infliximab *in utero* is significant.

Risk factors and risk groups:

Infants exposed to infliximab *in utero*.

Preventability:

12 months waiting period following the birth is recommended before the administration of live vaccines to infants exposed *in utero* to infliximab. Infants up to 12 months of age exposed *in utero* to infliximab should be closely monitored by paediatricians for signs of infection or low white blood cell count such as persistent fever.

Additional risk minimisation measures for this risk have been discussed in detail in Section V.2.

Impact on the risk-benefit balance of the product:

Remsima IV/SC and Inflectra IV are similar to the reference product Remicade that is already authorised in the EU. Remsima IV/SC and Inflectra IV and the reference product Remicade contain the same active substance. In accordance with the EU requirements, Remsima IV/SC and Inflectra IV has been shown to have a comparable quality, safety and efficacy profile to Remicade. Therefore, as for Remicade, the benefit of an effective treatment of RA, CD, UC, AS, PsA, and psoriasis outweighs the identified risk of BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab.

Public health impact:

The potential public health impact is not known.

MedDRA term:

PT: Maternal exposure during pregnancy.

Important identified risk: Demyelinating disorders

Potential mechanisms:

The mechanism is not known.

Evidence source(s) and strength of evidence:

Demyelinating disorders were identified as a class effect on review of the post-marketing data for all TNF inhibitors. After demyelinating disorders were identified as a risk, subjects with a history of demyelinating disorders were excluded from clinical trials. The role that TNF plays as an immunomodulator suggests that TNF blockade may promote the development of drug-induced

neuropathies by augmenting the number of activated peripheral T cells and thereby enhance autoimmune responses by altering antigen presenting cell function, potentiating T–cell receptor signalling, and/or decreasing apoptosis of autoreactive T cells. These autoreactive T cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens. A recent report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective. Since TNF inhibitors can neutralise both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF.

Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP, and hence the strength of the evidence is good.

Characterisation of the risk:

Frequency

CT-P13 IV Clinical studies:

Important Identified Risk – Demyelinating disorders **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) **(N=250)**			
Treatment	**CT-P13 IV only** **(N=128)**	**Switched from Remicade** **(N=84)**	**Total** **(N=212)**	**Remicade** **(N=122)**
N (%) Patients with TEAEs [1]	1 (0.8%)	0	1 (0.5%)	0
Total N of TEAEs	2	0	2	0
Number of Patients with TEAEs per 100 PY	0.452	0.000	0.339	0.000
95% CI for Number of Patients with TEAEs per 100PY	(0.011, 2.516)	(0.000, 5.002)	(0.009, 1.888)	(0.000, 2.715)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrence.

Note: Only TEAEs are included. Durations (years) are calculated as [date of last visit – date of first administration+1]/365.25. PY = Patient Years.

MedDRA dictionary, version 15.1

In clinical studies, there was 1 patient with 2 related events of demyelination occurring during treatment with CT-P13 and no case during treatment with Remicade.

No cases of demyelination were reported in clinical studies in subjects with RA.

According to the Remicade SmPC, use of TNF inhibitors, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, including MS, and peripheral demyelinating disorders, including Guillain-Barré syndrome. In clinical trials conducted with Remicade, these disorders have been reported to occur rarely.

CT-P13 SC Clinical studies:

There have been no cases of demyelinating disorders in the clinical studies conducted with CT-P13 SC.

Seriousness/outcomes

CT-P13 IV Clinical studies:

Important Identified Risk – Demyelinating disorders **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) **(N=250)**			
Treatment	**CT-P13 IV only** **(N=128)**	**Switched from Remicade** **(N=84)**	**Total** **(N=212)**	**Remicade** **(N=122)**
N (%) Patients with TEAEs [1]	1 (0.8%)	0	1 (0.5%)	0
Serious [2]	1 (0.8%)	0	1 (0.5%)	0
Outcomes [3]				
Missing	0	0	0	0
Recovered	0	0	0	0
Recovering	0	0	0	0
Did not recover	1 (0.8%)	0	1 (0.5%)	0
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious>Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal>Not Recovered/Not Resolved>Recovering/Resolving>Recovered/Resolved, Recovered/Resolved with Sequelae>Unknown+Missing

There has been 1 AS patient with 2 events of demyelination during treatment with CT-P13 considered as at least possibly-related compared to no case in the Remicade group. No unrelated cases have been identified. This one demyelination case was recovering/resolving with no action taken.

CT-P13 SC Clinical studies:

Not applicable. No cases were reported in association with CT-P13 SC.

Severity and nature of risk

CT-P13 IV Clinical studies:

Important Identified Risk – Demyelinating disorders **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) **(N=250)**			
Treatment	**CT-P13 IV only** **(N=128)**	**Switched from Remicade** **(N=84)**	**Total** **(N=212)**	**Remicade** **(N=122)**
N (%) Patients with TEAEs [1]	1 (0.8%)	0	1 (0.5%)	0
Severity [2]				
Missing	0	0	0	0
Grade 1	1 (0.8%)	0	1 (0.5%)	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 3>Grade 2>Grade 1>Missing

In clinical studies, there were 2 events of mild demyelination in one patient (1 event serious) in the CT-P13 treatment group considered as at least possibly related compared with no case in the Remicade group. No unrelated cases have been identified.

CT-P13 SC Clinical studies:

Not applicable. No cases were reported in association with CT-P13 SC.

Post-marketing experience:

As of 31 March 2023, 68 cases (74 events) of demyelinating disorders were reported from post-marketing data from the pooled data of Remsima IV/SC and Inflectra IV across all indications. 31 events were reported as recovered or recovering; 43 events were not recovered or unknown and there were no reported fatal events. Based on the review of the data, no new safety information was identified.

In pooled analysis on AESI, 4393 subjects were treated with at least one dose of CT-P13 across the six post-marketing, non-interventional observational studies for the authorised indication. Overall, 2 subjects (0.05 %) in the overall safety population (across all indications) reported at least one demyelinating disorder reaction, one subject each in the CT-P13 group (0.03%) and the Remicade to CT-P13 group (0.14%) respectively. All subjects were treated for the indication of CD.

Incidence rates per 100 patient year of CT-P13 of demyelinating disorders were 0.062 in total treatment group across all indications and 0.151 in the CD indication.

Impact on the quality of life

The impact cannot be predicted in individual cases. Impact may vary from mild symptoms to disabling symptoms.

Risk factors and risk groups:

Patients with a history of demyelinating disorders, or a family history

Preventability:

Predictability and preventability of the development of demyelination are not known. In patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of Remsima IV/SC and Inflectra IV treatment should be carefully considered before initiation of Remsima IV/SC and Inflectra IV therapy and discontinuation of Remsima IV/SC and Inflectra IV therapy should be considered if signs or symptoms of demyelinating disorders develop ('Special Warnings and Precautions for Use' section of the SmPC).

Impact on the risk-benefit balance of the product:

Remsima IV/SC and Inflectra IV are similar to the reference product Remicade that is already authorised in the EU. Remsima IV/SC and Inflectra IV and the reference product Remicade contain the same active substance. In accordance with the EU requirements, Remsima IV/SC and Inflectra IV has been shown to have a comparable quality, safety and efficacy profile to Remicade. Therefore, as for Remicade, the benefit of an effective treatment of RA, CD, UC, AS, PsA, and psoriasis outweighs the identified risk of demyelinating disorders.

Public health impact:

Demyelinating disorders during treatment with infliximab are rare. The public health impact is likely to be very small.

MedDRA term:

HLGT: Demyelinating disorders.

Important identified risk: Malignancy

Potential mechanisms:

The mechanism is not understood. Immunosuppression may play a role in allowing the proliferation of tumour cells.

Evidence source(s) and strength of evidence:

According to the Remsima IV/SC and Inflectra IV SmPC, malignancies (some fatal) have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the post-marketing setting. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded.

In clinical studies with infliximab in which 5,780 patients were treated, representing 5,494 patient years, 26 non-lymphoma malignancies were detected as compared with 1 non-lymphoma malignancy in 1,600 placebo-treated patients representing 941 patient years. In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6,234 patients-years (3,210 patients), 38 cases of non-lymphoma malignancies were reported. TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines. Low

doses of TNF can increase tumour blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumour cells. Therefore, the neutralisation of TNF by infliximab may allow some types of tumour cells to survive.

Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP, and hence the strength of the evidence is good.

Characterisation of the risk:

Frequency

CT-P13 IV Clinical studies:

Important identified risk: Malignancy **Indication – Rheumatoid arthritis**				
	Studies 1.2+1.2Ext+3.1+3.2+3.3 (N=636)			
Treatment	**CT-P13 IV only (N=318)**	**Switched from Remicade (N=151)**	**Total (N=469)**	**Remicade (N=318)**
N (%) Patients with TEAEs [1]	5 (1.6%)	4 (2.6%)	9 (1.9%)	4 (1.3%)
Total N of TEAEs	5	4	9	5
Number of Patients with TEAEs per 100 PY	1.050	3.058	1.483	1.202
95% CI for Number of Patients with TEAEs per 100PY	(0.341, 2.450)	(0.833, 7.831)	(0.678, 2.815)	(0.327, 3.076)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrence.

Note: Only TEAEs are included. Durations (years) are calculated as [date of last visit – date of first administration+1]/365.25. PY = Patient Years.

MedDRA dictionary, version 15.1

Important identified risk: Malignancy **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) **(N=250)**			
Treatment	**CT-P13 IV only** **(N=128)**	**Switched from Remicade** **(N=84)**	**Total** **(N=212)**	**Remicade** **(N=122)**
N (%) Patients with TEAEs [1]	3 (2.3%)	0	3 (1.4%)	0
Total N of TEAEs	3	0	3	0
Number of Patients with TEAEs per 100 PY	1.355	0.000	1.016	0.000
95% CI for Number of Patients with TEAEs per 100PY	(0.279, 3.959)	(0.000, 5.002)	(0.210, 2.970)	(0.000, 2.715)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrence.

Note: Only TEAEs are included. Durations (years) are calculated as [date of last visit – date of first administration+1]/365.25. PY = Patient Years.

MedDRA dictionary, version 15.1

CT-P13 SC Clinical studies:

Important identified Risk – Malignancy **Indication – Rheumatoid arthritis**			
	Study CT-P13 3.5 (Part 1+Part 2) **(N=391)**		
Treatment	**CT-P13 IV** **(N=188)**	**CT-P13 SC** **(N=363)**	**Total** **(N=391)**
N (%) Patients with TEAEs[1]	0	1 (0.3%)	1 (0.3%)
Total N of TEAEs	0	1	1
Number of Patients with TEAEs per 100 PY	0.000	0.335	0.255
95% CI for Number of Patients with TEAEs per 100PY	(0.000, 3.961)	(0.008, 1.864)	(0.006, 1.421)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

Note: Only TEAEs occurred from maintenance phase are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

Durations (years) are calculated as [date of last visit (or the day before switching from IV to SC) - date of first administration of each treatment in maintenance phase +1]/365.25. PY = Patient Years.

Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 20.0 for Study 3.5 (Part 1 and Part 2)

Important identified Risk – Malignancy **Indication – Crohn's Disease and Ulcerative Colitis**			
	Study CT-P13 1.6 (Part 1+Part 2), 3.7 and 3.8 (N=924)		
Treatment	**CT-P13 IV (N=78)**	**CT-P13 SC (N=902)**	**Total (N=924)**
N (%) Patients with TEAEs[1]	1 (1.3%)	4 (0.4%)	5 (0.5%)
Total N of TEAEs	1	4	5
Number of Patients with TEAEs per 100 PY	2.557	0.338	0.408
95% CI for Number of Patients with TEAEs per 100PY	(0.065, 14.249)	(0.092, 0.864)	(0.133, 0.953)

[1] Includes all subjects who had one or more occurrences of adverse events that met the criteria of the identified risk, the subject is counted only once regardless of the number of events or the number of occurrences.

Note: Only TEAEs occurred from maintenance phase (including extension phase in CT-P13 3.7 and 3.8) are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only events on or after having CT-P13 SC were included in SC treatment group.

Durations (years) are calculated as [date of last visit (or the day before switching from IV to SC) - date of first administration of each treatment in maintenance phase +1]/365.25. PY = Patient Years.

Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 20.0 for Study 1.6 (Part 1), version 20.1 for Study 1.6 (Part 2) and version 25.0 for Study 3.7 and Study 3.8

Seriousness/outcomes

CT-P13 IV Clinical studies:

Important identified risk: Malignancy **Indication – Rheumatoid arthritis**				
	Studies 1.2+1.2Ext+3.1+3.2+3.3 (N=636)			
Treatment	**CT-P13 IV only (N=318)**	**Switched from Remicade (N=151)**	**Total (N=469)**	**Remicade (N=318)**
N (%) Patients with TEAEs [1]	5 (1.6%)	4 (2.6%)	9 (1.9%)	4 (1.3%)
Serious [2]	3 (0.9%)	4 (2.6%)	7 (1.5%)	4 (1.3%)
Outcomes [3]				
Missing	1 (0.3%)	0	1 (0.2%)	1 (0.3%)
Recovered	0	4 (2.6%)	4 (0.9%)	1 (0.3%)
Recovering	1 (0.3%)	0	1 (0.2%)	2 (0.6%)
Did not recover	3 (0.9%)	0	3 (0.6%)	0
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious>Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal>Not Recovered/Not Resolved>Recovering/Resolving>Recovered/Resolved, Recovered/Resolved with Sequelae>Unknown+Missing

Important identified risk: Malignancy **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) (N=250)			
Treatment	**CT-P13 IV only (N=128)**	**Switched from Remicade (N=84)**	**Total (N=212)**	**Remicade (N=122)**
N (%) Patients with TEAEs [1]	3 (2.3%)	0	3 (1.4%)	0
Serious [2]	2 (1.6%)	0	2 (0.9%)	0
Outcomes [3]				
Missing	0	0	0	0
Recovered	1 (0.8%)	0	1 (0.5%)	0
Recovering	1 (0.8%)	0	1 (0.5%)	0
Did not recover	1 (0.8%)	0	1 (0.5%)	0
Fatal	0	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most serious event is counted - Seriousness: Serious>Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal>Not Recovered/Not Resolved>Recovering/Resolving>Recovered/Resolved, Recovered/Resolved with Sequelae>Unknown+Missing

CT-P13 SC Clinical studies:

Important identified Risk – Malignancy **Indication – Rheumatoid arthritis**			
	Study CT-P13 3.5 (Part 1+Part 2) **(N=391)**		
Treatment	**CT-P13 IV** **(N=188)**	**CT-P13 SC** **(N=363)**	**Total** **(N=391)**
N (%) Patients with TEAEs[1]	0	1 (0.3%)	1 (0.3%)
Serious [2]	0	0	0
Outcomes [3]			
Missing	0	0	0
Recovered/Resolved	0	0	0
Recovering/Resolving	0	0	0
Not Recovered/Not Resolved	0	1 (0.3%)	1 (0.3%)
Fatal	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most serious event is counted - Seriousness: Serious/Non-serious

[3] Only the most severe outcome is counted - Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown, Missing

Note: Only TEAEs occurred from maintenance phase are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

Important Identified Risk – Malignancy **Indication – Crohn's Disease and Ulcerative Colitis**			
	Study CT-P13 1.6 (Part 1+Part 2), 3.7 and 3.8 (N=924)		
Treatment	**CT-P13 IV (N=78)**	**CT-P13 SC (N=902)**	**Total (N=924)**
N (%) Patients with TEAEs[1]	1 (1.3%)	4 (0.4%)	5 (0.5%)
Serious [2]	1 (1.3%)	2 (0.2%)	3 (0.3%)
Outcomes [3]			
Missing	0	0	0
Recovered/Resolved	1 (1.3%)	3 (0.3%)	4 (0.4%)
Recovering/Resolving	0	1 (0.1%)	1 (0.1%)
Not Recovered/Not Resolved	0	0	0
Fatal	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most serious event is counted – Seriousness: Serious/Non-serious

[3] Only the most severe outcome is counted – Outcomes: Fatal > Not Recovered/Not Resolved > Recovering/Resolving > Recovered/Resolved, Recovered/Resolved with Sequelae > Unknown, Missing

Note: Only TEAEs occurred from maintenance phase (including extension phase in CT-P13 3.7 and 3.8) are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only events on or after having CT-P13 SC were included in SC treatment group.

Severity and nature of risk

CT-P13 IV Clinical studies:

Important identified risk: Malignancy **Indication – Rheumatoid arthritis**				
	Studies 1.2+1.2Ext+3.1+3.2+3.3 (N=636)			
Treatment	**CT-P13 IV only (N=318)**	**Switched from Remicade (N=151)**	**Total (N=469)**	**Remicade (N=318)**
All adverse events N (%) [1]	5 (1.6%)	4 (2.6%)	9 (1.9%)	4 (1.3%)
Severity [2]				
Missing	0	0	0	0
Grade 1	3 (0.9%)	0	3 (0.6%)	0
Grade 2	1 (0.3%)	3 (2.0%)	4 (0.9%)	1 (0.3%)
Grade 3	1 (0.3%)	1 (0.7%)	2 (0.4%)	3 (0.9%)

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 3>Grade 2>Grade 1>Missing

Important identified risk: Malignancy **Indication – Ankylosing spondylitis**				
	Studies (1.1+1.3) (N=250)			
Treatment	**CT-P13 IV only (N=128)**	**Switched from Remicade (N=84)**	**Total (N=212)**	**Remicade (N=122)**
All adverse events N (%) [1]	3 (2.3%)	0	3 (1.4%)	0
Severity [2]				
Missing	0	0	0	0
Grade 1	1 (0.8%)	0	1 (0.5%)	0
Grade 2	0	0	0	0
Grade 3	2 (1.6%)	0	2 (0.9%)	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences

[2] Only the most severe event is counted - Severity: Grade 3>Grade 2>Grade 1>Missing

CT-P13 SC Clinical studies:

Important identified Risk – Malignancy **Indication – Rheumatoid arthritis**			
	Study CT-P13 3.5 (Part 1+Part 2) **(N=391)**		
Treatment	**CT-P13 IV** **(N=188)**	**CT-P13 SC** **(N=363)**	**Total** **(N=391)**
N (%) Patients with TEAEs[1]	0	1 (0.3%)	1 (0.3%)
Severity [2]			
Grade 1	0	0	0
Grade 2	0	1 (0.3%)	1 (0.3%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrences.

[2] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1

Note: Only TEAEs occurred from maintenance phase are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows.

For CT-P13 3.5 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

Important Identified Risk – Malignancy **Indication – Crohn's Disease and Ulcerative Colitis**			
	Study CT-P13 1.6 (Part 1+Part 2), 3.7 and 3.8 (N=924)		
Treatment	**CT-P13 IV (N=78)**	**CT-P13 SC (N=902)**	**Total (N=924)**
N (%) Patients with TEAEs[1]	1 (1.3%)	4 (0.4%)	5 (0.5%)
Severity [2]			
Grade 1	0	0	0
Grade 2	1 (1.3%)	1 (0.1%)	2 (0.2%)
Grade 3	0	2 (0.2%)	2 (0.2%)
Grade 4	0	1 (0.1%)	1 (0.1%)
Grade 5	0	0	0

[1] Includes all subjects who had one or more occurrences of an adverse event that met the criteria of the identified/potential risk, the subject is counted only once regardless of the number of events or the number of occurrence.

[2] Only the most severe event is counted - Severity: Grade 5>Grade 4>Grade 3>Grade 2>Grade 1

Note: Only TEAEs occurred from maintenance phase (including extension phase in CT-P13 3.7 and 3.8) are included. Treatment groups were categorized using the actual treatment group in Safety population with exceptions as follows;

- For CT-P13 1.6 Part 2, CT-P13 IV group switched their treatment to CT-P13 SC at Week 30. The events occurred before switching were included in IV treatment group and the events on or after switching were included in SC treatment group separately.

- For CT-P13 3.7 and 3.8, Placebo group administered CT-P13 SC from Week 56 or dose adjustment. Only events on or after having CT-P13 SC were included in SC treatment group.

Post-marketing experience:

As of 31 March 2023, 936 cases (1,081 events) of Malignancy were reported from post-marketing data from the pooled data of Remsima IV/SC and Inflectra IV across all indications. 210 events were reported as recovered or recovering; 808 events were not recovered or unknown and 63 events were fatal. Based on the review of the data, no new safety information was identified.

In pooled analysis on AESI, 4,393 subjects were treated with at least one dose of CT-P13 across the six post-marketing, non-interventional observational studies for the authorised indication. There were 18 subjects with TEAE of non-haematological malignancy in the total safety data set. No haematologic malignancies were reported in the data set. The crude incidence of non-haematological malignancy was 0.41%. Only 1 subject (0.14%) was reported to have a TEAE of non-haematologic malignancy in the switched from Remicade to CT-P13 group.

Incidence per 100 patient year for non-haematologic malignancy was 0.56 in the total analysed population. The greatest incidence was reported in subjects treated for RA (6 subjects, 1.17 per 100 patient years). Incidence rate per 100 patient years of subjects in AS, PsA/Ps, UC and CD were 0, 0, 0.69 and 0.53 respectively.

Impact on the quality of life

The impact on the patient will depend on the nature of the malignancy.

Risk factors and risk groups:

History of malignancy, immunosuppressant therapy, and/or HIV infection may increase the risk of malignancy. Phototherapy for psoriasis increases the risk of skin cancer. UC is associated with a higher risk of colon cancer.

Preventability:

Caution should be exercised when considering TNFα-antagonist therapy for patients with a history of malignant disease or when considering continuing treatment in patients who develop any form of malignancy ('Special Warnings and Precautions for Use' section of the SmPC). Since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with Remsima IV/SC and Inflectra IV is not established, the risk and benefits to the individual patient must be carefully reviewed and consideration should be given to discontinuation of therapy ('Special Warnings and Precautions for Use' section of the SmPC). Caution should also be exercised in considering treatment of patients with increased risk of malignancy due to heavy smoking.

Impact on the risk-benefit balance of the product:

Remsima IV/SC and Inflectra IV are similar to the reference product Remicade that is already authorised in the EU. Remsima IV/SC and Inflectra IV and the reference product Remicade contain the same active substance. In accordance with the EU requirements, Remsima IV/SC and Inflectra IV has been shown to have a comparable quality, safety and efficacy profile to Remicade. Therefore, as for Remicade, the benefit of an effective treatment RA, CD, UC, AS, PsA, and psoriasis outweighs the identified risk of Malignancy.

Public health impact:

Not assessable. The impact on the patient will depend on the nature of the malignancy.

MedDRA term:

SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps).

Important potential risk: Colon carcinoma/dysplasia (in paediatric ulcerative colitis)

Potential mechanisms:

TNF-α plays an important role in the immune response. Its suppression with a TNF-α inhibitor such as infliximab might contribute to a reduced immune response, increasing the risk of developing colon dysplasia and malignancies such as colon carcinoma.

Evidence source(s) and strength of evidence:

In a review of published studies concerning the risk of colon carcinoma in UC patients, the crude annual incidence rate of colon carcinoma in UC patients ranges from approximately 0.006 to 0.16%. It is assumed that the more widespread use of maintenance therapy for UC and surveillance colonoscopy are the causes of the risk decrease.

TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines. Low doses of TNF can increase tumour blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumour cells. Therefore, the neutralisation of TNF by infliximab may allow some types of tumour cells to survive.

Remsima/Inflectra IV is a biosimilar medicinal product. The reference product is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP, and hence the strength of the evidence is good.

Characterisation of the risk:

Frequency

No data from UC patients are available since CT-P13 studies with paediatric UC patients have not been conducted.

Seriousness/outcomes

In clinical studies with CT-P13 in RA and AS patients, no cases of colon neoplasm have been reported in Study CT-P13 1.1 and CT-P13 1.2; while 1 case of colon neoplasm has been reported as unrelated to study medication in study CT-P13 3.1 in the Remicade treatment arm.

Severity and nature of risk

No paediatric patients with UC have been treated with CT-P13 in clinical studies.

In clinical study programme, there were no cases of colon carcinoma in the CT-P13 treated group and 1 severe, unrelated case of colon neoplasm was reported in the Remicade group.

Post-marketing experience:

No cases were reported from post-marketing data of Remsima IV/SC and Inflectra IV.

Impact on the quality of life

The impact on the patient will depend on the nature of the lesion and the stage of the neoplasm. Advanced lesions may be life-threatening.

Risk factors and risk groups:

Patients with UC who have a history of previous colonic malignancy are at risk, as are patients with long-standing disease.

Preventability:

All patients with UC who are at increased risk for dysplasia or colon carcinoma (e.g., patients with long standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course ('Special Warnings and Precautions for Use' section of the SmPC). This evaluation should include colonoscopy and biopsies per local recommendations.

Impact on the risk-benefit balance of the product:

Remsima/Inflectra IV are similar to the reference product Remicade that is already authorised in the EU. Remsima/Inflectra IV and the reference product Remicade contain the same active substance. In accordance with the EU requirements, Remsima/Inflectra IV has been shown to have a comparable quality, safety and efficacy profile to Remicade. Therefore, as for Remicade, the benefit of an effective treatment of UC outweighs the potential risk of colon carcinoma/dysplasia (in paediatric UC) and currently paediatric UC indication is not proposed for the SC formulation.

Public health impact:

The public health impact is not known.

MedDRA term:

HLGT: Gastrointestinal neoplasms malignant and unspecified.

Important potential risk: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)

Potential mechanisms:

HFI is a rare hereditary autosomal recessive deficit in the main enzyme responsible for hepatic metabolism of fructose. The condition is normally diagnosed in infancy. Administration of sorbitol to patients with HFI may lead to intracellular accumulation of fructose 1-phosphate, which is highly toxic. In particular, intravenous administration poses a greater risk because it bypasses the body's natural defence mechanism. Patients with HFI may experience hypoglycaemia, acute hepatic failure, haemorrhagic syndrome, renal failure, and death.

Evidence source(s) and strength of evidence:

This important potential risk is based on the known effects of parenteral sorbitol-containing medicines to patients with HFI. Although patients with the rare genetic disorder of HFI are expected to avoid such products, there is a concern regarding those who are unaware of their underlying condition, are unconscious due to an acute medical condition, or are too young to have been diagnosed (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014). Therefore, Remsima 100mg and 350mg concentrate for solution for infusion, which contains 45mg of sorbitol per 1 mL are contraindicated in patients with HFI (regardless of their age).

Characterisation of the risk:

There are no clinical trials conducted with Remsima 100mg and 350mg concentrate for solution.

Risk factors and risk groups:

Patients diagnosed with HFI and patients who may be unaware of their underlying HFI, such as unconscious patients or children too young to be diagnosed, are considered at risk. The worldwide incidence of HFI is estimated pproximately 1 in 20,000 to 1 in 30,000 live births. The disorder is not apparent until the infant begins feeding on formula, juice, fruits, baby foods, or honey that contain fructose. In young children, a spontaneous aversion to fructose-containing foods may develop, which can delay the recognition or onset of clinical symptoms. This is particularly likely when caregivers accommodate the child's food preferences and avoid focusing fructose-containing products. (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014). In patients with HFI, prolonged or untreated exposure to sorbitol may result in severe metabolic disorders, including failure to thrive and renal or hepatic impairment.

Preventability:

The SmPC indicates that patients with HFI should be excluded from treatment with Remsima 100mg and 350mg concentrate for solution based on age-appropriate clinical ground. In addition, patients should inform their doctor if they or their child experience symptoms suggestive of HFI, such as aversion to sweet foods, vomiting, bloating, stomach cramps, or diarrhoea. Early identification of patients at risk is critical to prevent inadvertent exposure and reduce the likelihood of serious adverse outcomes.

Additional risk minimisation measures for this risk have been discussed in detail in Section V.2

Impact on the risk-benefit balance of the product:

Although HFI is a rare genetic disorder, sorbitol exposure in affected individuals can be life-threatening. This safety concern has a high impact on the benefit-risk balance of Remsima 100mg and 350mg concentrate for solution for infusion patients with HFI. However, the overall benefit-risk balance remains favourable for the general population when appropriate risk minimisation measures, such as contraindication and clear labelling, are implemented.

Public health impact:

The potential public health impact is not known. However, it is expected to be minimal given the rarity of HFI (estimated at 1 in 20,000 to 30,000 in the general population).

SVII.3.2. Presentation of the missing information

Missing Information- Long term treatment with SC infliximab (SC only)

Evidence source:

People may be treated with Remsima SC for longer than they have been in clinical studies. All of the safety concerns that have come to light from the available studies have been taken into account in the product information and the RMP. Some of the safety concerns, such as malignancy, may take a long time to develop. Remsima SC acts by interfering with the normal functioning of the immune system. There may be long-term consequences that have not yet been seen in patients that have been studied so far.

Population in need of further characterisation:

The safety of long-term treatment with Remsima SC formulation has not been established.

Part II: Module SVIII - Summary of the safety concerns

Table 9: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Serious infections including sepsis • BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab • Demyelinating disorders • Malignancy
Important potential risks	• Colon carcinoma/dysplasia (in paediatric ulcerative colitis) • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)
Missing information	• Long term treatment with SC infliximab (SC only)

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None.

III.2. Additional pharmacovigilance activities

Study CT-P13 SC 4.8 summary

Study short name and title:

An observational, prospective cohort study to evaluate safety of Remsima Subcutaneous in patients with Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis.

Rationale and study objectives:

Rationale:

To collect further safety information on patients treated with Remsima SC with regard to long-term safety.

Study objectives:

Primary Objective:

To assess the safety of Remsima Subcutaneous (SC) in Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Psoriasis (Ps) patients by evaluation of Adverse events of special interest (AESI)

Secondary Objective:

To evaluate additional safety of Remsima SC in RA, AS, PsA and Ps patients

Study design:

This is an observational, prospective cohort study to evaluate the safety of Remsima SC in the treatment of RA, AS, PsA and Ps. Only patients meeting all inclusion criteria and none of exclusion criteria will be enrolled in the study. The choice of treatment will be made by Investigator and/or if necessary, referring to patient's needs, and in line with the current standard of practice. Switching patients from the IV formulation to the SC formulation of Remsima will also be made at the discretion of the investigator. Remsima SC will be administered subcutaneously and Remsima IV will be administered intravenously during this study. Dose and regimen will comply with the approved posology of each product in the region where patients are enrolled.

- For patients in Remsima SC group:
  - Infliximab naïve patients will be administered two doses of Infliximab IV including Remsima IV infusion as an induction and will start administration of Remsima SC on the enrolment date which will be 4 weeks from the last induction dose. Enrolment date will be the date when the first Remsima SC is administered.
  - When subcutaneous loading is used for infliximab naïve patients (only patients with RA), Remsima SC should be given as a subcutaneous injection followed by additional injections at 1, 2, 3 and 4 weeks after the first injection, then every 2 weeks thereafter.

Patients will start administration of Remsima SC on the enrolment date and his or her enrolment date will be the date when the first Remsima SC is administered.

- If a patient has been treated with Remsima SC prior to enrolment, his or her dosing schedule will be continued appropriately according to the SmPC. The enrolment date will be the date when the first Remsima SC is administered after the patient signed informed consent form (ICF).
- If a patient switches to Remsima SC from the maintenance therapy of infliximab (IV) including Remsima IV, Remsima SC may be administered 8 weeks after the last administration of infliximab IV infusion on the enrolment date. For patients who will be switched to Remsima SC from infliximab IV maintenance therapy, the enrolment date will be the date when the first Remsima SC is administered.

- For patients in Remsima IV group (Only patients with AS, PsA and Ps):
  - Infliximab naïve patients will start administration of Remsima IV on the enrolment date which is the date when the first Remsima IV is administered.
  - If a patient has been treated with infliximab IV including Remsima IV prior to enrolment, his or her dosing schedule will be continued appropriately according to the SmPC. The enrolment date will be the date when the first Remsima IV is administered after the patient signed ICF.

The duration of the study will be from the first patient enrolled date into the study to 24 months after the date of last patient enrolled in the study. Each patient will be followed up to 24 months including End-of-Study (EOS) Visit. Enrolled patients who permanently discontinue from the study will be encouraged to remain in the study and be followed up until 6 months from the date of the last dose administration or 24 months from enrolled date, whichever is reached first. The data will be collected using the electronic case report form (eCRF). Patient's visit schedules will follow local standard of care typically coinciding with the schedule of injections of Remsima SC or infusions of Remsima IV. Study assessments will be collected at baseline and recommended to be done at least every 3 months by their treating physician, as part of routine care. Adverse Events of Special Interest (AESI), other Serious Adverse Events (SAEs), and any adverse events (AEs) will be recorded at all visits throughout the study. Laboratory test results conducted during routine care practice will be collected.

Study population:

Male or female patients with RA, AS, PsA or Ps aged ≥ 18 years old will be considered for enrolment in the study if they meet all of the inclusion criteria and none of the exclusion criteria.

Milestones:

Milestone	**Planned date**
Protocol finalised	18 October 2022
FPFV	13 January 2023
3-year report	3Q 2025
LPLV	1Q 2027
Final report available	3Q 2027

III.3 Summary Table of additional Pharmacovigilance activities

Table 10: Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
CT-P13 SC 4.8 An observational, prospective cohort study to evaluate safety of Remsima Subcutaneous in patients with Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis Status: Ongoing	Primary Objective: To assess the safety of Remsima subcutaneous (SC) in Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Psoriasis (Ps) patients by evaluation of adverse events of special interest (AESI) Secondary Objective: To evaluate additional safety of Remsima SC in RA, AS, PsA and Ps patients	Long-term safety in patients with RA, AS, PsA, Ps	Protocol finalised	18 October 2022
			FPFV	13 Janunary 2023
			3-year report	3Q 2025
			LPLV	1Q 2027
			Final report available	3Q 2027

Part IV: Plans for post-authorisation efficacy studies

Table 11: Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table 12: Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Serious infections including sepsis	Routine risk communication: • Severe infections such as sepsis is listed as a contraindication in SmPC section 4.3. • Serious infections including sepsis is listed as special warnings and precautions for use in SmPC section 4.4. • Warning that the suppression of TNF-α may mask symptoms of infection such as fever in SmPC section 4.4. • Warning that patients taking TNF-blockers are more susceptible to serious infections. Some of these infections have been fatal in SmPC section 4.4. • Serious infections including sepsis is listed as an adverse reaction in SmPC section 4.8. • Serious infection is listed as contraindication and warning and precautions in package leaflet (PL) section 2. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima/Inflectra is indicated in SmPC section 4.2. • Guidance that patients treated with Remsima/Inflectra should be given the PL and the patient reminder card in SmPC section 4.2. • Warning that patients must be monitored closely for infections including tuberculosis before, during and after treatment with infliximab in SmPC section 4.4. • Advice that administration of infliximab should be discontinued, if patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until the infection is controlled in SmPC section 4.4. • Advice that tell your doctor if you have an infection even if it is a very minor one or if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common before you are given Remsima/Inflectra in PL section 2. Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.

Safety concern	Routine risk minimisation activities
Important identified risk: BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab	Routine risk communication: • Warning that in infants exposed *in utero* to infliximab, fatal outcome due to disseminated BCG infection has been reported following administration of BCG vaccine after birth in SmPC section 4.4. • Agranulocytosis is listed as an adverse reaction in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima/Inflectra is indicated in SmPC section 4.2. • Guidance that patients treated with Remsima/Inflectra should be given the PL and the patient reminder card in SmPC section 4.2. • Advice that administration of live vaccines (e.g., BCG vaccine) to infants exposed to infliximab *in utero* is not recommended for 12 months after birth and cases of agranulocytosis have also been reported, in SmPC section 4.6. • Advice that talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer) in PL section 2. Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.
Important identified risk: Demyelinating disorders	Routine risk communication: • Warning that use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, including MS, and peripheral demyelinating disorders, including Guillain-Barré syndrome in SmPC section 4.4. • Demyelinating disorders is listed as an adverse reaction in SmPC section 4.8. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning that in patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.
Important identified risk: Malignancy	Routine risk communication: • Malignancy is listed in SmPC section 4.8.

Safety concern	Routine risk minimisation activities
	• Cancer in children and adults is listed in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment for which Remsima/Inflectra is indicated in SmPC section 4.2. • Warning that, patients taking Remsima/Inflectra may have an increased risk of developing lymphoma or another cancer. Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Remsima/Inflectra in PL section 2. Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.
Important potential risk: Colon carcinoma/dysplasia (in paediatric ulcerative colitis)	Routine risk communication (Not applicable for SC): • Abnormal tissue swelling or growth is listed in PL section 4. Routine risk minimisation activities recommending specific clinical measures to address the risk (Not applicable for SC): • Guidance that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment RA, IBD, AS, PsA or psoriasis in SmPC section 4.2. • Warning that, all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or PSC), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course in SmPC section 4.4. • Advice that, this evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that Remsima/Inflectra IV treatment influences the risk for developing dysplasia or colon cancer in SmPC section 4.4. Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.
Important potential risk: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for	Routine risk communication : • Patients with HFI is listed as a contraindication in SmPC section 4.3 and 4.4, PL section 2, and Outer packaging section 7. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance that, a detailed history with regards to HFI symptoms has to be taken of each patient prior to receiving Remsima concentrate for solution for infusion, and that, in case of inadvertent administration and suspicion of fructose intolerance, the infusion has to be stopped immediately, normal

Safety concern	Routine risk minimisation activities
solution for infusion only)	glycaemia has to be re-established and organ function has to be stabilized by means of intensive care in SmPC section 4.4. • Warning that, tell your doctor if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea before you are given Remsima concentrate for solution for infusion in PL section 2. Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.
Missing Information: Long term treatment with SC infliximab (SC only)	Routine risk communication (SC only): • None Routine risk minimisation activities recommending specific clinical measures to address the risk (SC only): • None Other routine risk minimisation measures beyond the Product Information: • Legal status: Medicinal product subject to restricted medical prescription.

V.2. Additional Risk Minimisation Measures

Patient reminder card

Objectives:

To provide patients with a constant reminder that can be carried in a purse or wallet of the more important safety concerns associated with Remsima IV/SC and Inflectra IV treatment.

To remind the patient to tell his/her doctor of important symptoms that may suggest that he/she has developed one of the safety concerns on the reminder card.

To provide the patient with a document that he/she can show to any health professional that may not be familiar with the treatment he/she is receiving.

To remind the patient that both he/she and his doctor must keep a record of the brand name and batch number of the Remsima IV/SC and Inflectra IV treatment he/she has received.

Patients must be given a patient reminder card highlighting the following risks:

- Severe potentially life-threatening infections, lung infections, blood infections
- Infections with germs (including fungi, some viruses, and yeast) that would not normally cause infections in humans
- Tuberculosis
- A rare infection after vaccination or low white blood cell count in infants whose mother received Remsima during the pregnancies or while breast-feeding
- Reactivation of hepatitis B infection in people who have previously been infected by HBV reactivation
- Severe metabolic harms including hypoglycaemia, acute hepatic failure, haemorrhagic syndrome, renal failure, and death due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)

Rationale for the additional risk minimisation activity:

The intent of this patient reminder card is to educate patients on important safety information that they need to be aware of before and during treatment with Remsima IV/SC and Inflectra IV. Also, to ensure that special information regarding the patient's current therapy and its important risks is held by the patient at all times and reaches the relevant healthcare professional when needed.

Target audience and planned distribution path:

Patients who receive Remsima IV/SC and Inflectra IV must be given a patient reminder card that summarises the safety information about the medicine. The patient reminder card is provided as part of the product packaging.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Signal detection: The applied trend analysis tool will compare relative reported frequencies (actual versus historic) as per ADR type according to internal procedure. Obtained ratios, equal or above a value of 3 will be considered a signal and subjected to further signal verification activities. This method will allow the identification of relative changes in reporting frequency, e.g., caused by a decrease in the effectiveness of risk minimisation measures or in the case of emerging new risk

factors and represents a pragmatic quantitative means of monitoring at least secular changes in the frequency of reporting of serious preventable ADRs.

Removal of additional risk minimisation activities

Not applicable.

V.3 Summary of risk minimisation measures

Table 13: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Serious infections including sepsis	Routine risk minimisation measures: *SmPC section 4.2 where advice is given that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima/Inflectra is indicated.* *SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the package leaflet and the patient reminder card.* *SmPC section 4.4 where a warning is given that patients must be monitored closely for infections including TB before, during and after treatment with infliximab.* *SmPC section 4.4 where warning is given that the suppression of TNF-α may mask symptoms of infection such as fever.* *Severe infections such as sepsis is listed as a contraindication in SmPC section 4.3.* *Serious infections including sepsis is listed as special warnings and precautions for use in SmPC section 4.4.* *Serious infections including sepsis is listed as an adverse reaction in SmPC section 4.8.* *PL section 2 where a warning is given that, tell your doctor if you have an infection or if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common before you are given Remsima/Inflectra.* *Serious infection is listed as contraindication and warning and precautions in PL section 2.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *Patient reminder card.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 SC 4.8*

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important identified risk: BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab	Routine risk minimisation measures: *SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the package leaflet and the patient reminder card.* *SmPC section 4.4 where a warning is given that infants exposed in utero to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth.* *SmPC section 4.6 where guidance is given that administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab in utero is not recommended for 12 months after birth and cases of agranulocytosis have also been reported.* *Agranulocytosis is listed as an adverse reaction in SmPC section 4.8.* *PL section 2 where a warning is given that, talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *Patient reminder card.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*
Important identified risk: Demyelinating disorders	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome.* *SmPC section 4.4 where guidance is given that the in patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 SC 4.8*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Demyelinating disorders is listed as an adverse reaction in SmPC section 4.8. *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	
Important identified risk: Malignancy	Routine risk minimisation measures: *SmPC section 4.4 where warning is given that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.* *Malignancy is listed in SmPC section 4.8.* *PL section 2 where a warning is given that, patients taking Remsima/Inflectra may have an increased risk of developing lymphoma or another cancer. Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Remsima/Inflectra.* *Cancer in children and adults is listed in PL section 4.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 SC 4.8*
Important potential risk: Colon carcinoma/dysplasia (in paediatric ulcerative colitis)	Routine risk minimisation measures (not applicable for SC): *SmPC section 4.4 where a warning is given that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.* *SmPC section 4.4 where guidance is given that this evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that Remsima/Inflectra treatment*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None.*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	influences the risk for developing dysplasia or colon cancer. *Abnormal tissue swelling or growth is listed in PL section 4.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	
Important potential risk: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)	Routine risk minimisation measures: *SmPC Section 4.3 where a contraindication is given for patients with HFI.* *SmPC Section 4.4 where a contraindication is given that Remsima concentrate for solution for infusion should not be administered to patients with HFI, and where a recommendation is given that a detailed history with regards to HFI symptoms has to be taken of each patient prior to receiving Remsima concentrate for solution for infusion, and that, in case of inadvertent administration and suspicion of fructose intolerance, the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.* *PL Section 2 where a contraindication is given that Remsima concentrate for solution for infusion should not be administered to patients with HFI, and where a warning is given that, tell your doctor if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea before you are given Remsima concentrate for solution for infusion.* *Outer packaging Sections 7 where a contraindication is given for patients with HFI.* Additional risk minimisation measures: *Patient reminder card.*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *None*
Missing Information:	Routine risk minimisation measures:	Routine pharmacovigilance activities beyond adverse

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Long term treatment with SC infliximab (SC only)	*Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*	reactions reporting and signal detection: *None.* Additional pharmacovigilance activities: *CT-P13 SC 4.8*

Part VI: Summary of the risk management plan

Summary of risk management plan for Remsima IV/SC and Inflectra IV (Infliximab)

This is a summary of the risk management plan (RMP) for Remsima IV/SC and Inflectra IV. The RMP details important risks of Remsima IV/SC and Inflectra IV, how these risks can be minimised, and how more information will be obtained about Remsima IV/SC and Inflectra IV's risks and uncertainties (missing information).

Remsima IV/SC and Inflectra IV's summary of product characteristics (SmPCs) and its package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how Remsima IV/SC and Inflectra IV should be used.

This summary of the RMP for Remsima IV/SC and Inflectra IV should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is a part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Remsima IV/SC and Inflectra IV’s RMP.

I. The medicine and what it is used for

Remsima/Inflectra IV is authorised in adults with the following diseases:

- Rheumatoid arthritis (RA) (an immune-system disease causing inflammation of the joints). Remsima/Inflectra IV is used with methotrexate (a medicine that acts on the immune system);
- Crohn’s disease (CD) (a disease-causing inflammation of the digestive tract), when the disease is moderate to severe or fistulising (with the formation of fistulae, abnormal passageways between the gut and other organs);
- Ulcerative colitis (UC) (a disease-causing inflammation and ulcers in the lining of the gut);
- Ankylosing spondylitis (AS) (a disease-causing inflammation and pain in the joints of the spine);
- Psoriatic arthritis (PsA) (a disease causing red, scaly patches on the skin and inflammation of the joints);
- Psoriasis (a disease causing red, scaly patches on the skin).

Remsima/Inflectra IV is also used in patients aged between 6 and 17 years with severe, active CD or severely active UC, when they have not responded to or cannot take other medicines or treatments (see SmPC for the full indication). It contains infliximab as the active substance and it is given by intravenous route.

Remsima SC is authorised in adults with the following diseases:

- Rheumatoid arthritis (RA) (an immune-system disease causing inflammation of the joints). Remsima SC is used with methotrexate (a medicine that acts on the immune system);
- Crohn’s disease (CD) (a disease-causing inflammation of the digestive tract), when the disease is moderate to severe or fistulising (with the formation of fistulae, abnormal passageways between the gut and other organs);

- Ulcerative colitis (UC) (a disease-causing inflammation and ulcers in the lining of the gut);
- Ankylosing spondylitis (AS) (a disease-causing inflammation and pain in the joints of the spine);
- Psoriatic arthritis (PsA) (a disease causing red, scaly patches on the skin and inflammation of the joints);
- Psoriasis (Ps) (a disease causing red, scaly patches on the skin).

Further information about the evaluation of Remsima IV/Inflectra IV/Remsima SC's benefits can be found in Remsima IV/Inflectra IV/Remsima SC's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

Remsima

https://www.ema.europa.eu/en/medicines/human/EPAR/remsima

Inflectra

https://www.ema.europa.eu/en/medicines/human/EPAR/inflectra

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Remsima IV/SC and Inflectra IV, together with measures to minimise such risks and the proposed studies for learning more about these risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and HCPs;
- Different packaging for the different formulations (IV and SC)
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In case of Remsima IV/SC and Inflectra IV, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including periodic safety update report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Remsima IV/SC and Inflectra IV is not yet available, it is listed under 'missing information' below.

bII.A List of important risks and missing information

Important risks of Remsima IV/SC and Inflectra IV are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Remsima IV/SC and Inflectra IV. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Serious infections including sepsis • BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab • Demyelinating disorders • Malignancy
Important potential risks	• Colon carcinoma/dysplasia (in paediatric ulcerative colitis) • Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)
Missing information	• Long term treatment with SC infliximab (SC only)

II.B Summary of important risks

Important identified risk: Serious infections including sepsis	
Evidence for linking the risk to the medicine	A United States of America (USA) incidence cohort showed that RA patients were at risk of developing infections compared with non-RA patients. The hazard ratios for objectively confirmed infections, infections requiring hospitalisation and any documented infection in patients with RA were 1.70 (95% confidence interval [CI] 1.42–2.03), 1.83 (95% CI 1.52–2.21), and 1.45 (95% CI 1.29–1.64), respectively, after adjustment for age, sex, smoking status, leukopenia, corticosteroid use, and diabetes mellitus. Since RA patients are treated with immunosuppressive drugs, it is not clear whether this is related to the underlying disease or the treatment. Before the methotrexate and anti-tumour necrosis factor (TNF) era, studies showed a general increase in mortality due to infection in RA patients. RA appears to increase the risk for bacterial, tubercular, fungal, opportunistic, and viral infections, with all infections being more common in more active and severe RA. TNF acts to regulate and enhance appropriate inflammatory, innate and adaptive immune responses to pathogenic organisms and hence inhibition of TNF by Remsima IV/SC and Inflectra IV may suppress these beneficial activities of TNF and increase the potential for serious infections. Sepsis constitutes a systemic response to infection which is characterised by both a pro-inflammatory response mediated by cytokines such as TNF and Interleukins (IL)-l and an anti-inflammatory

Important identified risk: Serious infections including sepsis	
	indicated by the expression of IL-10 and transforming growth factor-β (TGF-β). Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP and hence the strength of the evidence is good.
Risk factors and risk groups	Risk factors for serious infections including sepsis includes immunosuppressive medications (such as transplant recipients), including steroids, treatment with chemotherapy drugs or radiation, splenectomy, longstanding diabetes, acquired immune deficiency syndrome (AIDS), or cirrhosis, large burns or severe trauma and infections such as pneumonia, meningitis, cellulitis, urinary tract infection. Very young people and elderly people are at risk of these infections.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 where advice is given that Remsima/Inflectra treatment is to be initiated and supervised by qualified physicians experienced in the diagnosis and treatment of conditions for which Remsima/Inflectra is indicated.* *SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the PL and the patient reminder card.* *SmPC section 4.4 where a warning is given that the patients must be monitored closely for infections including TB before, during and after treatment with infliximab.* *SmPC section 4.4 where warning is given that the suppression of TNF-α may mask symptoms of infection such as fever. Severe infections such as sepsis is listed as a contraindication in SmPC section 4.3.* *Serious infections including sepsis is listed as special warnings and precautions for use in SmPC section 4.4.* *Serious infections including sepsis is listed as an adverse reaction in SmPC section 4.8.* *PL section 2 where a warning is given that, tell your doctor if you have an infection or if you have ever lived in or travelled to an area where infections called histoplasmosis, coccidioidomycosis, or blastomycosis are common before you are given Remsima/Inflectra.* *Serious infection is listed as contraindication and warning and precautions in PL section 2.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *Patient reminder card.*

Important identified risk: Serious infections including sepsis	
Additional pharmacovigilance activities	*CT-P13 SC 4.8* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk: BCG breakthrough infection and agranulocytosis in infants with *in utero* exposure to infliximab	
Evidence for linking the risk to the medicine	In infants exposed *in utero* to infliximab, fatal outcome due to disseminated Bacillus Calmette-Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP and hence the strength of the evidence is good.
Risk factors and risk groups	Risk factors for Bacillus Calmette–Guérin (BCG) breakthrough infection and agranulocytosis includes administration of live vaccines to infants *in utero* which are at risk of BCG breakthrough infection and agranulocytosis.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.2 where advice is given that patients treated with Remsima/Inflectra should be given the PL and the patient reminder card.* *SmPC section 4.4 where a warning is given that infants exposed in utero to infliximab, fatal outcome due to disseminated BCG infection has been reported following administration of BCG vaccine after birth.* *SmPC section 4.6 where guidance is given that administration of live vaccines (e.g. BCG vaccine) to infants exposed to infliximab in utero is not recommended for 12 months after birth and cases of agranulocytosis have also been reported.* *Agranulocytosis is listed as an adverse reaction in SmPC section 4.8.* *PL section 2 where a warning is given that, talk to your doctor if you have recently received or are scheduled to receive treatment with a therapeutic infectious agent (such as BCG instillation used for the treatment of cancer).* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *Patient reminder card.*
Additional pharmacovigilance activities	*None*

Important identified risk: Demyelinating disorders	
Evidence for linking the risk to the medicine	Demyelinating disorders were identified as a class effect on review of the post-marketing data for all TNF inhibitors. After demyelinating disorders were identified as a risk, subjects with a history of demyelinating disorders were excluded from clinical trials. The role that

Important identified risk: Demyelinating disorders	
	TNF plays as an immunomodulator suggests that TNF blockade may promote the development of drug-induced neuropathies by augmenting the number of activated peripheral T cells and thereby enhance autoimmune responses by altering antigen presenting cell function, potentiating T –cell receptor signalling, and/or decreasing apoptosis of autoreactive T cells. These autoreactive T cells might also drive the maturation of B cells into cells secreting autoantibodies to neuronal-specific antigens. A recent report in a murine model of experimental autoimmune encephalomyelitis suggests that membrane TNF is neuroprotective. Since TNF inhibitors can neutralise both soluble and membrane TNF, they may remove the neuroprotection provided by membrane TNF. Remsima IV and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP and hence the strength of the evidence is good.
Risk factors and risk groups	Patients with a history of demyelinating disorders, or a family history
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where a warning is given that use of TNF-blocking agents, including infliximab, has been associated with cases of new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis, and peripheral demyelinating disorders, including Guillain-Barré syndrome.* *SmPC section 4.4 where guidance is given that the in patients with pre-existing or recent onset of demyelinating disorders, the benefits and risks of anti-TNF treatment should be carefully considered before initiation of infliximab therapy. Discontinuation of infliximab should be considered if these disorders develop.* *Demyelinating disorders is listed as an adverse reaction in SmPC section 4.8.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	*CT-P13 SC 4.8* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risks: Malignancy	
Evidence for linking the risk to the medicine	According to the Remsima IV/SC and Inflectra IV SmPC, malignancies (some fatal) have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents (initiation of therapy ≤18 years of age), including infliximab in the

Important identified risks: Malignancy	
	post-marketing setting. A risk for the development of malignancies in patients treated with TNF-blockers cannot be excluded. In clinical studies with infliximab in which 5,780 patients were treated, representing 5,494 patient years, 26 non-lymphoma malignancies were detected as compared with 1 non-lymphoma malignancy in 1,600 placebo-treated patients representing 941 patient years. In long-term safety follow-up of clinical studies with infliximab of up to 5 years, representing 6,234 patients-years (3,210 patients), 38 cases of non-lymphoma malignancies were reported. TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines. Low doses of TNF can increase tumour blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumour cells. Therefore, the neutralisation of TNF by infliximab may allow some types of tumour cells to survive. Remsima IV/SC and Inflectra IV is a biosimilar medicinal product and Remsima SC has the same INN. The reference product for Remsima IV and Inflectra IV is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP and hence the strength of the evidence is good.
Risk factors and risk groups	Risk factor of malignancy in patients includes history of malignancy, immunosuppressant therapy, HIV infection. Additionally, phototherapy for psoriasis increases the risk of skin cancer. Moreover, UC is associated with a higher risk of colon cancer.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where warning is given that there is an increased background risk for lymphoma and leukaemia in RA patients with long-standing, highly active, inflammatory disease, which complicates risk estimation.* *Malignancy is listed in SmPC section 4.8.* *PL section 2 where a warning is given that, Patients taking Remsima/Inflectra may have an increased risk of developing lymphoma or another cancer. Tell your doctor if you have or have ever had lymphoma (a type of blood cancer) or any other cancer before you are given Remsima/Inflectra.* *Cancer in children and adults is listed in PL section 4.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	*CT-P13 SC 4.8* See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risks: Colon carcinoma/dysplasia (in paediatric ulcerative colitis)	
Evidence for linking the risk to the medicine	In a review of published studies concerning the risk of colon carcinoma in UC patients. The crude annual incidence rate of colon carcinoma in UC patients ranges from approximately 0.006 to 0.16%. It is assumed that the more widespread use of maintenance therapy for UC and surveillance colonoscopy are the causes of the risk decrease. TNF has been shown to exert cytotoxic and/or cytostatic effects on a number of human and murine tumour cell lines. Low doses of TNF can increase tumour blood vessel permeability, thus augmenting tissue concentrations of chemotherapeutic agents, as well as enhance the cytolytic effect of NK and CD8+ T cell killing of immunogenic tumour cells. Therefore, the neutralisation of TNF by infliximab may allow some types of tumour cells to survive. Remsima/Inflectra IV is a biosimilar medicinal product. The reference product is Remicade. The evidence of the above-mentioned risk is derived from Remicade RMP and hence the strength of the evidence is good.
Risk factors and risk groups	Patient with UC who have a history of previous colonic malignancy are at risk, as are patients with longstanding disease.
Risk minimisation measures	Routine risk minimisation measures (Not applicable for SC): *SmPC section 4.4 where a warning is given that all patients with UC who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing UC or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course.* *SmPC section 4.4 where guidance is given that this evaluation should include colonoscopy and biopsies per local recommendations. Current data do not indicate that Remsima/Inflectra treatment influences the risk for developing dysplasia or colon cancer.* *Abnormal tissue swelling or growth is listed in PL section 4.* *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	*None*

Important potential risks: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)	
Evidence for linking the risk to the medicine	This important potential risk is based on the known effects of parenteral sorbitol-containing medicines to patients with HFI. Although patients with the rare genetic disorder of HFI are expected to avoid such products, there is a concern regarding those who are unaware of their

Important potential risks: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)	
	underlying HFI, are unconscious due to an acute medical condition, or are too young to have been diagnosed (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014). Therefore, Remsima 100mg and 350mg concentrate for solution for infusion, which contains 45mg of sorbitol per 1 mL are contraindicated in patients with HFI (regardless of their age).
Risk factors and risk groups	Patients diagnosed with HFI and patients who may be unaware of their underlying HFI, such as unconscious patients or children too young to be diagnosed (especially under 2 years of age), are considered at risk. The worldwide incidence of HFI is estimated pproximately 1 in 20,000 to 1 in 30,000 live births. The disorder is not apparent until the infant begins feeding on formula, juice, fruits, baby foods, or honey that contain fructose. In young children, a spontaneous aversion to fructose-containing foods may develop, which can delay the recognition or onset of clinical symptoms. This is particularly likely when caregivers accommodate the child's food preferences and avoid focusing fructose-containing products. (European Medicines Agency: Information for the package leaflet regarding fructose and sorbitol used as excipients in medicinal products for human use; EMA/CHMP/460886/2014). In patients with HFI, prolonged or untreated exposure to sorbitol may result in severe metabolic disorders, including failure to thrive and renal or hepatic impairement.
Risk minimisation measures	Routine risk minimisation measures: *SmPC Section 4.3 where a contraindication is given for patients with HFI.* *SmPC Section 4.4 where a contraindication is given that Remsima concentrate for solution for infusion should not be administered to patients with HFI, and where a recommendation is given that a detailed history with regards to HFI symptoms has to be taken of each patient prior to receiving Remsima concentrate for solution for infusion, and that, in case of inadvertent administration and suspicion of fructose intolerance, the infusion has to be stopped immediately, normal glycaemia has to be re-established and organ function has to be stabilized by means of intensive care.* *PL Section 2 where a contraindication is given that Remsima concentrate for solution for infusion should not be administered to patients with HFI, and where a warning is given that, tell your doctor if you (or your child) have HFI or if your child can no longer take sweet foods or drinks because they feel sick, vomit or get unpleasant effects such as bloating, stomach cramps or diarrhoea before you are given Remsima concentrate for solution for infusion.* *Outer packaging Sections 7 where a contraindication is given for patients with HFI.* *Legal status: Medicinal product subject to restricted medical prescription.*

Important potential risks: Serious metabolic harms due to sorbitol exposure in patients with hereditary fructose intolerance (100mg and 350mg concentrate for solution for infusion only)	
	Additional risk minimisation measures: *Patient reminder card.*
Additional pharmacovigilance activities	*None*

Missing information: Long term treatment with SC infliximab (SC only)	
Risk minimisation measures	Routine risk minimisation measures: *Legal status: Medicinal product subject to restricted medical prescription.* Additional risk minimisation measures: *None.*
Additional pharmacovigilance activities	*CT-P13 SC 4.8* See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of Remsima IV/SC and Inflectra IV.

II.C.2 Other studies in post-authorisation development plan

Study CT-P13 SC 4.8: An observational, prospective cohort study to evaluate safety of CT-P13 Subcutaneous in patients with Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis and Psoriasis

Purpose of the study:

Rationale:

To collect further safety information on patients treated with Remsima SC with regard to long-term safety.

Study objectives:

Primary Objective:

To assess the safety of Remsima Subcutaneous (SC) in Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Psoriasis (Ps) patients by evaluation of Adverse events of special interest (AESI)

Secondary Objective:
To evaluate additional safety of Remsima SC in RA, AS, PsA and Ps patients

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

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Follow-up forms

There are no specific adverse event follow up forms for Remsima IV/SC and Inflectra IV.

Annex 6 – Details of proposed additional risk minimisation activities

Approved key messages of the additional risk minimisation measures for Inflectra IV Physician educational material:

- The Summary of Product Characteristics for Inflectra IV (100 mg powder for concentrate for solution for infusion) contains full prescribing information which should be read and understood before prescribing infliximab (Module 1.3.1).

In addition to the Summary of Product Characteristics, following additional risk minimisation activity will be implemented:

- Patient reminder card

Patient reminder card

The patient reminder card contains important safety information that a patient needs to be aware of before and during treatment with Inflectra. This reminder card is helpful to the patient as it highlights the risk of tuberculosis, Bacillus Calmette–Guérin (BCG) breakthrough infection, reactivation of hepatitis B infection and other serious infections. The key messages of patient reminder card have been provided below:

The Contact details of the Inflectra prescriber: <name>; <telephone number>.

Before treatment with Inflectra inform your doctor if you have

- an infection even if it is a very minor one.
- ever had TB, or if you have been in close contact with someone who has had TB.
- hepatitis B or if you know or suspect you are a carrier of the hepatitis B virus.

During treatment with Inflectra inform your doctor

- straight away if you have signs of an infection (Signs include a fever, feeling tired, (persistent) cough, shortness of breath, weight loss, night sweats, diarrhoea, wounds, dental problems, burning when urinating or 'flu-like' signs).
- In case you have received Inflectra while you were pregnant or if you are breast-feeding, it is important that you inform your baby's doctor about it before your baby receives any vaccine. Your baby should not receive a 'live vaccine', such as BCG (used to prevent tuberculosis) within 12 months after birth or while you are breast-feeding, unless your baby's doctor recommends otherwise.

Draft key messages of the additional risk minimisation measures for Remsima IV/SC

Physician educational material:

- The Summary of Product Characteristics for Remsima IV (100 mg powder for concentrate for solution for infusion and 100mg and 350mg concentrate for solution for infusion) and Remsima SC (120 mg solution for injection) contains full prescribing information which should be read and understood before prescribing infliximab (Module 1.3.1).

In addition to the Summary of Product Characteristics, following additional risk minimisation activity will be implemented:

- Patient reminder card

Patient reminder card

The patient reminder card contains important safety information that a patient needs to be aware of before and during treatment with Remsima. This reminder card is helpful to the patient as it highlights the risk of tuberculosis, Bacillus Calmette–Guérin (BCG) breakthrough infection, reactivation of hepatitis B infection, other serious infections and life-threatening risk associated with intravenous administration of Remsima 100mg and 350mg concentrate for solution for infusion in patients with HFI. The key messages of patient reminder card have been provided below:

The Contact details of the Remsima prescriber: <name>; <telephone number>.

Before treatment with Remsima inform your doctor if you have

- an infection even if it is a very minor one.
- ever had TB, or if you have been in close contact with someone who has had TB.
- hepatitis B or if you know or suspect you are a carrier of the hepatitis B virus.
- Hereditary Fructose Intolerance (HFI)

During treatment with Remsima inform your doctor

- straight away if you have signs of an infection (Signs include a fever, feeling tired, (persistent) cough, shortness of breath, weight loss, night sweats, diarrhoea, wounds, dental problems, burning when urinating or 'flu-like' signs).
- In case you have received Remsima while you were pregnant or if you are breast-feeding, it is important that you inform your baby's doctor about it before your baby receives any vaccine. Your baby should not receive a 'live vaccine', such as BCG (used to prevent tuberculosis) within 12 months after birth or while you are breast-feeding, unless your baby's doctor recommends otherwise.

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