Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Infliximab (rmc)

Proprietary Product Name: Remsima, Emisima, Flixceli, Inflectra

Sponsor: Pharmbio Pty Ltd[1]

June 2020

TGA Health Safety Regulation

[1] The sponsorship for the product has changed subsequent to registration. Details are provided in the body of the AusPAR.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ADA	Anti-drug antibodies
ADCC	Antibody dependent cell mediated cytotoxicity
AE	Adverse event
ALT	Alanine aminotransferase
AS	Ankylosing spondylitis
ASAS	Assessment of Spondyloarthritis International Society
AST	Aspartate aminotransferase
AUC_{τ}	Area under concentration time curve over the dosing interval
$AUC_{0-\infty}$	Area under concentration time curve from time zero to infinity
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body mass index
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CD	Crohn's disease
CI	Confidence interval
CL_{ss}	Clearance at steady state
$C_{av,ss}$	Average serum concentration at steady state
$C_{max,ss}$	Maximum serum concentration at steady state
$C_{min,ss}$	Trough plasma level at steady state
CrCL	Creatinine clearance
CRP	C-reactive protein
CS	Corticosteroids

Abbreviation	Meaning
CTCAE	Common Terminology Criteria for Adverse Events
CT-P13	Biosimilar infliximab (rch) (Inflectra)
CV	Coefficient of variation
DAS	Disease Activity Score
DHPL	Dear Healthcare Professional Letter
DMARD	Disease modifying anti-rheumatic drug
eCRF	Electronic Case report form
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicine Agency (EU)
EOS	End-of-study
ESR	Erythrocyte sedimentation ratio
EU	European Union
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBI	Harvey-Bradshaw index
Ig	Immunoglobulin
IGRA	Interferon gamma release assay (a TB blood test)
ITT	Intention-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
LOCF	Last observation carried forward
LPS	Lipopolysaccharide
LPMC	Lamina propria mononuclear cells

Abbreviation	Meaning
MTX	Methotrexate
NK	Natural killer (cells)
NMSCs	Non-melanoma skin cancers
NOAEL	No observable adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
NRS	Numerical Rating Scale
PBRER	Periodic benefit-risk evaluation report
PBMC	Peripheral blood mononuclear cell
PCDAI	Paediatric Crohn's Disease Activity Index
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
PRAC	Pharmacovigilance risk assessment committee (EMA)
PsA	Psoriatic arthritis
PSURs	Periodic safety update reports
PTF	Peak to trough fluctuation ratio
PY	Patient-Years
QOL	Quality of Life
RA	Rheumatoid arthritis
RF	Rheumatoid factor
rmc	Recombinant mouse cells
SAE	Serious adverse event
SCCAI	Simple clinical colitis activity index
SDAI	Simplified Disease Activity Index
SD	Standard deviation
SLE	Systemic lupus erythematosus

Abbreviation	Meaning
SmPC	European Summary of Product Characteristics
SOC	System Organ Class
SSZ	Sulfasalazine
sTNFα	Soluble form of TNFα
$T_{½}$	Half-life
TB	Tuberculosis
TEAE	Treatment emergent adverse event
tmTNFα	Transmembrane TNFα
TNF	Tumour Necrosis Factor
TNFα	Tumour Necrosis Factor alpha
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state

I. Introduction to product submission

Submission details

Type of submission:	An application to register a biosimilar
Decision:	Approved
Date of decision:	5 August 2015
Date of entry onto ARTG	19 August 2015;[2]
Active ingredient:	Infliximab (rmc)
Product names:	Remsima, Emisima, Flixceli, Inflectra;[3]
Sponsor's name and address:	Pharmbio Pty Ltd;[4] 23 Blackwall Rd Woy Woy NSW 2256
Dose form:	Lyophilised powder for Injection and Water for Injections.
Strength:	100mg
Container:	Vial
Pack size:	1
Approved therapeutic use:	*Rheumatoid Arthritis in adults* *Inflectra in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:* *-patients with active disease despite treatment with methotrexate* *-patients with active disease who have not previously received methotrexate.* *Inflectra should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.* *Ankylosing Spondylitis* *Inflectra is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease* *Psoriatic arthritis* *Inflectra is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult*

[2] Not all of the trade names were registered at the same time. Inflectra was entered onto the ARTG on 19 August 2015. Remsima, Emsima and Flixceli were entered onto the ARTG on 27 November 2015.
[3] In most references to the product, only the trade name Inflectra (or CT-P13) will be cited.
[4] The original sponsor at the time of submission was Pharmbio Pty Ltd. Following approval sponsorship was transferred to Hospira Pty Ltd. The current sponsor for Inflectra is Pfizer Australia Pty Ltd; the current sponsor for Remsima, Emisima, and Flixceli is Celltrion Healthcare Australia Pty Ltd.

	patients with active and progressive psoriatic arthritis who have responded inadequately to disease modifying anti-rheumatic drug (DMARD) therapy. *Inflectra may be administered in combination with methotrexate.* *Psoriasis* *Inflectra is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.* *Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)* *Inflectra is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.* *Refractory Fistulising Crohn's Disease* *Inflectra is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.* *Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)* *Inflectra is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.*
Route of administration:	Intravenous infusion (IV)
Dosage:	The dosage is the same as for the innovator product. Please see the Product Information (PI) for details.
ARTG numbers:	217064, 217066, 217063, 217065

Product background

This AusPAR describes the application by Pharmbio Pty Ltd (the sponsor during the TGA evaluation process; please note the current sponsor for Inflectra is Pfizer Australia Pty Ltd and for Remsima, Emisima, and Flixceli is Celltrion Healthcare Australia Pty Ltd); to register CT-P13 (infliximab (rmc)) (with the trade names Remsima, Emisima, Flixceli, and Inflectra) as a biosimilar medicine of infliximab (rmc), for the same indications approved for the innovator product Remicade (the reference medicinal product) as follows:

Rheumatoid Arthritis in adults

> *Inflectra in combination with methotrexate is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:*
>
> > *patients with active disease despite treatment with methotrexate*
> >
> > *patients with active disease who have not previously received methotrexate.*

Inflectra should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis

Inflectra is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease

Psoriatic arthritis

Inflectra is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease modifying anti-rheumatic drug (DMARD) therapy.

Inflectra may be administered in combination with methotrexate.

Psoriasis

Inflectra is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease in Adults and in Children and adolescents 6 to 17 years

Inflectra is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Inflectra is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Inflectra is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional.

The sponsor is applying for the same dosage as Remicade.

The development of CT-P13 has been guided by European Union (EU) requirements, which are adopted by the TGA.

Drug class and therapeutic indication

Infliximab is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity to both soluble and membrane bound forms of human tumour necrosis alpha (TNFα) but not to lymphotoxin (TNFβ). Infliximab inhibits binding of TNFα to its receptors and neutralises the biological activity of TNFα.

The cytokine TNFα is produced mainly by macrophages as well as a broad range of other cell types including lymphoid cells, mast cells, endothelial cells, cardiac myocytes, adipose tissue, fibroblasts and neural tissue. TNFα exhibits a wide spectrum of activity, including coordinating host immune and inflammatory response to infectious, malignant and autoimmune conditions. Initial TNFα expression in response to infection or injury is beneficial, sustained or excessive expression has been identified in several chronic inflammatory disorders including rheumatoid arthritis (RA) and Crohn's disease (CD).

Regulatory status

At the time the TGA considered this application, a similar application had been approved in numerous countries including the European Union, Canada, and Japan. It was also under consideration in numerous countries including New Zealand and US. Table 1 shows the dose form and indications considered in a subset of the countries.

Table 1: Overseas regulatory status

Country	Dose form	Indications	Application status and date
European Union	100 mg/vial powder for solution for infusion for IV administration	Rheumatoid arthritis Adult Crohn's disease Paediatric Crohn's disease Paediatric Ulcerative Colitis Ankylosing spondylitis Psoriatic Arthritis Psoriasis	Approved on 10 September 2013
Canada	100 mg/vial powder for solution for infusion for IV administration	Rheumatoid arthritis Ankylosing spondylitis Psoriatic Arthritis Psoriasis Ulcerative Colitis* Paediatric Ulcerative Colitis* Crohn's disease* Paediatric Crohn's disease*	Approved on 15 January 2014 * approved in all indications in June 2016
US	100 mg/vial powder for solution for infusion for IV administration	Crohn's disease Paediatric Crohn's disease Ulcerative Colitis Paediatric Ulcerative Colitis Rheumatoid arthritis in combination with methotrexate Ankylosing spondylitis Psoriatic Arthritis Plaque Psoriasis	Submitted on 8 August 2014 Approved April 2016

Product Information

The Product Information (PI) approved with the submission, which is described in this AusPAR, can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration time line

The following table captures the key steps and dates for this application.

Table 2: Registration timeline for Submission PM-2013-03247-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	29 November 2013
First round evaluation completed	2 May 2014
Sponsor provides responses on questions raised in first round evaluation	2 July 2014
Second round evaluation completed	5 November 2014
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 November 2014
Sponsor's pre-Advisory Committee response and request for mutual stop clock	14 November 2014
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	6 March 2015
Sponsor's pre-Advisory Committee response	20 March 2015
Advisory Committee meeting	2 April 2015
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice (second round for further advice)	14 May 2015
Sponsor's pre-Advisory Committee response (for second round)	25 May 2015
Advisory Committee meeting	2 June 2015
Registration decision (Outcome)	5 August 2015
Completion of administrative activities and registration on the ARTG	19 August 2015[5]
Number of working days from submission dossier acceptance to registration decision*	253

[5] Not all of the trade names were registered in Australia at the same time. Inflectra was entered onto the ARTG on 19 August 2015. Remsima, Emsima and Flixceli were entered onto the ARTG on 27 November 2015.

II. Quality findings

Drug substance (active ingredient)

The biological activity of Remicade (infliximab (rmc)) is considered representative of the mechanism of action and pharmacological effect of CT-P13. An extensive comparability exercise using, Remicade has been performed.

Infliximab bears the Fc portion of complement activating human immunoglobulin (IgG1) and binds to Fc receptors with different patterns of expression on immune cells including monocytes, macrophages, granulocytes, NK cells, B cells and platelets.

Structure

CT-P13 drug substance is a chimeric human-murine monoclonal IgG1 antibody subclass, and like other IgG subclasses, has a glycoprotein with one N-linked glycosylation site on the Asn300 in the CH2 domain of each heavy chain. The detected oligosaccharides are mostly G0F and G1F structures. Minor species are also detected. Each heavy chain consists of 450 amino acids with 11 cysteine residues and each light chain consists of 214 amino acids with 5 cysteine residues. All cysteine residues in the heavy and light chains are involved in either intra- or inter- disulphide bonding. C terminal lysine variation is also observed.

Manufacture

The drug substance, CT-P13, is produced in murine hybridoma cells by recombinant DNA technology. CT-P13 protein is purified from the clarified cell culture broth through a series of chromatographic and filtration steps.

Physical, chemical and biological properties

CT-P13 drug substance is a colourless to light yellow and slightly opalescent to opalescent solution. It should be free of foreign particles with an approximate pH of 7.2.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use. Appropriate validation data have been submitted in support of the test procedures.

Drug product

Formulation

The sponsor has used the same pharmaceutical form and formulation throughout development, and the proposed CT-P13 drug product formulation is identical to the one, which was clinically qualified and is also the same as the innovator drug product, Remicade.

The infliximab drug product is formulated as a white lyophilised powder in a glass vial with a rubber stopper and a flip off seal. The formulated drug product is composed of; 100 mg of CT-P13, sodium dihydrogen phosphate monohydrate, di-sodium hydrogen phosphate di-hydrate, sucrose and polysorbate 80.

The lyophilisate is reconstituted with 10 mL of sterile water for injection to yield a single dose formulation of 10 mg/mL infliximab at pH 7.2. Each vial is designed to deliver a single dose of 100 mg infliximab.

Manufacture

There is sterile filtration of the final bulk through sterile filters. The following steps take place following the final formulation;

- vial and stopper preparation process (washing, sterilisation and depyrogenation)
- aseptic filling process
- lyophilisation process
- capping and crimping process
- visual inspection
- label and packaging.

Stability

The drug product stability data supports a shelf life of 12 months;[6] when stored at 5 ± 3°C.

In use stability

The stability data support the reconstituted and diluted drug product is stable both in refrigerated and at room temperature for up to 48 hours.

Biopharmaceutics

Biopharmaceutic data are not usually required for this product because the medicine is administered intravenously via infusion. Since this product is being assessed as a biosimilar, a comparability study with the reference product Remicade has been performed, which includes equivalent pharmacokinetic profiles in a clinical study.

Quality summary and conclusions

Summary of evaluation and issues of importance

Inflectra, infliximab (rmc), (CT-P13) has been developed as a biosimilar medical product to the reference product Remicade.

The sponsor has adequately addressed many of the issues that were raised in response in the quality evaluation. Various hold times, process validations, and tightening of product release specifications have been implemented by the sponsor at the request of the TGA. [Information redacted].[7]

However, the overall quality assessment of CT-P13 gives assurance that the product is of a similarly high quality to other monoclonal antibodies. The submitted documentation with regards to chemical, pharmaceutical and biological documentation comply with the relevant guidelines, while the fermentation and purification of the drug substance are well described, adequately controlled and appropriately validated. The physicochemical and biological characteristics of the drug substance have been well characterised using

[6] Since initial approval, the shelf life has been extended to 36 months via post approval variation.
[7] Issues discussed did not impact on the final quality assessment.

appropriate methods and have appropriate in-process controls and specifications to control the process. The manufacturing process of the final drug product has been described and validated to a satisfactory level, while the quality of the finished product is adequately controlled by appropriate test methods, in-process controls and release specifications. Appropriate stability studies have been performed to support the shelf life of the product (12 months).[6]

From a quality aspect, biosimilarity with the reference product Remicade has been sufficiently demonstrated. There are notable observable differences that have been relatively well studied and described, and these differences are noted for the Delegate below. The following table (Table 3) summarises the physicochemical and biological test methods used in the comparability between CT-P13 and Remicade.

Table 3: Comparability between CT-P13 and Remicade

Test Method	Aim of Method	Comparability
Primary structure		
Amino acid analysis	Determination of amino acid composition	No notable difference
Peptide mapping (LC-MS) in combination with MS/MS	Comparison of peptide coverage and chemical modifications	No notable difference
Peptide mapping (HPLC)	Comparison of tryptic peptide map by visual inspection	No notable difference
N-terminal Sequencing	Comparison of N-terminal sequences	No notable difference
C-terminal sequencing	Comparison of C-terminal sequences	No notable difference
Reduced Mass	Comparison of molecular weights by mass spectrometry	No notable difference
Higher order structure		
Disulphide bonds	Comparison of disulphide bond location	No notable difference
Free thiol analysis	Comparison of the amount of free-sulph-hydryl groups	No notable difference
FTIR	Comparison of secondary structures	No notable difference
CD	Comparison of secondary structure	No notable difference
DSC	Comparison of thermal stability and determination of thermal transition temperatures	No notable difference
SEC-HPLC	Comparison of aggregate content and monomeric purity	Possible higher %HMW species in CT-P13 compared to Remicade

Test Method	Aim of Method	Comparability
CE-SDS (reduced/non-reduced)	Comparison of electrophoretic mobility and purity under non-reducing and reducing conditions	Observable increase in monomer IgG compared to Remicade
Charged isoforms		
IEC	Comparison of isoelectric points	No notable difference
IEC-HPLC	Comparison of charged variant distribution	Possible increase in oxidation levels in CT-P13 compared to Remicade
Glycosylation		
Sialic acid analysis	Comparison of sialic acid content	No notable difference
Monosaccharide analysis	Comparison of neutral and amino sugar composition	No notable difference
Oligosaccharide profiling	Comparison of glycosylation pattern	No notable difference
N-linked glycan analysis	Comparison of oligosaccharide structures, attachment sites and distribution	No notable difference
Content		
Protein concentration (UV)	Comparison of protein concentration	Possible higher protein content in CT-P13
Product specific ELISA	Comparison of infliximab DS content	No notable difference
Biological activity		
Binding to various Receptors (SPR and ELISA) FcγRI FcγRIIa FcγRIIb FcγRIIIa FcγRIIIb FcRn hTNFα hTNFβ C1q	Comparison of binding to different receptors using surface plasmon resonance and/or ELISA	Significantly different binding of CT-P13 (102%) to FcγRIIIa compared to Remicade (130%)

Test Method	Aim of Method	Comparability
CDC (complement – dependent cytotoxicity)	Comparison of CDC effect on Jurkat cells by lysis	No notable difference
ADCC (antibody dependent cell-mediated cytotoxicity)	Comparison of ADCC effect on Jurkat cells as target cells and NK cells from healthy donor as effector cells	No notable difference

Conclusions and recommendations

The overall quality of Inflectra infliximab (rmc) is considered acceptable. From a biosimilar perspective, the overall comparability of Inflectra infliximab (rmc) with the reference product Remicade has been suitably demonstrated.

It is recommended that approval for registration of Inflectra infliximab (rmc) be given.

Additional points for the Delegate to consider:

The Delegate was informed that the comparability study that was performed to demonstrate biosimilarity between Inflectra and the reference product Remicade has characterised some small but notable differences between the two products. The evaluator considers it is important for the Delegate to note this when considering the overall decision. This is particularly relevant given that the 'biosimilar medicine' registration pathway allows the proposed indications for the biosimilar product to be identical to that of the already registered reference product, despite the clinical studies for the biosimilar product to have been only performed in one of the indications. In this particular submission, clinical trials for the biosimilar were conducted in a Phase I ankylosing spondylitis (AS) group, and a Phase III rheumatoid arthritis (RA) group, whereas the sponsor is claiming all of the indications for Remicade (RA, AS, PsA, psoriasis, Crohn's disease (CD), refractory fistulising CD, ulcerative colitis (UC)) for the biosimilar product. Considering this claim for common indications, it is important that physicochemical and biological differences between the reference product and biosimilar product that might have different downstream clinical effects, depending on the indication, should be considered from a clinical perspective.

The mechanism of action of infliximab is complex, it is currently widely accepted that neutralisation of soluble TNF (sTNF) and transmembrane TNF (tmTNF) is responsible for the efficacy in RA by preventing TNF from binding to its receptor and mediating downstream cellular functions. However, other mechanisms are likely to be involved in inflammatory bowel diseases that are related to binding to the transmembrane form of TNF and include reverse signalling in addition to Fc related effector functions. The relative contribution of both TNF blocking and Fc mediated effector functions in each indication is not well understood.

A minor difference identified between Inflectra (CT-P13) and Remicade is the affinity of FcγRIIIa binding (CT-P13 = 102% versus Remicade = 130% ($p < 0.0001$). The quality evaluator is unable to make a critical clinical assessment, however the data and justification supplied by the sponsor does support the notion that the difference in FcγRIIIa binding probably does not have a significant impact on the antibody dependent cell mediated cytotoxicity.

III. Nonclinical findings

General comments

The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical program, in terms of the topics covered is adequate according to the EMA Guideline;[8] but some aspects are noted to be inconsistent with the guideline.

EU sourced Remicade was used as the comparator (reference) product in all of the nonclinical studies. Australian sourced Remicade was not used, and the nonclinical component of the dossier contained no information or claim regarding the comparability of the EU and Australian reference product(s).

Pharmacology

Overall comparability of the sponsor's infliximab drug product and (EU sourced) Remicade was demonstrated in a set of in vitro assays that examined:

- binding affinity for human TNFα
- binding to FcγRI, FcγRIIa, FcγRIIIa receptors, to FcRn (neonatal Fc receptor), and to C1q (a subcomponent of complement C1)
- neutralisation of human TNFα in a cell based functional assay; and
- induction of complement dependent cytotoxicity, apoptosis, and antibody dependent cell mediated cytotoxicity.

The range of assays conducted fulfils that recommended in the EU guideline.[8] These experiments were performed in phases using various batches of the sponsor's form of infliximab, including, ultimately, drug product manufactured by the proposed commercial process and at the proposed commercial site. Some statistically significant differences between the Inflectra and Remicade forms were seen in some of the binding experiments, but any differences were small in magnitude, not consistently seen across studies and not confirmed in functional assays.

Like Remicade, the sponsor's form of infliximab did not show affinity for human TNFβ or TNFα from mouse, rat, dog, pig or rhesus monkey, and showed very limited and equivalent cross reactivity across a panel of 40 human tissues.

No in vivo pharmacological comparability study was submitted. This is considered acceptable given the findings from the in vitro studies.

Pharmacokinetics

Toxicokinetic data in rats showed lower systemic exposure (by approximately 20% on average) following IV administration of the Inflectra compared to Remicade. The sponsor argues that this result appears to have been due to the sparse sampling regimen employed (just six time points over a week), but given that the same sampling regimen was used and that there was only a single instance out of 48 (six time points, two occasions, two dose levels, two sexes) when the mean serum concentration in the Inflectra group exceeded that in the analogous Remicade group, it seems more likely that the difference is real. Serum maximal concentrations (C_{max}) and areas under the curve (AUC) were both lower

[8] EMA/CHMP/BMWP/403543/2010 EMA Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies: Nonclinical and Clinical Issues

(by 7 to 35%) on both dosing occasions investigated (Day 1 and Day 8), in both sexes and at both dose levels. The difference is not considered to impact the validity of the comparative toxicity studies (such as it is) and in any case, bioequivalence in humans was claimed to have been demonstrated.

Toxicology

Two comparative repeat dose toxicity studies of 2 weeks duration were conducted in rats. These were good laboratory practice (GLP) compliant, and involved administration by the clinical route (IV) once weekly (that is, animals received a total of two doses). They were conducted with drug material not manufactured by the proposed commercial process, although in vitro pharmacology data (and apparently also physicochemical data in the quality dossier) support the material being representative of it. Findings with the two forms of infliximab were comparable in all cases, and comprised transient hypoactivity, reduced body weight gain, slight increases in platelets and reticulocytes, slight changes in serum protein and creatine phosphokinase levels, increased liver weight, and histopathological changes in liver (Kupffer cell hyperplasia) and thymus (increased lymphocyte necrosis) that were always of minimal severity. These findings, including the histopathological changes, were not always consistently observed across studies. The no observable adverse effect level (NOAEL) is considered to be the highest dose studied, 50 mg/kg/week, estimated to yield > 20 times the serum AUC in patients receiving 5 mg/kg Inflectra every 8 weeks (taking into account the different dosing frequency).

It must be noted, however, that these studies are of little predictive value given their short duration and their conduct in a species lacking pharmacodynamic responsiveness to the drug. The sponsor '*considered that repeat dose toxicity studies performed in the rat were relevant to compare the general off-target product toxicity (including immunogenicity) of (the sponsor's drug product) with the reference medicinal product, Remicade*'. This is in conflict with the EMA guideline;[8] which explicitly recommends against toxicity studies in non-relevant species, including to assess unspecific toxicity, and also recommends against animal studies conducted to predict immunogenicity in humans (given their general lack of predictivity).

No comparative toxicity study in a relevant species has been submitted, but this type of study is not required under the EMA guideline.[8] Such a study would pose ethical concerns and questions regarding feasibility, as it would need to involve chimpanzees, the only currently identified suitable animal species.

Pregnancy classification

The sponsor has proposed Pregnancy Category C.[9] This matches the existing category for Remicade and is considered appropriate.

Nonclinical summary and conclusions

The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical program is adequate under the relevant EU guideline.

[9] Australian Category C for the use of medicines in pregnancy is defined as*: 'Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details'.*

These studies were conducted using EU sourced Remicade as the reference product. No nonclinical study involving comparability against Australian sourced Remicade was submitted.

Comparability between the form of infliximab in Inflectra (and associated products) and the form of the drug in EU sourced batches of Remicade was shown in terms of pharmacological activity in a comprehensive set of in vitro binding and functional assays.

Two comparative repeat dose toxicity studies were submitted, both involving once weekly IV administration to rats for 2 weeks. Similar findings were seen between the Inflectra and Remicade forms of the drug. However, the short duration of these studies and the fact that the animal species used lacks pharmacodynamic responsiveness to infliximab does not allow a credible establishment of a comparable toxicological profile. Nevertheless, in accordance with the EU guideline on biosimilar monoclonal antibodies, the absence of a properly conducted comparative toxicity study is not considered a deficiency of the application.

The ability of the nonclinical studies to support comparability to Australian Remicade depends on the conclusion of the quality evaluator regarding the identity/comparability of Remicade products across jurisdictions. Provided that EU sourced Remicade is considered to be identical or highly comparable to the Australian product, there are no nonclinical objections to the registration of Inflectra for the proposed indications.

The nonclinical evaluator also made recommendations with regard to the draft PI and the risk management plan (RMP) but these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section.

Introduction

Clinical Rationale

TNFα plays a central role in the molecular and cellular events occurring in the pathogenesis of several autoimmune inflammatory conditions. Elevated concentrations of TNFα have been found in the sera and stools of patients with inflammatory bowel disease, in the joints of those with active RA and PsA, and in the skin lesions of psoriasis. Anti TNF medicines work by neutralising the activity of soluble TNF and preventing its binding to the 2 main TNF receptors. These receptors are expressed on the membrane of monocytes and T lymphocytes, and circulate in the blood in soluble forms. In addition, anti TNF drugs also bind to tmTNF, thus inhibiting its binding on the surface of cells such as T lymphocytes in the bowel wall and synovial macrophages in RA. Transmembrane TNFα plays an important role in the formation of granulomas, which is seen in the pathology of CD. Remicade is approved for use in 7 treatment indications. The central therapeutic effect of Remicade in all these indications is mediated by TNFα blockade.

Guidance

The submission is consistent with the pre-submission guidance given by the TGA. In addition, much of the development program for CT-P13 was pre-approved after discussions with the EMA. When developing the clinical program for CT-P13, the sponsor specifically considered the EU guidelines for clinical trials and biotechnology products. In particular the Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues[8] and

the Guideline on Similar Biological Medicinal Products;[10] were taken into account. Although the planning phase of the clinical development program was completed before the 'Guideline on similar biological medicinal products containing monoclonal antibodies'[11] was published, the clinical trial program is in accordance with the principles of this document. Indication-specific guidelines with respect to RA;[12] and the AS guideline;[13] were also taken into account.

The TGA Delegate has recommended review and consideration of several EU regulatory guidelines pertaining to the submission, all of which have been adopted by the TGA:

- CPMP/EWP/556/95 Rev 1 'Points to Consider on Clinical Investigation of Medicinal Products other than NSAIDS for Treatment of Rheumatoid Arthritis.' Replaces: CPMP/EWP/556/95 (Adopted by TGA February 2001) Effective: 29 January 2007
- EMEA/CHMP/EWP/438/04 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis.' Effective: 5 February 2008
- CPMP/EWP/4891/03 'Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis.' Effective: 23 February 2010
- CHMP/EWP/2454/02 'Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis.' Effective: 28 July 2005 Adopted by the TGA with the following notation: Section 5.2.5 on this guideline suggests that regulatory approval requires a comparison with an active comparator (for example cyclosporine and methotrexate). Placebo controlled studies may also be acceptable in Australia.
- CPMP/EWP/2284/99 Rev 1 'Guideline on the Development of New Medicinal Products for the Treatment of Crohn's Disease.' Replaces: CPMP/EWP/2284/99 (Adopted by TGA on 10 January 2002) Effective: 25 February 2009
- CHMP/EWP/18463/2006 'Guideline on the Development of New Medicinal Products for the Treatment of Ulcerative Colitis.' Effective: 8 April 2009
- CHMP/437/04 (pdf, 109kb) 'Guideline on Similar Biological Medicinal Products.' Effective: 15 June 2006
- EMEA/CHMP/BMWP/14327/2006 'Guideline on Immunogenicity Assessment of Biotechnology Derived Therapeutic Proteins.' Effective: 22 June 2009
- EMEA/CHMP/BMWP/42832/2005 'Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues.' Effective: 29 September 2006
- EMEA/CHMP/BMWP/114720/2009 'Concept Paper on Immunogenicity Assessment of Monoclonal Antibodies Intended for In Vivo Clinical Use.' For information only, effective: 15 July 2009
- EMEA/CHMP/BMWP/632613/2009 'Concept Paper on Development of a Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies.' For information only, effective: 26 March 2010
- CPMP/ICH/2711/99 'Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population.' Effective: 19 April 2001

[10] CHMP/437/04 Guideline on Similar Biological Medicinal Products.
[11] EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies
[12] EMEA/CPMP/EWP/556/95 rev 1 Points to consider on clinical investigation of medicinal products other than non-steroid anti-inflammatory drugs (NSAID) for treatment of RA
[13]CPMP/EWP/4891/03 Guideline on clinical investigation of medicinal products for the treatment of Ankylosing Spondylitis,

- CHMP/EWP/89249/2004 'Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins.' Effective: 6 January 2009
- CPMP/EWP/QWP/1401/98 Rev 1 'Guideline on the Investigation of Bioequivalence.' Replaces: pp. 231 - 244 of Rules 1998 (3C). (Adopted by TGA 12 February 2002) Replaces: CPMP/QWP/EWP/1401/98 (Adopted by TGA 10 April 2002) Effective: 16 June 2011 Adopted by TGA with the following notation: 'While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations. The procedure for abridged applications claiming essential similarity to a reference product (that is, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia.'
- EMEA/CPMP/EWP/2158/99 'Guideline on the Choice of the Non-Inferiority Margin.' Effective: January 2006

In general, the sponsor has adhered to the relevant regulatory guidelines (that is EU developed guidelines adopted by the TGA) in this submission. At various times in this report, the relevant regulatory guideline will be referred to for consideration.

Contents of the clinical dossier

The submission contained the following clinical information:

- 2 clinical pharmacology studies (Studies CT-P13 1.1 and CT-P13 1.2). Both trials provided pharmacokinetic data, and 1 of the studies (Study CT-P13 1.2) contributed pharmacodynamic data.
- 1 pivotal efficacy/safety study (Study CT-P13 3.1) in adult patients with active RA. This study also collected clinical pharmacology data in a subset of treated patients.
- 2 clinical pharmacology studies (listed above) also provided data on efficacy and safety.

  In addition, the sponsor submitted a Clinical Overview, Summary of Biopharmaceutical Studies and associated Analytical Methods, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Pharmacology and literature references.
- The sponsor has also mentioned in this submission 2 additional small studies (Study CT-P13 3.3 (involving 10 Russian patients) and Study B1P13101 (Japanese ethnicity study)), but for both trials only a study protocol synopsis was included in the dossier. In addition, there was no English translation of the Japanese ethnicity trial.

Paediatric data

The submission did not include any paediatric data.

Good clinical practice

All three studies in this submission were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

There were no deficiencies that excluded the results of the submitted PK studies from consideration.

Evaluator's conclusions on pharmacokinetics

The PK of CT-P13 and Remicade were investigated in 3 clinical trials. Study CT-P13 1.1 was specifically designed to evaluate the PK of CT-P13, and to demonstrate equivalence of CT-P13 with Remicade for the co-primary endpoints being area under the plasma-concentration time curve over dosing interval (AUC_τ) and C_{max} at steady state. These co-primary endpoints are appropriate. It was agreed with the EMA to determine PK equivalence between Week 22 (Dose 5) and Week 30 (Dose 6) as it was predicted that the AUC_τ would cover at least 80% of the area under the plasma concentration-time curve from time zero (dosing) extrapolated to infinity ($AUC_{0-\infty}$) during this time period with serum infliximab concentration falling below 10% prior to Dose 5 and returning to below 10% before Dose 6. This was observed to be correct for Study CT-P13 1.1 (refer to Table 4). These assessments are appropriate, given the long half-life of infliximab and the potential for interference by anti-drug antibodies.

Table 4: Pre-dose and C_{max} concentrations of CT-P13 and Remicade from PK Population over dosing interval between Week 22 and Week 30

Time Point	CT-P13	Remicade
Pre-dose concentration at Week 22 (*µg/mL*)	**4.50**	**4.80**
% $C_{max\ ss}$ at week 22	2.93	3.19
$C_{max,ss}$ (µg/mL)	**153.52**	**150.39**
Pre-dose concentration at Week 30 (*µg/mL*)	**5.11**	**3.57**
% $C_{max\ ss}$ at week 22	3.32	2.37

EOI: end of infusion

Furthermore Study CT-P13 1.1 showed that CT-P13 was bioequivalent to the reference product Remicade in terms of AUC_τ and C_{max} at steady state between Weeks 22 and 30 with the 90% CIs of the ratio of geometric means for both area under the concentration versus time curve during a dosage interval (τ) (AUC_τ) and peak plasma concentration at steady state ($C_{max,ss}$) falling within the reference range of 80% to 125% for the entire PK population (which included patients that developed anti-drug antibodies). In addition, bioequivalence was also established in the antibody negative subset of the PK population.

In addition, the results of secondary PK parameters including average plasma concentration at steady state ($C_{av,ss}$), trough plasma concentration at steady state ($C_{min,ss}$), swing, mean residence time (MRT), peak trough fluctuation (PTF), half-life ($T_{½}$), clearance at steady state (CL_{ss}), volume of distribution at steady state (V_{ss}) determined in the CT-P13 group were comparable to those of the Remicade arm. These results are supported by the PK evaluation in RA patients (Study CT-P13 3.1). The analyses of the secondary PK parameters (including C_{max}, C_{min}, $C_{av,ss}$, T_{max}, and PTF) showed that the PK profile of CT-P13 is comparable to Remicade in this patient population as well.

As expected, overall exposure to infliximab was lower in the patients that developed anti-drug antibodies (that were predominantly neutralising), but the effects were comparable across both groups.

The submission does not contain any PK data obtained in children. As such, it is unknown whether or not there any significant PK differences between Remicade and CT-P13 exist, although it would seem unlikely.

The PK assessments involved 2 major indications of use for infliximab (RA and AS) and included patients who were taking concomitant methotrexate (MTX) (Study CT-P13 3.1) and those not on concomitant immunosuppression (Study CT-P13 1.1). The sponsor provided evidence from a literature review that there is no clear difference in the PK of infliximab across its various indications. Therefore, overall, the PK assessments provided are appropriate and the data provided by the sponsor provides sufficient evidence for PK bioequivalence. However, one of the deficiencies of the current PK dataset for CT-P13 is that comparative data has only been obtained over a limited dose range (3 to 5 mg/kg every 8 weeks). The dose of infliximab can be increased up to 10 mg/kg (every 6 to 8 weeks) in patients with CD, and it remains unclear whether PK differences may occur at higher infliximab doses.

Pharmacodynamics

Studies providing pharmacodynamic data

Two of the 3 studies (Studies CT-P13 3.1 and CT-P13 1.2, both enrolling adult subjects with active RA) in this submission contributed pharmacodynamic (PD) data.

Evaluator's conclusions on pharmacodynamics

Data collected for PD assessments were part of the 2 studies (Studies CT-P13 3.1 and CT-P13 1.2) which evaluated the effect of CT-P13 in adult patients with active RA. These trials measured changes from baseline to Weeks 14, 30 and 54 in serum inflammatory markers (CRP and ESR), anti-cyclic citrullinated peptide (CCP) antibody levels, and rheumatoid factor (RF) (IgA, IgG and IgM) titres and compared the results between those treated with CT-P13 to Remicade. Although there was considerable inter-individual variation in the results, the mean PD parameter concentrations in both treatment groups decreased from baseline at each time point measured up to Week 54. There was no evidence of a difference between CT-P13 and Remicade for the mean change from baseline in serum inflammatory markers (CRP and ESR), or RF levels (any Ig class). Statistical analysis indicated a difference (at the 5% level) between the CT-P13 and Remicade treatment groups for the mean change from baseline in anti-CCP antibody levels at Week 30 in Study CT-P13 3.1, but this difference was only observed at a single time point and is not of clinical significance on its own.

In summary, the PD results included in this submission are of limited value when comparing CT-P13 and Remicade for similarity of effect but no overt differences between the 2 formulations of infliximab were observed in adult RA treatment population.

Dosage selection for the pivotal studies

The dose and regimen of infliximab selected for the pivotal and supporting studies was based on the doses used in the Remicade registration trials. This is appropriate rationale for a biosimilar submission.

In all the trials (both indications), the dosing regimen of infliximab involved an initial dose loading phase (at Weeks 0, 2 and 6) followed by a maintenance treatment phase whereby infliximab was administered every 8 weeks. The dosing regimen is consistent with clinical practice and the current approved posology for Remicade.

Efficacy

Studies providing efficacy data; rheumatoid arthritis

Study CT-P13 3.1

Study CT-P13 3.1 was a randomised, double blind, parallel group, comparative equivalence trial. The primary objective of Study CT-P13 3.1 was to demonstrate that CT-P13 was equivalent in terms of efficacy to Remicade up to 30 weeks of treatment as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR 20).[14] The secondary efficacy objective of the trial was to evaluate the comparative efficacy of CT-P13 and Remicade up to Week 54.

Comment: The rationale provided by the sponsor for evaluating this patient group as the pivotal clinical trial population relates to RA being a major treatment indication for infliximab with the largest numbers of potential patients. The choice of this population (that is, patients with active RA that have not responded to MTX) and the inclusion and exclusion criteria reflects those of the pivotal registration trial (ATTRACT) for the originator product Remicade. The other pivotal RA licensing study for infliximab (ASPIRE) also recruited patients with active RA, but was somewhat different in design in that infliximab was given as first line therapy in combination with MTX. A larger treatment effect with infliximab versus control treatment was observed in the ATTRACT trial compared to the ASPIRE trial. Nonetheless, the choice of the patient population examined in Study CT-P13 3.1 was appropriately sensitive to detect a potential treatment difference between CT-P13 and Remicade.

Other efficacy studies

Study CT-P13 1.2

Study CT-P13 1.2 was a supporting trial in this submission. It was a pilot Phase I study that investigated the pharmacology and clinical effects (preliminary efficacy and safety) of CT-P13 compared to Remicade in the treatment of active RA in 19 adult patients in the Philippines.

Evaluator's conclusions on clinical efficacy for rheumatoid arthritis

The pivotal Phase III study in RA patients (Study CT-P13 3.1) was a well-designed trial that recruited an appropriate patient cohort (similar to the pivotal registration trial (the ATTRACT trial), of the originator product), had an appropriate primary endpoint (ACR20 response rate at Week 30, that was agreed to by the EMA and the TGA in pre-submission discussions), was appropriately powered for the stated equivalence margin and applied an appropriate statistical analysis (both intent-to-treat (ITT) and per protocol (PP) analyses). Although the pre-defined equivalence margin of ± 15% is at the upper limit of acceptability, the sponsor justified it. Furthermore, the equivalence margin was discussed prior to submission with the TGA and EMEA.

In the pivotal efficacy study (Study CT-P13 3.1), CT-P13 and Remicade demonstrated similar outcomes for the primary endpoint of the rate of ACR20 response at 30 weeks. This outcome was shown in both the ITT as well as in the PP population. The 95% CI for the treatment difference was within the predefined equivalence margin of - 15% to + 15%,

[14] ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥ 20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥ 20% improvement in 3 of the following 5 assessments - patient's assessment of pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function as measured by the health assessment questionnaire and CRP. ACR 50 and ACR 70 are similarly defined.

thereby supporting the therapeutic equivalence of CT-P13 to the reference product, Remicade (see Table 5).

Table 5: Proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 (Exact Binomial Method): All-randomised and PP populations. Study CT-P13 3.1

Treatment group	n/N' (%)	Estimate of Treatment Difference[1]	95% CI of Treatment Difference[2]
All-randomised Population			
CT-P13	184/302 (60.9)	0.02	(-0.06, 0.10)
Remicade®	178/304 (58.6)		
PP Population			
CT-P13	180/246 (73.2)	0.04	(-0.04, 0.12)
Remicade®	174/250 (69.6)		

Source: CSR CT-P13 3.1, Table 11-3, Post-text Table 14.2.2.1

Note: N'=the number of subjects with an assessment, n=the number of subjects with the event, (%)=n/N'*100.

[1] Estimate of the difference in proportions between the 2 treatment groups (CT-P13 – Remicade®) using the exact binomial test.

[2] Therapeutic equivalence was concluded if the 95% CI for the difference in proportions between the 2 treatment groups was entirely contained within the range -15% to 15%.

Similar efficacy could also be shown for all secondary efficacy endpoints including the individual components of the ACR response, rate of ACR50 and ACR70 response at Weeks 14, 30 and 54, quality of life (QOL) measurements based on the SF-36 questionnaire;[15] as well as the DAS28;[16] and EULAR;[17] response criteria. The median time to the onset of ACR20 response was statistically shorter in CT-P13 group (99 days versus 100 days), but the difference was not clinically meaningful. In addition, the multiplicity of outcome measures that were analysed may have affected this observation.

The comparison of the primary endpoint result (that is, ACR20 response rate at Week 30) of Study CT-P13 3.1 with the ATTRACT Study shows a slightly higher proportion of patients in the CT-P13 (60.9%) and Remicade group (58.6%) achieving clinical response in Study CT-P13 3.1. However, when comparing the results of Study CT-P13 3.1 with the results of other prospective trials, the rates of ACR20 response are within the range reported in published trials involving anti TNF medicines.

Supportive efficacy data from the pilot study (CT-P13 1.2) did not identify any clear differences in the outcomes of patients treated with CT-P13 compared to Remicade, but the overall number of subjects in this study was too small for any definitive conclusions to be drawn.

Overall, the efficacy data provided by the sponsor is sufficient to establish therapeutic equivalence between CT-P13 and Remicade for the indication of adult patients with active RA.

[15] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group.

[16] Disease activity score and DAS28 is a measure of the activity of rheumatoid arthritis. The DAS is based upon treatment decisions of rheumatologists in daily clinical practice.

[17] EULAR (European League against Rheumatism) response criteria are based on the assessment of disease activity using the Disease Activity Score (DAS), a statistically-derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.

Studies providing efficacy data; ankylosing spondylitis

Study CT-P13 1.1

Study CT-P13 1.1 was a randomised, double blind, parallel group Phase I study primarily designed to assess the PK equivalence and safety of multiple doses of CT-P13 (5 mg/kg) with the reference product, Remicade (5 mg/kg) administered by a 2 hour IV infusion per dose in patients with active AS. Efficacy endpoints were a secondary objective of the trial.

Study CT-P13 1.1 did not observe any treatment related differences in efficacy for CT-P13 compared with Remicade. However, this study was powered for demonstration of PK bioequivalence and not as a non-inferiority efficacy trial. Nonetheless, Study CT-P13 1.1 provides supportive evidence to the assertion of therapeutic equivalence of CT-P13 to Remicade in adult patients with active AS.

Justification for extension of approval to all approved Remicade indications

The Guideline on similar biological medicinal products containing monoclonal antibodies;[11] notes that '*extrapolation of clinical efficacy and safety data to other indications of the reference monoclonal antibody (mAb), not specifically studied during the clinical development of the biosimilar mAb, is possible based on the overall evidence of biosimilarity provided from the comparability exercise and with adequate justification. Applicants should support such extrapolations with a comprehensive discussion of available literature on the involved antigen receptor(s), and mechanism(s) of action*.'

Evaluator's conclusions on efficacy

The sponsor has provided substantial evidence from nonclinical studies (not assessed as part of this report) that show similarity in structure for CT-P13 compared to Remicade, as well as the comparable binding of CT-P13 and Remicade to soluble and transmembrane TNF.

The efficacy data provide in patients with AS (Study CT-P13 1.1) provides supportive evidence to suggest similar responses for CT-P13 and Remicade, but the trial was not designed as a powered non-inferiority study. Nonetheless, the sponsor's submission provides a compelling argument, based on the nonclinical findings of CT-P13 structure and function, in conjunction with bioequivalence data from PK studies and a single Phase III efficacy study in RA (Study CT-P13 3.1) that CT-P13 and Remicade are therapeutically equivalent. Extrapolation of the PK and efficacy data generated in the 3 trials in this submission which examined adult patients with RA and AS to other approved indications for Remicade such as active CD is justifiable on the basis of the results of the extensive pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the infliximab molecule) supported by the evidence that AS and CD share similar and overlapping pathophysiological immunological mechanisms and clinical features.

The extent and type of data submitted to justify approval of CT-P13 is in keeping with the guideline on similar biological medicinal products containing monoclonal antibodies.[11] Therefore, the evaluator concurs with the sponsor that there is sufficient evidence to approve CT-P13 for all indications that Remicade is currently approved for in Australia. This recommendation is consistent with the recent decision of the EMA (and a number of other jurisdictions worldwide).

Safety

Studies providing safety data

All 3 studies included in this submission provided safety data. In all 3 clinical trials, the safety population consisted of all patients who received at least 1 (full or partial) dose of either of the study treatments during any dosing period. In total, the safety population includes 439 patients who received at least 1 (full or partial) infusion of CT-P13. This is considered a sufficient number of patients obtaining several cycles of therapy in line with the EMA guideline.[12]

Evaluator's conclusions on safety

The safety profile of TNF inhibitors, including infliximab, is well characterised in the published literature.[18,19,20,21,22,23,24]

In this submission for the registration of CT-P13, the safety population consisted of 871 patients who were treated with at least 1 dose (full or partial) CT-P13 or Remicade during any dosing period. Of these patients, 621 were adult subjects with active RA (311 of whom received treatment with CT-P13, and 310 were given Remicade). In addition, 250 adult patients with active AS were evaluated in Study CT-P13 1.1 (128 treated with CT-P13, and 122 received Remicade). Overall, 242 patients with RA and 106 patients with AS have been exposed to CT-P13 for 54 weeks. The size of the safety population, and the duration of exposure to CT-P13 are acceptable, and are in keeping with EMA guidelines;[12] for presenting a safety population of sufficient size and follow-up duration to assess for possible registration.

The most frequently reported drug related treatment emergent adverse events (TEAEs) (experienced by ≥ 3% of patients) were mainly in the SOCs of infection and abnormal investigations (for example raised liver enzymes, haematological abnormalities). The frequency and severity of drug related TEAEs in all 3 studies was generally comparable between CT-P13 and Remicade. The same pattern of most commonly reported TEAEs was observed in both the RA and AS patient populations.

Given the mechanism of action of infliximab, infection is an adverse event of special interest. The overall number of TEAEs due to infections was comparable between the treatment groups receiving either formulation of infliximab. However, when the safety results (up to Week 54) of the 3 studies are combined there is a higher number of serious infections in the CT-P13 treated subjects versus those who received Remicade. In total, 18 serious infections were reported across all studies in 16 patients treated with CT-P13 compared with 12 serious infections in 10 patients treated with Remicade. In particular, these serious infections included 5 cases of pneumonia in patients treated with CT-P13 versus no reports in those receiving Remicade. In addition, a total of 7 cases of active

[18] Askling J, et al Haematopoietic malignancies in rheumatoid arthritis: lymphoma risk and characteristics after exposure to tumour necrosis factor antagonists. *Ann Rheum Dis* 2005; 64:1414-1420.
[19] Bathon J M et al A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *New Eng J Med* 2000; 343: 1586-1593.
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[21] Steenholdt C, et al. Severe infusion reactions to infliximab: aetiology, immunogenicity and risk factors in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2011; 34:51-58.
[22] Wiens A, et al. A meta-analysis of the efficacy and safety of using infliximab for the treatment of rheumatoid arthritis. *Clin Rheumatol* 2009; 28:1365-1373.
[23] Winthrop k L et al Nontuberculous Mycobacteria Infections and Anti–Tumor Necrosis Factor-α Therapy Emerg Infect Dis 2009; 15:1556-1561.
[24] Wolfe F, Michaud K. The effect of methotrexate and anti-tumor necrosis factor therapy on the risk of lymphoma in rheumatoid arthritis in 19,562 patients during 89,710 person-years of observation. *Arthritis Rheum* 2007; 56:1433-1439.

tuberculosis (TB) (including 3 cases of disseminated TB) occurred in patients treated with CT-P13 (1.6% of 437) compared with 1 case (0.2% of 431) in patients treated with Remicade. Infections including disseminated and extra-pulmonary cases of TB have been previously reported with Remicade. Although the overall numbers of events is low and it is difficult to draw a clear conclusion from this observation, the sponsor should provide further clarification on this issue.

Deaths that occurred in the studies conducted with CT-P13 were considered by the investigators to be not related to study medication. The observed drug related, treatment emergent SAEs were similar in RA and AS patients for both treatment groups. The most frequent drug related treatment emergent SAEs in RA and AS patients were infusion related reactions and disseminated TB.

The frequency of RA and AS patients who were discontinued due to drug related TEAEs was similar in both treatment groups. The most frequent drug related TEAEs leading to permanent study treatment discontinuation were infusion related reactions, latent TB, drug hypersensitivity and increased alanine transaminase (ALT).

Reactions related to infusion of study medication occurred in Study CT-P13 3.1 (both treatment groups), and Study CT-P13 1.1 (Remicade group only). None of the SAEs was indicative of delayed hypersensitivity reactions. Drug related infections occurred at a similar rate in patients receiving CT-P13 and Remicade in all 3 studies. However, in Study CT-P 3.1 a higher number of subjects treated with CT-P13 (4 out of 302) were reported to have experienced anaphylactic reactions compared to Remicade (1 out of 300) and the significance of this observation remains unclear.

One case of drug related serious neutropenia and 1 case of serious hepatobiliary events were reported. These cases are consistent with the Australian PI for Remicade and published literature.

In both infliximab treatment groups, single cases of malignancies were reported. However, no lymphoproliferative disorders were reported. This is an identified risk for infliximab that is outlined in the RMP and the proposed Australian PI. Other previously identified safety concerns with infliximab such as heart failure, systemic lupus erythematosus or lupus like syndrome, and demyelinating disorders were not reported in any of the studies in the CT-P13 trial program.

The current safety dataset for CT-P13 is limited to 54 weeks of treatment follow-up and it would be important to continue collecting data beyond this time frame as part of post-marketing pharmacovigilance if approval was granted. Nonetheless, the safety data for Remicade exceeds 10 years of treatment follow-up and it is likely that CT-P13 will demonstrate a similar safety profile over longer term follow-up based on the similar short term safety experience between the 2 formulations of infliximab. In addition, it is likely that both formulations of infliximab will demonstrate a similar safety profile in all of the patient populations for which Remicade is currently approved.

In conclusion, the analysis of AEs reported during treatment with CT-P13 and the reference product Remicade have not revealed any significant differences in the incidence and type of AEs. In addition, no new safety signals have emerged from the submitted dataset to indicate the known risk profile of infliximab has altered.

First round benefit-risk assessment

First round assessment of benefits

The benefits of CT-P13 in the proposed usage are:

- Comparable efficacy response rates to Remicade in improving the symptoms and signs, function and QOL of adult patients with active RA
- Comparable efficacy response rates to Remicade in improving the symptoms and signs, function and QOL of adult patients with active AS
- Provision of an alternative formulation of infliximab to treat various autoimmune inflammatory conditions such as inflammatory arthritis, CD and psoriasis.

First round assessment of risks

The risks of CT-P13 in the proposed usage are:

- Increased risk of infection (serious, opportunistic and tuberculosis) which is comparable to alternative infliximab therapy Remicade
- Increased risk of infusion related reactions, which occurred at a similar frequency to those who received Remicade in the clinical trials
- Safety not established in those with a high risk of infection as these patients were excluded from the trial populations (that is some limitations to external validity)
- In general, safety data in patients with inflammatory arthritis limited to < 54 weeks of follow-up.

First round assessment of benefit-risk balance

The benefit-risk balance of CT-P13 is favourable for the treatment of active RA and AS in adult patients. However, there is no direct data currently available on the risk-balance of CT-P13 beyond 54 weeks of treatment. This submission contains robust data to support the claim that CT-P13 is clinically equivalent to the reference product, Remicade for treating adult patients with active RA and AS. Both conditions are sensitive clinical models for assessing the efficacy and safety profile of infliximab therapy. The sponsor has provided a review of the literature on the role of TNFα in the disorders covered by the therapeutic indications of Remicade and the potential mechanisms of action of the various anti TNF medications.

The mechanism of action of infliximab is complex but the primary mode of action results from direct blocking of TNF receptor mediated biological activities. Infliximab binds to both soluble and tmTNF, thereby blocking its capacity to bind TNF receptors, and hence preventing various pro-inflammatory cellular responses that are recognised to occur in autoimmune conditions ranging from RA to CD and psoriasis. The sponsor has justified the extrapolation of indications for CT-P13 to include those approved for Remicade on the basis of biosimilarity. Extrapolation of the PK, efficacy and safety data generated in the 3 trials in this submission which examined adult patients with RA and AS to other approved indications for Remicade such as active CD is justifiable on the basis of the results of the extensive pre-clinical studies (that is, in vitro and ex vivo comparability data on the functionalities of the infliximab molecule) supported by the evidence that AS and CD share similar and overlapping pathophysiological immunological mechanisms and clinical features.

There is an increased risk of infection (serious, opportunistic and TB) with CT-P13 which is comparable to Remicade. The 3 submitted studies also show a risk of infusion related reactions with infliximab. However, there are some limitations to the current dataset that will require ongoing pharmacovigilance. The efficacy and safety of CT-P13 in patients at a high risk of infection is not established. In addition, there is no information about the safety and efficacy of switching to CT-P13 from Remicade, or vice versa. Furthermore, the current dataset has evaluated CT-P13 use in adult subjects over a limited dose range (3 to 5 mg/kg every 8 weeks), and the submission has not provided any information (clinical or pharmacokinetic) on the use of CT-P13 in children and adolescents or those with inflammatory bowel disease where the dose of infliximab can be increased up to 10 mg/kg every 6 to 8 weeks.

First round recommendation regarding authorisation

The clinical evaluator recommends acceptance of the sponsor's proposed registration of CT-P13 to include all the current treatment indications for Remicade. The current submission provides robust evidence that CT-P13 is therapeutically equivalent to Remicade in improving the signs and symptoms, as well as function and QOL in adult patients with active RA and AS.

The clinical evaluator recommends that approval of the sponsor's proposed registration of CT-P13 be subject to satisfactory response to the questions raised (below), and regular periodic safety update reports.

Clinical questions and second round evaluation of clinical data submitted in response to questions

For questions raised in the first round clinical evaluation and the evaluation of the sponsor's response, please see Section VI: Overall Conclusion and risk/benefit assessment (below).

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to the clinical questions, the benefits of CT-P13 in the proposed usage are unchanged from those identified in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to the clinical questions, the risks of CT-P13 in the proposed usage are unchanged from those identified in the first round assessment of risks. Reassuringly, the sponsor has provided data with longer durations of treatment follow-up (up to 2 years), which do not appear to indicate any new safety concerns (incidence or type) with CT-P13. Furthermore, a limited number of patients who have switched from Remicade to CT-P13 after 1 year of therapy appear to have no additional safety concerns for up to 12 months after switching infliximab formulations.

After consideration of the responses to the clinical questions, the benefit-risk balance of CT-P13, given the proposed usage, is favourable. There is no change to the opinion expressed in the first round assessment of benefit-risk balance.

The clinical evaluator recommends acceptance of the sponsor's proposed registration of CT-P13 to include all of the 6 current treatment indications for Remicade. The current submission provides robust evidence that CT-P13 is therapeutically equivalent to Remicade in improving the signs and symptoms, as well as function and QOL in adult patients with active RA and AS. In terms of safety, the 2 formulations of infliximab appear to be clinically equivalent for the majority of safety concerns; however, the CT-P13 clinical study program does show a higher incidence of active TB and serious pneumonia in patients treated with CT-P13 compared to Remicade, which remains of unclear explanation. Nonetheless, the incidence of these 2 serious infection related events is within historical expectations for infliximab in the target population.

The clinical evaluator recommends that approval of the sponsor's proposed registration be subject to regular periodic safety update reports, the provision by the sponsor to the TGA of the final clinical study reports for the proposed post-marketing studies (as outlined in the updated RMP) and an undertaking to perform a post-marketing study in paediatric patients with inflammatory bowel diseases (collecting PK and clinical data). At present, there is no data for CT-P13 therapy in children and this represents a significant area of missing information (contained within RMP). However, based on the demonstration of biosimilarity between CT-P13 and Remicade, no new specific safety concerns with infliximab use in children and adolescents would be anticipated with CT-P13 compared to Remicade.

In the RMP, the sponsor has stated that it plans to conduct a non-inferiority study in adult patients with CD (Study CT-P13 3.4), which is comparing CT-P13 with Remicade. The clinical evaluator does not recommend the conduct of this trial as a condition of registration in Australia as there is a sufficient volume of safety information in adults. Although there are some minor differences in the safety profile of infliximab between adult patients with inflammatory arthritis compared to those with inflammatory bowel diseases, no new major safety concerns with CT-P13 versus Remicade would be expected. Furthermore, RA and AS are sufficiently sensitive clinical models to allow the extrapolation of biosimilar medicine data to other treatment indications (such as inflammatory bowel diseases), which have similar clinically relevant pathophysiology. Nonetheless, the sponsor should be asked to provide the interim and clinical study reports from Study CT-P13 3.4 in a timely manner to the TGA.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (EU Risk Management Plan Version 4.0 (dated May 2013, Data Lock Point 15 April 2013) and Australian Specific Annex Version (no version given, undated)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns that are shown at Table 6.

Table 6: Ongoing safety concerns provided by the sponsor in their RMP submission

Identified or potential risks or missing information	Description of risk category
Important identified risks	HBV reactivation Congestive heart failure Opportunistic infections Serious infections including sepsis (excluding opportunistic infections and tuberculosis) Tuberculosis Serum sickness (delayed hypersensitivity reactions) Hematologic reactions Systemic lupus erythematosus/Lupus-like syndrome Demyelinating disorders Lymphoma (not HSTCL) Hepatobiliary events Hepatosplenic T cell lymphoma (HSTLC) Intestinal or perianal abscess (in Crohn's disease) Serious infusion reactions during a re-induction regimen following disease flare Sarcoidosis sarcoid-like reactions Paediatric malignancy Leukaemia
Important Potential Risks	Malignancy (excluding lymphoma) Colon carcinoma/dysplasia (in ulcerative colitis) Skin cancer Pregnancy exposure Infusion reaction associated with shortened infusion duration (in RA) Bowel stenosis, stricture, obstruction (in Crohn's disease)
Important missing information	Long-term safety in adult patients with ulcerative colitis, psoriatic arthritis, or psoriasis Long-term safety in children with Crohn's disease and ulcerative colitis Long-term safety in children Safety in very young children (< 6 years) Use of infliximab during lactation Lack of efficacy Hypersensitivity

Pharmacovigilance plan

The sponsor proposes routine and additional pharmacovigilance activities.

The presentation of the submitted EU-RMP document is considered acceptable, but qualified (see Table 8 below).

Annex V does not contain any study protocols, in particular none for the planned studies. A small number of protocols were submitted with the clinical module. The sponsor is advised to submit the missing protocols of the studies listed in Annex V of the RMP.

It is noted that the submitted PI does not match the currently approved PI of the reference product, in particular in the 'dosage and administration' section. This may be related to recent changes to the reference product PI. The sponsor should provide a compelling justification for the discrepancy.

The Australian Specific Annex to the EU-RMP Version 4.0 makes reference to additional risk minimisation activities (such as the patient card and the education programme), but does not provide details to the same extent as the EU-RMP does.

The additional pharmacovigilance activities are summarised in Table 7.

Table 7: Additional pharmacovigilance activities

Additional activity	Assigned safety concern	Estimated planned submission of final data
Study CT-P13 1.2: A randomized, double-blind, parallel-group, Phase 1 study to evaluate the initial pharmacokinetics, efficacy, and safety of CT-P13 compared with Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Philippines)	HBV reactivation Congestive heart failure Opportunistic infections Serious infections Tuberculosis Serum sickness Hematologic reactions SLE/lupus-like syndrome Demyelinating disorders Lymphoma (not HSTCL) Hepatobiliary events HSTCL Sarcoidiosis/sarcoid-like reactions Leukaemia Malignancy (excluding lymphoma) Skin cancer Pregnancy exposure Lack of efficacy Hypersensitivity	September 2013
Study CT-P13 1.3: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 in patients with ankylosing spondylitis who were treated with Infliximab (Remicade or CT-P13) in Study CT-P13 1.1 (Global)	Same as for Study CT-P13 1.2	December 2013
Study CT-P13 3.2: An open-label, single-arm, extension study to demonstrate long-term efficacy and safety of CT-P13 when co-administered with methotrexate in patients with rheumatoid arthritis who were treated with infliximab (Remicade or CT-P13) in Study CT-P13 3.1 (Global)	Same as for Study CT-P13 1.2	December 2013
Study CT-P13 3.3: Phase 3 study to demonstrate equivalence in efficacy and safety of CT-P13 Compared With Remicade when co-administered with methotrexate in patients with active rheumatoid arthritis (Russia)	Same as for Study CT-P13 1.2	August 2014
Study B1P13101: Double-blind, Parallel-group, Comparative study of CT-P13 and Remicade in Treatment of Patients with Rheumatoid Arthritis (Japan)	Same as for Study CT-P13 1.2	September 2013

Additional activity	Assigned safety concern	Estimated planned submission of final data
Study B2P13111 Extension Study of the Phase I/II Clinical Study of CT-P13 in Treatment of Patients with Rheumatoid Arthritis (Japan)	Same as for Study CT-P13 1.2	February 2015
Registry CT-P13 4.2: An Observational, Prospective Cohort Study to Evaluate Safety and Efficacy of Inflectra in Patients with Rheumatoid Arthritis (EU and Korea). Protocol available	Same as for Study CT-P13 1.2 with the following additional; Serious infusion reactions during a re-induction regimen following a disease flare Infusion reaction associated with shortened infusion duration (in RA) Use of infliximab during lactation	May 2026
Post Marketing Surveillance of Inflectra 100 mg (Infliximab) (Monoclonal antibody recombinant DNA product) to Evaluate Safety and Efficacy in Korea.	Same as for Study CT-P13 1.2 with the following additional; Intestinal and perianal abscess (in CD) Serious infusion reactions during a re-induction regimen following a disease flare Colon carcinoma/dysplasia (in UC) Infusion reaction associated with shortened infusion duration (in RA) Bowel stenosis, stricture, obstruction (in CD) Long-term safety in adult patients with ulcerative colitis, psoriatic arthritis, or psoriasis Use of infliximab during lactation	October 2016
British Society for Rheumatology Biologics Register – Rheumatoid Arthritis (BSRBRRA): A longitudinal observational study of patients with rheumatoid arthritis treated with biologic and other new advanced targeted therapies (UK). Protocol available	Same as for Study CT-P13 4.2.	March 2026
Registry CT-P13 4.3: An observational, prospective cohort study to evaluate the safety and efficacy of Inflectra in patients with Crohn's disease (CD), and Ulcerative Colitis (UC) (EU and Korea). Planned	Same as for Study CT-P13 1.2 with the following additional Intestinal and perianal abscess (in CD) Serious infusion reactions during a re-induction regimen following a disease flare Paediatric malignancy Colon carcinoma/dysplasia (in UC) Bowel stenosis, stricture, obstruction (in CD) Long-term safety in adult patients with ulcerative colitis, psoriatic arthritis, or psoriasis Long-term safety in children with Crohn's disease and ulcerative colitis Long-term safety in children	May 2026

Additional activity	Assigned safety concern	Estimated planned submission of final data
	Use of infliximab during lactation	
Study CT-P13 3.4: A Randomized, Double-Blind, Parallel-Group, Phase 1/3 Study to Demonstrate Comparable Efficacy, Pharmacokinetic Profile, and Safety of CT-P13 to Remicade in Patients with Active Crohn's Disease (Global). Planned	Same as for Study CT-P13 1.2 with the following additional: Intestinal and perianal abscess (in CD) Bowel stenosis, stricture, obstruction (in CD)	June 2016
Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT) Long-term Observation of Treatment with Biologics in Rheumatoid Arthritis (Germany). Planned. Protocol available	Same as for Study CT-P13 4.2	March 2026

Risk minimisation activities

The sponsor proposes routine and additional risk minimisation activities.

Although the safety profile of reference medicinal product Remicade, and thus also for Inflectra, is favourable, the sponsor recognises the need to manage risks that may occur during the course of treatment with Inflectra.

Besides the identified risks, heart failure and serious infections (including TB, reactivation of hepatitis B virus (HBV), sepsis and opportunistic infections), all other identified safety concerns will be managed by routine pharmacovigilance activities, labelling (that is, the warnings and information contained within the European Summary of Product Characteristics (SmPC) and package leaflet), which aim to reduce the probability of an adverse reaction occurring or its severity should it occur. The safety database is proposed to be supplemented, along with long term extension study data.

Risk minimisation activities in the form of a patient alert card and educational programmes for health care providers will be made available in printed format and online and reflect those provided for the reference product in the EU. Additionally, the risk minimisation measures will serve to facilitate and encourage the recording of batch number and brand name of products administered to patients to assist in the gathering and assessment of safety information following product switching.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses.

Table 8: Reconciliation of issues outlined in the RMP report

Recommendation in RMP advice document	Sponsor's response (or summary of the response)	RMP evaluator's comment
The sponsor should make the changes to the nonclinical part of the Safety Specification, as recommended by the nonclinical evaluator.	The sponsor will submit a revised RMP accordingly.	It is noted the appropriate changes have been made. This is acceptable.
The sponsor should provide a version number and date for the current and any subsequent ASA documents.	The sponsor will submit a revised ASA and this document will be dated and a version number included for documents control.	It is noted the appropriate changes have been made. This is acceptable.
With regard to the response to consolidated questions raised by the TGA, it appears that only one table has been changed in the EU-RMP and as a result the document now lacks internal consistency (for example in other parts of the EU-RMP and the ASA, the change has not been made). The sponsor should update EU-RMP and the ASA accordingly and supply updated versions.	The sponsor will submit revised RMP and update the ASA accordingly.	It is noted the appropriate changes have been made. This is acceptable.
The proposed Australian educational materials are not attached to the response to consolidated questions raised by the TGA, but the EU educational materials that contain the black triangle symbol. Furthermore, the RMP evaluator was unable to locate the 'patient material' to which the sponsor referred in the response. The sponsor should provide the actual materials to be used as additional risk minimisation items.	The draft Australian educational materials (based on the EU material) will be provided separately.	This is acceptable.
'Skin cancer' should be reclassified and become an important identified risk.	The sponsor has reviewed the Innovator/Reference Product Remicade PI, and noted that safety updates were made in September 2014 and the	It is noted the appropriate changes have been made to the RMP. However, updates

Recommendation in RMP advice document	Sponsor's response (or summary of the response)	RMP evaluator's comment
	proposed biosimilars has been updated accordingly.	have not been made to the ASA.
'Off-label use' should be added an Important Potential Risk.	It is premature to create such a letter at this point in time. The sponsor will work with the TGA after ACPM to develop an appropriate dear health care professional (DHPL) letter if required.	It is noted the appropriate changes have been made to the RMP. However, updates have not been made to the ASA.
'Medication errors' should be added an Important Potential Risk.	It is premature to create such a letter. The sponsor will work with the TGA following post-ACPM to develop an appropriate DHPL if required.	It is noted the appropriate changes have been made to the RMP. However, updates have not been made to the ASA.
In the 'Name of the medicine' section, or in another prominent place at the beginning of the PI document, the PI should include a statement that infliximab (Inflectra) is a biosimilar to infliximab (Remicade) and should not be used interchangeably with other infliximab products (or a statement to that effect).	The sponsor has addressed all requested changes to the PI.	It is noted the appropriate changes have been made. This is acceptable, pending approval by the Delegate.
In the 'Precautions' section, the PI should include a statement that psoriasis patients should be monitored for non-melanoma skin cancers, in particular those exposed to prior prolonged phototherapy treatment (or a statement to that effect).	The sponsor has addressed all requested changes to the PI The proposed PI has been amended as requested to include the additional statement. The proposed text has been made identical to the reference product, which the sponsor notes has also updated this information following a recent safety related change to its PI. Updated marked and clean copies of the proposed PI are provided.	It is noted the appropriate changes have been made. This is acceptable, pending approval by the Delegate.
Legionella infections associated with infliximab have been reported in the	The sponsor disagrees with the insertion of this request. The sponsor's infliximab is a biosimilar of Remicade and the PI is based upon the Australian	

Recommendation in RMP advice document	Sponsor's response (or summary of the response)	RMP evaluator's comment
medical literature;[25] a 2011 FDA safety communication;[26] and the current FDA label for Remicade. It is recommended to the Delegate to consider adding this information to the proposed PI.	reference product PI. It is noted Remicade Australian PI does not include this in their PI. The sponsor provided a response to this recommendation as part of its initial response dated 29 June 2014 as follows: 'The current proposed PI has been prepared in accordance with the innovator PI as required. The requested additional infection is not included in the current Remicade PI and there was no pneumonia caused by bacteria belonging to the genus Legionella in Inflectra study, registry and PMS so far.' This information remains the same at this time. The company has conducted a comprehensive review of the Remicade PI updated in September 2014, and notes that 'Legionella infections' has not been included on the Remicade PI. Post marketing data for Inflectra still have not identified any adverse events reporting pneumonia caused by bacteria belonging to the genus Legionella. The sponsor therefore does not agree with this infection being included only on the proposed Inflectra PI and so this recommendation has not been adopted. If in the future the Remicade PI is amended to include this infection then the proposed PI will be updated to reflect the Australian reference product's PI.'	

[25] Multiple references including: Bodro M et al Legionellosis and biologic therapies. *Respir Med* 2014; 108:1223-1228. Hofmann A et al. Fulminant legionellosis in two patients treated with infliximab for Crohn's disease: case series and literature review. *Can J Gastroenterol* 2009; 23: 829-833.
[26] US Food and Drug Administration (2011). FDA Drug Safety Communication: Drug labels for the Tumor Necrosis Factor-alpha (TNFα) blockers now include warnings about infection with Legionella and Listeria bacteria.

Recommendation in RMP advice document	Sponsor's response (or summary of the response)	RMP evaluator's comment
In the 'adverse events' section, the PI should add 'basal cell carcinoma' and 'squamous cell carcinoma' as adverse events.	The sponsor has addressed all requested changes to the PI. The proposed PI has been amended as requested to include the additional adverse events. These adverse events have been included within the post marketing adverse event tables which is identical to the reference product which the sponsor notes has also updated this information following a recent safety related change to its PI in September 2014. Updated marked and clean copies of the proposed PI are provided.	It is noted the appropriate changes have been made. This is acceptable, pending approval by the Delegate.
The sponsor should add a DHPL as an additional risk minimisation activity. This letter should contain at least the following information: A statement that Inflectra is not interchangeable with other infliximab products; The contraindications of Inflectra; The approved indications of Inflectra; The indications for which other infliximab products are approved and used, but for which Inflectra has no approval, and a statement that Inflectra must not be used for those indications; A statement that Inflectra must be administered by a healthcare professional experienced in the use of this product; A reference to the approved PI document for further safety information.	The sponsor strongly disagrees until a final decision has been made to the approved indications with the provision of a DHPL. It is premature at time to create such a letter when the final decision has not been made. The sponsor will work with the TGA following post-ACPM to develop an appropriate DHCPL if required.'	The requirement for the DHPL is not optional. The sponsor should submit their draft DHPL to the TGA, once informed about the approved indications.
The activity DHPL should be assigned to the relevant ongoing safety concerns	It is premature to create such a letter. The sponsor will work with the TGA following post-	This recommendation is not concerned with the creation

Recommendation in RMP advice document	Sponsor's response (or summary of the response)	RMP evaluator's comment
(including 'off-label use' and 'medication errors').	ACPM to develop an appropriate DHCPL if required.'	of a letter, but with the inclusion of the DHPL additional risk minimisation activity in the ASA.
All existing additional risk minimisation activities should be assigned to the relevant ongoing safety concerns (including 'off-label use' and 'medication errors').	'It is premature to create such a letter. The sponsor will work with the TGA following post-ACPM to develop an appropriate DHCPL if required.'	This recommendation is not concerned with the creation of a letter, but with the inclusion of the DHPL additional risk minimisation activity in the ASA.

Summary of recommendations

1. The ASA should reflect the changes made in the EU-RMP with regard to 'skin cancer', 'off-label use' 'medication errors' (that is reclassification of 'skin cancer' and addition of 'off-label use' 'medication errors').
2. The sponsor should prepare additional risk minimisation activities to the satisfaction of the TGA, including the DHPL. It may acceptable to submit this within 3 months of approval, but before supply to the Australian market.
3. Legionella infections associated with infliximab have been reported in the medical literature, a 2011 FDA safety communication and the current FDA label for Remicade. It is recommended to the Delegate to consider adding this information to the proposed PI.

Suggested wording for conditions of registration

The suggested wording is:

Implement EU Risk Management Plan Version 4.0 (dated May 2014, DLP 15 April 2013) and Australian Specific Annex Version 1.0 (dated 24 November 2014), and any future updates (where TGA approved) as a condition of registration

Provide interim reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan through PSURs/PBRERs

Provide final reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan, once available

Implement Additional Risk Minimisation Activities, within 3 months of approval, where approved by the TGA PSAB, as a condition of registration.

III. Overall conclusion and risk/benefit assessment

The sections below present the Delegates' overview of the submission and request for advice from the Advisory Committee on Prescription Medicines (ACPM).

Timeline

A request for advice from the ACPM was initially sent to the sponsor on 6 November 2014 with the submission planned for the December 2014 ACPM meeting. Following receipt of the document, the sponsor requested a meeting with the TGA to discuss the concerns raised in relation to the inflammatory bowel disease and psoriasis indications. This meeting, on 14 November 2014, was followed by a request from the sponsor for a clock stop and the opportunity to address the matters discussed at the meeting and for the sponsor to respond to the various issues raised by the Delegate and the other clinical units at the TGA. The TGA agreed to this request and the sponsor submitted additional information (in a response referred to as post TGA meeting response) which has been reviewed and was considered in a revised request for ACPM advice detailed below.

The submission was presented to the April 2015 ACPM meeting for advice, and subsequently to the June 2015 ACPM meeting for additional advice.

Delegate's overview and request for advice April 2015 ACPM

This submission covers 7 indications that are normally managed by 3 separate Delegates (from clinical units 1, 3 and 4) at the TGA. Therefore, the request for ACPM advice was composed of three parts and a summary of issues was also provided in each of the three parts.

1. The three rheumatology indications of RA, AS and PsA along with the PI, CMI, are discussed by clinical unit 3 (the Delegate) (presented below).
2. The three inflammatory bowel disease indications; for CD in adults and children, refractory fistulising CD and UC are discussed by clinical unit 1 (see Attachment 2)
3. The psoriasis indication is discussed by clinical unit 4 (see Attachment 2)

Background by the Delegate

The primary issues with this submission for the rheumatology indications and in general is as follows:

1. The first major issue concerns the adequacy of the evidence in RA and AS and the ability to extrapolate this evidence and what is known about the pathophysiology of the diseases in the various indications and the mechanism of action of infliximab to the indications without specific clinical trial data, namely PsA, CD, UC and plaque psoriasis.
2. The second major issue concerns the differences observed in the rates of TB and serious pneumonia between Inflectra and Remicade.
3. The third major issue concerns the ways in which information about the biosimilarity to the reference product should be communicated in the PI, CMI and any educational materials including dear health professional letters (DHPLs).

Quality

The proposed CT-P13 drug product formulation is identical to the one that was used in the clinical trials and is also the same sort of formulation and presentation as used for Remicade. It is formulated as a white lyophilised powder.

The lyophilisate is reconstituted with 10 mL of sterile water for injection to yield a single dose formulation of 10 mg/mL infliximab at pH 7.2. Each vial is designed to deliver a single dose of 100 mg of the drug substance.

The submitted documentation with regard to the chemical, pharmaceutical and biological characteristics comply with the relevant guidelines. The fermentation and the purification of the drug substance are well described, adequately controlled and appropriately validated. The physiochemical and biological characteristics of the drug substance have been well characterised using appropriate methods and have appropriate in process controls and specifications. The manufacturing process of the final drug product has been described and validated to a satisfactory level while the quality of the finished product is adequately controlled by appropriate test methods, in-process controls and release specifications. Appropriate stability studies have been performed to support the shelf life of the product (12 months).[6] Biopharmaceutic data are not required for medicines administered intravenously via infusion. However, since this product was assessed as a biosimilar, various comparability studies have been performed with the reference product, Remicade.

There were a number of testing parameters for which there were observable differences between the reference and testing products, and these parameters are listed below:

- Higher percentage of high molecular weight species in CT-P13 compared with those in Remicade
- CT-P13 has less intact monomer IgG compared with Remicade
- A small, less than 1%, difference between the oxidation levels in CT-P13 and Remicade
- A 4% higher protein content in CT-P13 compared with that in Remicade
- A small detectable difference in glycosylation profile with slightly higher amounts of GOF and GO in CT-P13 compared with Remicade
- The slightly higher amount of mannose in CT-P13 compared to Remicade
- Binding to the receptor FcγRIIIa: 102% for CT-P13 compared with 130% for Remicade.

Higher percentage of high molecular weight species in CT-P13 compared with Remicade

The sponsor provided additional data from analysis of more batches of CT-P13 and Remicade of different ages at the time of testing. The difference in aggregation levels was shown to be smaller in the new data compared with the old. Stability data also demonstrated that the age of the product had no impact on aggregate content. There was also additional data to suggest that the high molecular weight forms present in CT-P13 are similar to those present in Remicade. There was also data from patients with AS and RA which demonstrated no difference in anti-drug antibody (ADA) and neutralising antibody development between the test and the reference products for up to 1 year of treatment.

CT-P13 has less intact monomer IgG compared with remicade

Less intact monomer IgG, mainly due to a higher proportion of non-assembled forms was detected in CT-P13 drug product. The intact IgG content was slightly lower in CT-P13 (95%) compared to EU sourced Remicade (98%). The main fragment was determined to be H2L1 constituting over 50% of all fragments and non-assembled forms in CT-P13. Samples were purified with varying amounts of H2L1 and were shown to have comparable TNFα binding affinity by enzyme-linked immunosorbent assay (ELISA) and in vitro TNFα neutralisation activity. These studies demonstrated that the approximate 3% difference in the amount of H2L1 fragment does not have a detectable effect on Fab- or Fc-related activity. There was also no discernible impact on immunogenicity.

A small, less than 1%, difference between the oxidation levels in CT-P13 and remicade

The less than 1% difference in mean oxidation and mean deamidation levels between CT-P13 and EU sourced Remicade was shown to be statistically significant. However,

under conditions of forced oxidative stress in which the level of oxidation of the methionines approached 20%, no impact was observed on biological activity as determined by a number of highly sensitive in vitro assays.

A 4% higher protein content in CT-P13 compared with that in remicade

The sponsor has addressed the difference in protein content by performing additional tests of 7 batches each of CT-P13 and EU-approved and sourced Remicade. The new analysis indicated that there was no significant difference in the protein concentration and that the original difference could have been attributed to batch-to-batch variation.

A small detectable difference in glycosylation profile with slightly higher amounts of GOF and GO in CT-P13 compared with remicade

The slight difference in afucosylated glycans in two products did not have any discernible impact on immunogenicity following repeated administration using the sensitive assays performed in the clinical study programme. The PK study in AS patients and the therapeutic equivalence study in RA patients showed a broadly equivalent incidence of antibodies against CT-P13 and EU sourced Remicade. The slight difference in oligosaccharide profile did not have an impact on the primary mechanism of action, TNFα neutralisation and tmTNFα binding activities. Nor was it shown to have any effect on the level of binding to NK cells or on antibody-dependent cell-mediated cytotoxicity (ADCC) activity. Degree of afucosylation may have an effect on Fcγ receptor binding. The implications of this with regard to the comparative efficacy of the two products in the inflammatory bowel disease indications, is taken up in greater detail in the review by clinical unit 1 (see Attachment 2).

The slightly higher amount of mannose in CT-P13 compared to remicade

Analysis of additional batches of CT-P13 drug product and Remicade demonstrated that there was no difference in mannose content of the two products.

Binding to the receptor FcγRIIIa: 102% for CT-P13 compared with 130% for remicade

The first point made by the sponsor in the response (to questions raised by TGA) was that the difference in the FcγRIIIa binding affinity was observed in *in vitro* experiments, which were not conducted under physiological conditions. Additional *in vitro* and *ex vivo* investigations into the effects of differences in FcγRIIIa binding affinity were carried out. The difference in FcγRIIIa binding to CTP-13 and Remicade was not apparent in the presence of serum in an ex vivo NK cell model. ADCC was only induced using transfected cells that express artificially high levels of tmTNFα (for example transfected Jurkat cells) that are not representative of naturally derived cells. No differences were observed in ADCC activity when peripheral blood mononuclear cells (PBMCs) or whole blood, were used as effector cells. ADCC was not detectable ex vivo using human cells such as lipopolysaccharide-stimulated (LPS-stimulated) monocytes as target. The sponsor also demonstrated that lamina propria monocytes isolated from inflammatory bowel disease patients express low levels of tmTNFα and would therefore be unlikely to be capable of inducing ADCC activity. This difference in the degree of FcγRIIIa binding between test and reference and the issue of FcγRIIIa polymorphism and the relationship of the latter to ADCC activity all may have implications with regard to being able to extrapolate the clinical trial evidence of efficacy in RA and AS to efficacy in inflammatory bowel disease. The implications of these differences with regard to the comparative efficacy of the two products in the inflammatory bowel disease indications are discussed in greater detail in the review by clinical unit 1 (see Attachment 2).

The sponsor was also asked to provide further information on the proportion of CT-P13's action on TNFα compared with other modes of action such as Fc-mediated effector functions and how this may differ between each of the proposed indications for Inflectra. The sponsor was asked for a specific comment on whether the mechanism of action of

Remicade and that of Inflectra in inflammatory bowel disease are likely to be dissimilar from the mechanism of action of each medicine for the other indications.

The sponsor provided a summary of TNFα functionality, stating firstly that TNFα is a pleiotropic cytokine with numerous biological functions. Transmembrane TNFα, the precursor of the soluble form of TNFα (sTNFα), is expressed on activated macrophages and lymphocytes as well as on a number of other cell types. For example, in the skin mast cells appear to be the predominant source of pre-formed TNFα and it is released upon inflammatory stimulus. Binding of sTNFα to its receptor, results in activation of a range of intracellular signalling pathways. The activation of the latter in turn results in the formation of pro-inflammatory cytokines, tissue damage and cytotoxicity. Binding of TNFα to another receptor can result in apoptosis and to yet another receptor can result in reverse signalling which can have immunosuppressive effects.

The sponsor provided a detailed table summarising the role of TNFα in different diseases and summarising the manner in which infliximab is thought to act in each of those diseases (Table 9).

Table 9: Role of TNFα in disease, genetic association between diseases, infliximab mediated effects and impact of treatment

Indication	Role of TNFα	Genetic Association Between Diseases	Primary Target for Infliximab[1]	Infliximab Mediated Effects	Impact of Infliximab Treatment
RA	**Synovial inflammation:** TNFα → 1) ↑ adhesion mols. + chemokines → influx of leukocytes → 2) ↑ cytokines from activated T cells and MΦ. **Cartilage damage:** 1) cytokine-induced cytokine release. 2) activation of synovial fibroblasts → TNFα and IL-1β → further proinflammatory mediators (IL-1β, IL-6, IL-18 TNFα, vascular endothelial growth factor and matrix-degrading enzymes). **Bone erosion:** differentiation into mature osteoclasts driven by cytokines (TNFα and IL-1)	Genome-wide association (GWAS) studies have shown a genetic overlap of disease pathways between AS, RA, Ps, PsA, CD and UC (Tsui *et al.*, 2014).	sTNFα	- Inhibits cytokine/selectin release - Inhibits osteoclast maturation - Inhibits recruitment of immune cells Inhibits angiogenesis	Reduce levels of Rheumatoid factors and markers of systemic inflammation, attenuate angiogenesis, decrease cytokine (e.g. IL-6, IL-1β, TNFα and VEGF), chemokine and adhesion molecule expression in synovial tissue and fluid, diminish serum levels of cytokines and chemokines, and inhibit damage to cartilage and bone. Decrease the number of macrophages and T cells in synovial tissue of patients with RA (refer to 'Sequence 0000 5.4 smeets-2003').
AS	Along with IL-1, TNFα induces downstream effects in response to proinflammatory cytokines	Genome-wide association (GWAS) studies have shown a genetic overlap of disease pathways between AS, RA, Ps, PsA, CD and UC (Tsui *et al.*, 2014).	sTNFα	- Neutralization of TNFα - Inhibits cytokine/selectin release - Inhibits osteoclast maturation - Inhibits recruitment of immune cells	Robust attenuation of functional and pathological features of the disease is observed when TNFα is blocked Downregulates T cell capacity for production of IFN and TNFα (Zou *et al.*, 2002).
PsA	Joint inflammation and bone erosion caused by similar processes as observed in RA patients.	Genome-wide studies have shown a genetic overlap between PsA, Ps, RA and IBD with some loci implicated in the TNF pathway (Bluett & Barton, 2012)	sTNFα	- Inhibits cytokine/selectin release - Cytokine/selectin release - Osteoclast maturation	Decrease the number of leucocytes (predominantly T cells) in both synovial tissue and psoriatic lesions
Ps	Blocking TNFα signaling significantly reduces T cell numbers in the lesions in the skin of patients which leads to attenuation of disease development	Genome-wide association (GWAS) studies have shown a genetic overlap of disease pathways between AS, RA, Ps, PsA, CD and UC (Tsui *et al.*, 2014).	sTNFα	- Neutralization of TNFα - Inhibits cytokine/selectin release - Inhibits T cell proliferation - Protects from apoptosis of keratinocytes	Decrease the number of leucocytes (predominantly T cells) in psoriatic lesions
CD and UC	Implicated in the chronic inflammation evident in CD and UC patients Damage to epithelial cells via necrosis or apoptosis → loss of epithelial barrier. Inhibitory impact of TNFα on apoptosis of T lymphocytes residing in lamina propria → immunodysregulation and perpetual mucosal inflammation. Proposed as the initiating factor that drives mucosal degradation, ulceration and fistulas (refer to 'Sequence 0000 5.4 di-sabatino-2007').	Shared genetic susceptibility factors (host immune response for example) (Ho *et al.*, 2011)	sTNFα	- Inhibits cytokine release - Inhibits myofibroblast stimulation - Inhibits MMP increase	Binds to tmTNFα, hence affecting the downstream signaling cascade, making it effective in CD and UC patients; results in induction of regulatory macrophages which has been shown to be important in wound healing Exerts both proinflammatory action by blocking tmTNFα binding to its receptors and anti-inflammatory effects through stimulation of reverse signaling pathways.
			tmTNFα	- Reverse signalling inhibits apoptosis and possibly cytokine release - Induction of regulatory macrophages	
			tmTNFα (Fc mediated)	- Induction of regulatory macrophages	

[1] sTNFα = soluble TNFα; tmTNFα = transmembrane TNFα

For the two indications studied in the CT-P13 clinical programme, namely AS and RA, the sponsor asserts that the primary and possible sole mechanism of action of infliximab involves binding to and neutralising of sTNFα. In addition, the primary mechanism of action of other anti-TNFα medicines in other indications for which Remicade is licensed in

Australia that is, psoriasis, PsA, CD and UC, is also considered to involve binding to and neutralising of sTNFα.

In the inflammatory bowel disease indications, which include adult and paediatric CD and UC, binding to tmTNFα is also considered to play a prominent role, particularly through reverse signalling. It is currently unclear and there are conflicting reports in the literature as to whether ADCC plays a role in the therapeutic effect of infliximab or other TNFα antagonists. The role of ADCC and the difference in ADCC activity between the two products, as mentioned earlier, may have implications for being able to assume efficacy of the test product Inflectra in inflammatory bowel disease, on the basis of clinical trial evidence only in RA and AS.

The quality evaluator also reviewed a bridging study that compared EU sourced Remicade to Australian sourced Remicade and concluded that the data demonstrated that Remicade from the two jurisdictions was highly comparable.

Quality conclusions and recommendations

The overall quality of Inflectra, infliximab (rmc) is considered acceptable. From a biosimilar perspective, the overall comparability of Inflectra, infliximab (rmc) with the reference product Remicade has been satisfactorily demonstrated. There are no quality objections to approval.

Nonclinical

The nonclinical dossier contained comparative studies on pharmacology, pharmacokinetics and repeat dose toxicity. The scope of the nonclinical programme was judged to be adequate by the nonclinical evaluator when viewed against the requirements under the relevant EU guideline.

The nonclinical studies were conducted using EU sourced Remicade as the reference product. No nonclinical study involving comparability against Australian sourced Remicade was submitted.

According to the nonclinical evaluation, comparability between the form of infliximab in Inflectra and the form of the drug in EU sourced batches of Remicade was shown in terms of pharmacological activity in a comprehensive set of in vitro binding and functional assays.

Two comparative repeat dose toxicity studies were submitted, both involving once weekly IV administration to rats for 2 weeks. Similar findings were seen between the Inflectra and the Remicade forms of the drug. The nonclinical evaluator did note that both the short duration of these studies and the fact that the animal species used lacks pharmacodynamic responsiveness to infliximab do not permit a credible establishment of a comparative toxicological profile. However, the nonclinical evaluator went on to note that, in accordance with the EU guideline on biosimilar monoclonal antibodies, the absence of a properly conducted comparative toxicity study is not considered a deficiency of the application. The sponsor commented on this in the post TGA meeting response, which was reviewed by the TGA and considered acceptable.

The conclusion of the nonclinical evaluator was that the ability of the nonclinical studies to support comparability of Inflectra to Australian Remicade depends on the conclusion of the quality evaluator regarding the identity/comparability of Remicade products across jurisdictions. The nonclinical evaluator was of the opinion that, provided EU sourced Remicade is considered identical or highly comparable to the Australian product then there would be no nonclinical objections to the registration of Inflectra for the proposed indications. As already noted, the quality evaluator concluded that data from a bridging study did indeed demonstrate that Remicade from the two jurisdictions, EU and Australia, was highly comparable.

The nonclinical evaluator has made recommendations for amendments to the proposed PI and to the nonclinical safety specification of the RMP.

Nonclinical comments on the response to second round issues raised by the TGA

On 21 August 2014, the sponsor was sent an additional request to clarify various mechanistic principles regarding Inflectra and the various proposed indications. Advice was sought from the nonclinical evaluator for rheumatological indications.

In the view of the nonclinical evaluator, the sponsor provided an exhaustive review of all the potential mechanisms of action for infliximab as well as the relative importance of such mechanisms in the various proposed indications.

Potential mechanisms of action

Potential mechanisms of action include:

1. Binding and neutralisation of sTNFα leading to the blocking of:
    - Induction of pro-inflammatory cytokines such as interleukins (IL-1 and IL-6)
    - Enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes
    - Activation of neutrophil and eosinophil functional activity
    - Induction of acute phase reactants such as C-reactive protein (CRP) and other liver proteins as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes, and
    - Induction of apoptosis of tissue cells such as intestinal epithelial cells through the activity of sTNFα on the TNF-R1 receptor.
2. Binding to tmTNFα leading to:
    - Blocking of the interaction of tmTNFα with TNF-R2 (and TNF-R1)
    - Stimulation of reverse signalling pathways;[27] resulting in the suppression of secretion of pro-inflammatory cytokines such as interleukins (IL-1, IL-10 and IL-12) from monocytes, and
    - Stimulation of apoptosis in monocytes and T cells.
3. Fc-dependent effector actions including:
    - Induction of regulatory macrophages, and
    - Activation of ADCC by acting on FcγRIIIa receptors on NK cells.

Relative contribution of various mechanisms of action to RA, AS and PsA

The nonclinical evaluator was of the opinion that:

- There are considerable overlaps between RA, AS and PsA in terms of tissues that are targeted by inflammation and the detrimental effects of TNFα on cartilage, synovium and bone.
- The sponsor had provided thorough, detailed evidence to support the view that TNFα plays a pivotal role in the pathophysiological processes that are characteristic of these three indications and that neutralisation of TNFα is the primary mechanism of action.

[27] Reverse signalling involves TNFα acting as a receptor as well as a ligand. In the receptor role, tmTNFα signals back into the tmTNFα expressing cell (hence the term 'reverse signalling') activating signalling pathways which can lead to numerous effects including cell activation, apoptosis and cytokine suppression, depending on the state of the cell.

- The most compelling evidence is the fact that structurally very different anti-TNFα agents, including those without Fc functionality (certolizumab pegol) or those incapable of reverse signalling (etanercept) are all effective treatments for these indications, suggesting that it is the shared ability of these compounds to neutralise TNFα via Fab-mediated and not Fc-mediated functions which underlines their clinical efficacy.

Relative contribution of various mechanisms to Crohn's disease and ulcerative colitis

Advice was initially sought by clinical unit 1 managing the inflammatory bowel disease indications from their toxicologist. In the opinion of the latter, available evidence indicates that infliximab exerts multiple actions that are not solely due to its ability to recognise and bind with human TNFα. Fc-dependent interactions, such as the recruitment of regulatory macrophages and ADCC have been identified as relevant in inflammatory bowel conditions. Qualitative differences between Inflectra and Remicade were flagged as having the potential to affect FcγRIIIa-dependent mechanisms. The sponsor addressed this by repeating a study comparing binding affinities of Inflectra (CT-P13) and Remicade using NK cells isolated from CD patients with FcγRIIIa-158 polymorphisms. There were no differences in relative binding affinities between CT-P13 and Remicade. LPS-stimulated monocytes as target cells and PBMCs as sources of NK cells did not elicit ADCC cytotoxicity with either Remicade or CT-P13 whereas Jurkat T cells produced a similarly robust reaction with both products. The sponsor did not confirm if the ADCC study was performed using cells with the FcγRIIIa-158V polymorphism, which are more responsive to infliximab and evoke ADCC. Without confirming the allotype of the donors used to perform these experiments, it is difficult to explicitly rule out a role for ADCC elicited by infliximab bound tmTNFα acting on FcγRIII-expressing NK cells, given that some CD patient FcγRIIIa allotypes are more responsive to infliximab than others. Because of these uncertainties, a contributing role for Fc-dependent mechanisms in the actions of infliximab in inflammatory bowel disease indications cannot be explicitly ruled out. These uncertainties may have implications for the ability to extrapolate the clinical trial evidence of efficacy in the rheumatological indications to evidence of efficacy in the inflammatory bowel disease indications. The sponsor has responded to this matter and this has been discussed in more detail below.

Clinical

Clinical evaluator's summary

The clinical evaluator has recommended approval of infliximab for all requested indications by the sponsor. The evaluator advised that the submission provided robust evidence that CT-P13 is therapeutically equivalent to Remicade in improving the signs and symptoms as well as function and quality of life in adult patients with active RA and AS. The evaluator considered that the two formulations of infliximab appear to be clinically equivalent for the majority of safety concerns however there was a higher incidence of active TB and serious pneumonia in patients treated with CT-P13 compared to Remicade that remains of unclear explanation. However, the evaluator considered that the incidence of these two serious infection related events is within historical expectations for infliximab in the target population.

Delegate's review of the clinical information

Pharmacokinetics

Study CT-P13 1.1

This was a randomised, double blind, multicentre, parallel group Phase I study designed to compare the pharmacokinetics and safety of multiple doses of CT-P13 (5 mg/kg) with the reference product, Remicade (5 mg/kg) administered by a 2 hour IV infusion per dose in patients with active AS. It was conducted at 46 sites in 10 countries between December 2010 and July 2012. Patients were randomly assigned in a 1:1 ratio to receive either CT-P13 or Remicade as a single dose of study treatment on the first day of each dosing period. The total duration of the study was up to 68 weeks.

The primary objective of Study CT-P13 1.1 was to demonstrate comparable pharmacokinetics ($AUC_{0-\tau}$ and C_{max}) at steady state (between Weeks 22 and 30) between the test and reference products in patients with active AS. The secondary objectives of the trial were to assess the long-term efficacy, PK and overall safety of CT-P13 in comparison with Remicade up to Week 54.

Study CT-P13 1.1 enrolled a total of 250 subjects (125 in each treatment group). Of these, 223 (113 in the CT-P13 group and 110 in the Remicade group) were included in the PK analysis population. Of these 223 subjects, 158 (81 in the CT-P13 group and 77 in the Remicade group) were included in the anti-drug antibody negative cohort for PK evaluation.

The primary PK results and the results of the bioequivalence evaluation for the entire PK population and the antibody negative PK population cohort were provided. Study CT-P13 1.1 demonstrated that PK parameters were comparable between the two treatment groups and hence supported the bioequivalence of CT-P13 and Remicade on PK grounds. The results were confirmed for the antibody negative population cohort. In the 'post TGA meeting' response, the sponsor provided data on the antibody positive population results which indicated that the result for AUC is outside the normal bioequivalence limits of 80 to 125% however it was within for the C_{max} result. These results are presented below. The sponsor concluded that the result showed no significant difference between CT-P13 and EU approved Remicade however the results are beyond the normal limits and wider than the antibody negative population as also shown below. The results, excluding outliers, were also more varied and are included in Table 12.

Table 10: Primary pharmacokinetic parameters of CT-P13 and Remicade in Study CT-P13 1.1; ADA-positive population; All data

Parameter	Treatment	n	Geometric Mean	Ratio(%) of Geometric Means	95% CI of the Ratio (%)
AUC_{τ}(hr*g/mL)	CT-P13	3	22683.33	108.28	85.25 to 137.54
	Remicade	3	20948.01		
$C_{max, ss}$ (g/mL)	CT-P13	3	131.8	96.96	82.15 to 114.44
	Remicade	3	135.92		

Note: The analysis is based on non-visit-based approach which means to evaluate the incidence of patients who developed antibodies up to and including the Week54 (Dose 9). AUCτ: Area under the curve over a dosing interval, CI: Confidence interval, Cmax,ss: Maximum serum concentration at steady state, n: number of available patients for PK parameter calculation in ADA positive population

Table 11: Bioequivalence evaluation of CT-P13/Remicade: Study CT-P13 1.1; PK (antibody negative) population

Parameter	Treatment	n	Geometric mean	Ratio (%) of Geometric Means	90% CI of Ratio (%)
AUC_τ *(h*µg/mL)*	CT-P13	80	37714.16	101.85	(92.95 – 111.59)
	Remicade	77	37030.17		
$C_{max,ss}$ *(µg/mL)*	CT-P13	81	152.74	103.27	(95.39 – 111.79)
	Remicade	77	147.91		

Table 12: CT-P13 1.1: Secondary pharmacokinetic parameters of infliximab; Anti-drug antibody (ADA) positive population, excluding outlier

Parameter	Treatment	n	Geometric Mean	Ratio (%) of Geometric Means	95%CI of the Ratio (%)
Dose 1 (Week 0)					
C_{max} (µg/mL)	CT-P13	31	141.78	101.16	87.01 - 117.60
	Remicade®	34	140.16		
C_{min} (µg/mL)	CT-P13 5	31	16.72	77.63	47.50 - 126.89
	Remicade®	34	21.53		
T_{max} (h)	CT-P13	31	2.33	103.62	94.49 - 113.63
	Remicade®	34	2.25		
Dose 2 (Week 2)					
C_{max} (µg/mL)	CT-P13	32	160.39	91.55	81.17 - 103.26
	Remicade®	34	175.18		
C_{min} (µg/mL)	CT-P13	31	6.98	79.28	42.58 - 147.59
	Remicade®	34	8.8		
T_{max} (h)	CT-P13	32	2.4	100.01	90.52 - 110.49
	Remicade®	34	2.4		
Dose 3 (Week 6)					
C_{max} (µg/mL)	CT-P13	32	148.3	96.10	83.72 - 110.31
	Remicade®	34	154.32		
C_{min} (µg/mL)	CT-P13	32	1.94	107.02	61.70 - 185.64
	Remicade®	34	1.82		
T_{max} (h)	CT-P13	32	2.42	102.20	92.58 - 112.81
	Remicade®	34	2.36		
Dose 4 (Week 14)					
C_{max} (µg/mL)	CT-P13	32	147.09	102.12	90.11 - 115.73
	Remicade®	34	144.04		
C_{min} (µg/mL)	CT-P13	32	1.04	110.23	70.87 - 171.46
	Remicade®	34	0.95		
T_{max} (h)	CT-P13	32	2.43	100.63	90.51 - 111.87
	Remicade®	34	2.41		
Dose 5 (Week 22)					
$C_{av,\ ss}$ (µg/mL)	CT-P13	31	16.76	107.54	84.36 - 137.08
	Remicade®	34	15.59		
CL_{ss} (mL/hr)	CT-P13	31	16	87.72	69.85 - 110.15
	Remicade®	34	18.25		
$C_{min,\ ss}$ (µg/mL)	CT-P13	29	0.7	88.91	61.77 - 127.97
	Remicade®	34	0.79		
Degree of Fluctuation	CT-P13	29	7.89	91.32	75.46 - 110.51
	Remicade®	34	8.64		
$T_{1/2}$ (hr)	CT-P13	26	195.05	94.72	84.37 - 106.35
	Remicade®	24	205.92		
MRT (hr)	CT-P13	26	209.49	91.37	75.29 - 110.89
	Remicade®	24	229.27		
Swing	CT-P13	29	183.98	108.01	72.45 - 161.03
	Remicade®	34	170.33		
T_{max} (hr)	CT-P13	32	4.01	130.37	86.82 - 195.76
	Remicade®	34	3.08		
V_{ss} (mL)	CT-P13	26	3007.16	86.78	72.24 - 104.24
	Remicade®	24	3465.37		

Table 12: (continued). CT-P13 1.1: Secondary pharmacokinetic parameters of infliximab; Anti-drug antibody (ADA) positive population, excluding outlier

Dose 6 (Week 30)					
C_{max} (µg/mL)	CT-P13	29	127.65	94.22	75.77 - 117.16
	Remicade®	33	135.49		
C_{min} (µg/mL)	CT-P13	28	0.61	88.62	63.71 - 123.26
	Remicade®	33	0.69		
T_{max} (h)	CT-P13	29	2.43	94.25	84.68 - 104.90
	Remicade®	33	2.58		
Dose 7 (Week 38)					
C_{max} (µg/mL)	CT-P13	30	115.77	91.86	73.99 - 114.03
	Remicade®	32	126.03		
C_{min} (µg/mL)	CT-P13	26	0.59	104.15	85.20 - 127.31
	Remicade®	32	0.57		
T_{max} (h)	CT-P13	30	2.5	106.10	95.94 - 117.34
	Remicade®	32	2.36		
Dose 8 (Week 46)					
C_{max} (µg/mL)	CT-P13	27	101.18	78.56	54.84 - 112.53
	Remicade®	31	128.8		
C_{min} (µg/mL)	CT-P13	26	0.71	124.18	80.05 - 192.64
	Remicade®	29	0.57		
T_{max} (h)	CT-P13	27	2.47	100.52	88.93 - 113.62
	Remicade®	31	2.46		
Dose 9 (Week 54)					
C_{max} (µg/mL)	CT-P13	26	111	106.73	73.30 - 155.41
	Remicade®	30	104		
T_{max} (h)	CT-P13	26	2.46	98.16	87.99 - 109.51
	Remicade®	30	2.5		

Note: The analysis is based on non-visit-based approach which means to evaluate the incidence of patients who developed antibodies up to and including the Week54 (Dose 9).
$C_{av,ss}$: Average serum concentration at steady state, CI: Confidence interval, CL_{ss}: Total body clearance at steady state, C_{max}: Maximum serum concentration, C_{min}: Minimum serum concentration, $C_{min,ss}$: Minimum serum concentration at steady state, MRT: Mean residence time, n: number of available patients for PK parameter calculation in ADA positive population, $T_{1/2}$: Terminal elimination half-life, T_{max}: Time to reach maximum serum concentration, V_{ss}: Volume of distribution at steady state

Study CT-P13 3.1

Supportive PK data was collected in the pivotal Phase III study, CT-P13 3.1. This trial assessed, C_{min}, C_{max}, $C_{av,ss}$, PTF (peak to trough fluctuation ratio) and T_{max} in patients with RA. A total of 606 patients were enrolled in the study and 578 of these were included in the PK population, 290 in the CT-P13 group and 288 in the Remicade group. Less than half of all patients in the PK subset (n = 237) remained anti-drug antibody negative, 115 in the CT-P13 group and 122 in the Remicade group. The PK endpoint results at each of Weeks 22, 30 and 54 were similar for the test and reference drug groups with similar results in the anti-drug antibody negative subset. In the post TGA meeting response, the sponsor provided data on the antibody positive population results that indicated similar PK results between CT-P13 and Remicade however, PK was a secondary endpoint and did not include formal bioequivalence assessment. The results excluding outliers are included in Table 13.

Table 13: CT-P13 3.1: Secondary PK parameters of Infliximab; ADA positive population, excluding outlier

Parameter	Treatment	n	Geometric Mean	Ratio (%) of Geometric Means	95%CI of the Ratio (%)
Dose 1 (Week 0)					
C_{max} (µg/mL)	CT-P13	153	87.9	98.53	91.41 - 106.20
	Remicade®	146	89.21		
C_{min} (µg/mL)	CT-P13	153	2.52	102.65	97.95 - 107.57
	Remicade®	146	2.45		
T_{max} (h)	CT-P13	152	14.03	95.89	78.23 - 117.54
	Remicade®	142	14.64		
Dose 2 (Week 2)					
C_{max} (µg/mL)	CT-P13	154	106.92	104.77	97.33 - 112.78
	Remicade®	146	102.05		
C_{min} (µg/mL)	CT-P13	154	2.46	97.42	92.24 - 102.89
	Remicade®	146	2.53		
T_{max} (h)	CT-P13	153	4.29	77.88	58.07 - 104.46
	Remicade®	145	5.5		
Dose 3 (Week 6)					
C_{max} (µg/mL)	CT-P13	152	92.63	102.83	92.22 - 114.65
	Remicade®	145	90.08		
C_{min} (µg/mL)	CT-P13	152	2.4	97.01	90.96 - 103.47
	Remicade®	145	2.48		
T_{max} (h)	CT-P13	152	0.98	115.53	94.37 - 141.44

Table 13 (continued). CT-P13 3.1: Secondary PK parameters of Infliximab; ADA positive population, excluding outlier

Parameter	Treatment	n	Geometric Mean	Ratio (%) of Geometric Means	95%CI of the Ratio (%)
	Remicade®	143	0.85		
Dose 4 (Week 14)					
C_{max} (µg/mL)	CT-P13	153	85.75	105.40	92.70 - 119.84
	Remicade®	143	81.36		
C_{min} (µg/mL)	CT-P13	153	2.55	104.60	98.84 - 110.69
	Remicade®	143	2.43		
T_{max} (h)	CT-P13	151	0.67	98.34	85.08 - 113.67
	Remicade®	138	0.68		
Dose 5 (Week 22)					
C_{max} (µg/mL)	CT-P13	149	86.47	111.40	98.48 - 126.03
	Remicade®	141	77.62		
T_{max} (hr)	CT-P13	149	2.55	103.02	98.39 - 107.88
	Remicade®	141	2.48		
C_{min} (µg/mL)	CT-P13	141	0.61	100.74	86.60 - 117.18
	Remicade®	134	0.61		
$C_{av,ss}$ (µg/mL)	CT-P13	141	44.11	110.61	97.89 - 124.99
	Remicade®	134	39.88		
PTF	CT-P13	141	1.93	100.28	96.11 - 104.64
	Remicade®	134	1.92		
Dose 6 (Week 30)					
C_{max} (µg/mL)	CT-P13	141	75.2	95.48	85.14 - 107.08
	Remicade®	135	78.76		
C_{min} (µg/mL)	CT-P13	141	2.41	100.83	94.46 - 107.63
	Remicade®	135	2.39		
T_{max} (h)	CT-P13	134	0.53	98.64	91.81 - 105.99
	Remicade®	125	0.54		
Dose 7 (Week 38)					
C_{max} (µg/mL)	CT-P13	138	78.21	108.27	94.92 - 123.50
	Remicade®	128	72.24		
C_{min} (µg/mL)	CT-P13	138	2.37	97.46	92.49 - 102.69
	Remicade®	128	2.43		
T_{max} (h)	CT-P13	133	0.54	95.02	83.34 - 108.33
	Remicade®	120	0.57		
Dose 8 (Week 46)					
C_{max} (µg/mL)	CT-P13	131	73.44	105.56	94.08 - 118.45
	Remicade®	119	69.57		
C_{min} (µg/mL)	CT-P13	131	2.37	100.94	96.28 - 105.83
	Remicade®	119	2.35		
T_{max} (h)	CT-P13	128	0.54	91.52	79.87 - 104.87
	Remicade®	116	0.59		
Dose 9 (Week 54)					
C_{max} (µg/mL)	CT-P13	125	69.5	105.44	91.31 - 121.75
	Remicade®	108	65.91		
T_{max} (h)	CT-P13	125	2.37	98.51	93.72 - 103.54
	Remicade®	108	2.41		

Note: The analysis is based on non-visit-based approach which means to evaluate the incidence of patients who developed antibodies up to and including the Week54 (Dose 9).
$C_{av,ss}$: Average serum concentration at steady state, CI: Confidence interval, C_{max}: Maximum serum concentration, C_{min}: Minimum serum concentration, n: number of available patients for PK parameter calculation in ADA positive population, PTF: Peak-to-Trough Fluctuation ratio, T_{max}: Time to reach maximum serum concentration

Study CT-P13 1.2

Study CT-P13 1.2 enrolled a total of 19 subjects (9 in the CT-P13 group and 10 in the Remicade group). It was a pilot Phase I study, which investigated the pharmacology and preliminary efficacy and safety of CT-P13 compared to Remicade in the treatment of active RA in 19 adult patients in the Philippines. Mean C_{max} values and other PK parameters such as C_{av}, C_{trough} and PTF were similar for Doses 1, 2 and 3 between the test and reference

products. Secondary PK parameters including C_{max} and $C_{trough,ss}$ out to 38 weeks were also comparable. There was no formal statistical analysis of results.

PK conclusions

The clinical evaluator was of the view that the test and reference products were comparable in PK characteristics in the populations tested. The sponsor had also provided evidence from a literature review that there was no clear difference in the PK of infliximab across its various indications. Overall, the clinical evaluator was satisfied that PK comparability between test and reference had been demonstrated although they did point out that comparative data in the evaluated PK dataset had only been obtained over a limited dose range (3 to 5 mg/kg every 8 weeks). While the latter is the range for the rheumatological indications and for psoriasis, the dose of infliximab may, in certain cases, be increased to 10 mg/kg every 6 to 8 weeks in the inflammatory bowel disease indications. The sponsor was asked to comment on this in the clinical questions posed after the first round evaluation.

Pharmacodynamics

Data were collected for PD assessments as part of the two studies, Studies CT-P13 3.1 and CT-P13 1.2, which examined the effects of CT-P13, in comparison with Remicade, in adult patients with active RA. These trials measured changes from baseline to Weeks 14, 30 and 54 in serum inflammatory markers (CRP and ESR), anti-CCP antibody levels and RF (IgA, IgG and IgM) titres. Although there was considerable inter individual variation in the results, the mean PD parameter values in both treatment groups decreased from baseline at each time point up to Week 54. There were no overt differences observed between test and reference.

Efficacy rheumatoid arthritis

Study CT-P13 3.1

Study CT-P13 3.1 was a randomised, double blind, parallel group, comparative equivalence trial in female and male patients aged 18 to 75 years with active RA who had not achieved an adequate response with MTX alone. The total duration of the study was up to 68 weeks and consisted of 4 treatment periods, screening phase, dose loading phase (1 dose at each of 0, 2 and 6 weeks), maintenance phase (a further 6 doses every 8 weeks) and end of study (8 weeks after last dose).

Efficacy evaluations were performed at Weeks 14, 30 and 54 (or at end of study if not at Week 54). The primary objective of the study was to demonstrate comparability of efficacy between test and reference up to 30 weeks treatment as determined by ACR 20. The secondary efficacy objective of the trial was to compare the efficacy of test and reference up to Week 54. There were a number of secondary efficacy endpoints.

At baseline, patients were randomly assigned in a 1:1 ratio to receive either CT-P13 or Remicade. Patients were required to continue methotrexate (MTX) use at a dose of 15 to 25 mg/week (oral or parenteral) with dose and route maintained to the end of the study. The primary efficacy analysis was performed on two patient cohorts, all-randomised patients (essentially ITT) and the per-protocol population.

Therapeutic equivalence was to be concluded if the 95% CI for the treatment difference between the proportions in each group achieving ACR 20 at Week 30 was entirely within the range (-15% to 15%). The clinical evaluator explained in some detail the rationale for the choice of the equivalence margin and was of the opinion that the rationale was acceptable but at the maximum acceptable margin. Sample size calculations were deemed appropriate with the final estimate of 584 patients needed for randomisation.

A total of 1077 subjects were screened for the trial, and 606 patients were randomly assigned to study treatment (302 in the CT-P13 group and 304 in the Remicade treatment arm). Two patients in each of the treatment groups did not receive any of their allocated infliximab treatment. The majority of subjects in each treatment group completed the study: 77.2% (233 out of 302) in the CT-P13 arm and 73.0% (222 out of 304) in the Remicade group. The 2 most common reasons for discontinuation were AEs and withdrawal of consent. For patients who discontinued study treatment, the median time on infliximab was similar between the 2 treatment groups (152 days for CT-P13 and 155 days for Remicade).

Demographic characteristics were similar in the 2 treatment groups and were reflective of the population that may receive infliximab in clinical practice. The mean age of patients was 48.8 years (median 50 years). As expected with RA, there was a higher percentage of female patients (82.7%; 501 out of 606) compared with male subjects (17.3%; 105 out of 606). The majority of patients were Caucasian (72.9%; 442 out of 606), and 11.7% (71 out of 606) were of Asian background. The mean BMI (SD) of enrolled patients was 26.37 (5.27) kg/m^2.

As noted by the clinical evaluator, the study report for Study CT-P13 3.1 contained limited information about the baseline RA disease characteristics of the enrolled subjects. In particular, the trial report did not contain information about the duration of RA prior to inclusion, and the type and extent of prior therapy. The baseline doses of MTX doses were consistent with contemporary practice in Australia before consideration of biological DMARD therapy. However, the study report for Study CT-P13 3.1 did not contain sufficient information about the extent and pattern of previous DMARD therapy in the enrolled population and the sponsor was asked to comment on this in the first set of questions.

Results for the primary efficacy outcome

The results of the primary efficacy outcome for the all-randomised (ITT) and PP populations were provided. In the ITT dataset, the proportion of subjects achieving an ACR20 response at Week 30 in the CT-P13 group was 60.9% (184 out of 302), which was similar to that observed in the Remicade arm (58.6%; 178 out of 304).

In both the ITT and PP populations, the 95% CIs of the difference between the 2 groups were within the pre-specified equivalence margins of ± 15% (- 6% to 10% for the ITT population, and - 4% to 12% for the PP cohort), thus concluding therapeutic equivalence.

Other efficacy endpoints

Similar efficacy could also be shown for all secondary efficacy endpoints including the individual components of the ACR response, rate of ACR50 and ACR70 response at Weeks 14, 30 and 54, QOL measurements based on the SF-36 questionnaire;[15] as well as the DAS28;[16] and EULAR;[17] response criteria, however these did not take into account multiplicity effects. The median time to the onset of ACR20 response was statistically shorter in CT-P13 group (99 days versus 110 days), but the difference was not clinically meaningful.

The mean change (decrease) from baseline to Week 54 in the joint damage score was similar in each of the treatment groups. The baseline mean (SD) joint damage score in the CT-P13 group was 104.6 (67.05) units, and the mean joint damage score was 103.6 (67.81) units in the Remicade arm. At 54 Weeks, the mean joint damage score (SD) decreased by 32.5 (26.85) units in the CT-P13 group (n = 182), and the same index decreased by 28.7 (30.66) units in the Remicade arm (n = 174). Normally, to support an indication for the prevention of structural damage, data demonstrating maintenance of effect out to 2 years is required by the TGA (in line with the relevant EU requirements). This issue was addressed later in the submission in response to questions.

Study CT-P13 1.2

Study CT-P13 1.2 was a supporting trial in this submission. It was a pilot Phase I study, which investigated the pharmacology and preliminary efficacy and safety of CT-P13 compared to Remicade in the treatment of active RA in 19 adult patients in the Philippines.

In total, 22 patients were screened for involvement in this study, and 19 were subsequently randomised and received study treatment. Nine patients were randomised to and received CT-P13, 9 patients were randomised to and received Remicade and 1 patient (Patient [information redacted]) was randomised to Remicade but received both CT-P13 and Remicade. At Dose 9 (Week 54), 3 patients had discontinued (2 in the CT-P13 group and 1 in the Remicade group). All of the treatment discontinuations were due to AEs.

Demographic characteristics were similar in the two treatment groups. The median age of patients in the CT-P13 group was 57 years, and the median age of participants in the Remicade arm was 47 years. All but one of the 18 enrolled patients were female. The mean weight of enrolled patients was 57 kg.

At Week 14, the ACR20 response rate in the Remicade group was 88.9% (8 out of 9) compared with 62.5% (5 out of 8) in the CT-P13 arm. At Week 30, the ACR20 response rate was 71.4% (5 out of 7) in the CT-P13 group versus 50.0% (4 out of 8) in the Remicade arm. Given the small overall number of participants in this study, there is insufficient data to conclude whether or not CT-P13 and Remicade are therapeutically equivalent. Overall, there were no clear differences in the outcomes of those patients treated with CT-P13 compared with those treated with Remicade however, the numbers are too small to draw definitive conclusions.

Efficacy ankylosing spondylitis

Study CT-P13 1.1

Study CT-P13 1.1 was a randomised, double blind, parallel group Phase I study primarily designed to assess the PK equivalence and safety of multiple doses of CT-P13 (5 mg/kg) with the reference product, Remicade (5 mg/kg) administered by a 2 hour IV infusion per dose in patients with active AS. Efficacy endpoints formed a secondary objective of the trial.

The subjects included male and female subjects aged 18 to 75 years (inclusive) who had been diagnosed with active AS according to the 1984 modified New York classification criteria[28] for at least 3 months prior to screening.

The efficacy endpoints in Study CT-P13 1.1 were:

- Proportion of patients achieving ASAS20;[29] response
- Proportion of patients achieving ASAS40 response
- Mean change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI);[30]
- Mean change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI)
- Mean change from baseline in Bath Ankylosing Spondylitis Metrology Index (BASMI)

[28] van der Linden S et al Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis and Rheumatism* 1984; 27: 361-368
[29] ASAS20 = improvement of 20% on Assessment of SpondyloArthritis International Society (ASAS) scale
[30] BASDAI consists of a one through 10 scale (one being no problem and 10 being the worst problem) which is used to answer 6 questions pertaining to the 5 major symptoms of AS

- Mean change from baseline in chest expansion.

Patients were randomised to study drug in a 1:1 ratio. A total of 370 patients were screened and 250 patients were randomly assigned to study treatment (125 patients in each treatment group). More than 80% of patients in each of the treatment groups completed 54 weeks of follow-up in the study.

Demographic characteristics were similar in the 2 treatment groups and were reflective of the AS population that may receive infliximab in clinical practice. The mean age of patients was 48.8 years (median 50 years). As expected, the majority of patients were male (80.8%; 202 out of 250) with a median age of 38 years. The majority of patients were White (75.6%; 189 out of 250) and recruited from European centres (69.2%; 173 out of 250). The mean BMI (SD) of enrolled patients was 25.6 (4.25) kg/m^2. Most patients (> 90 %) in each treatment group were receiving anti-inflammatory and anti-rheumatic medicines at baseline.

The mean BASDAI and BASFI scores at baseline were similar for the CT-P13 (6.74 and 6.20, respectively) and Remicade groups (6.57 and 6.24, respectively).

The proportions of patients achieving a clinical response satisfying the ASAS20 and ASAS40 criteria at Weeks 14, 30 and 54 were comparable in the test and reference treatment groups. These results are shown in Table 14.

Table 14. CT-P13 3.1: Proportion of patients achieving clinical response according to the ASAS20 and ASAS40 criteria (Weeks 14, 30 and 54); all-randomised population - CT-PI3 t. t

Visit	Efficacy Parameter	Treatment Group	Responders n/N[3] (%)	Odds Ratio[1]	95% CI of the Odds Ratio
Week 14	ASAS20	CT-P13	72/115 (62.6)	0.91	0.53, 1.54
		Remicade®	79/122 (64.8)		
		Goodness-of-fit test (*P* value 0.819)[2]			
	ASAS40	CT-P13	48/115 (41.7)	0.85	0.51, 1.42
		Remicade®	56/122 (45.9)		
		Goodness-of-fit test (*P* value 0.875)[2]			
Week 30	ASAS20	CT-P13	79/112 (70.5)	0.91	0.51, 1.62
		Remicade®	84/116 (72.4)		
		Goodness-of-fit test (*P* value 0.854)[2]			
	ASAS40	CT-P13	58/112 (51.8)	1.19	0.70, 2.00
		Remicade®	55/116 (47.4)		
		Goodness-of-fit test (*P* value 0. 893)[2]			
Week 54	ASAS20	CT-P13	71/106 (67.0)	0.89	0.50, 1.59
		Remicade®	75/108 (69.4)		
		Goodness-of-fit test (*P* value 0.360)[2]			
	ASAS40	CT-P13	58/106 (54.7)	1.26	0.73, 2.15
		Remicade®	53/108 (41.1)		
		Goodness-of-fit test (*P* value 0.543)[2]			

Justification for extension of approval to all approved Remicade indications

The clinical evaluator discussed the possible mechanisms of action of the class of TNFα inhibitors. The evaluator concludes that extrapolation of the PK and efficacy data generated in the three trials in this submission which examined adult patients with RA and AS to other approved indications for Remicade such as active CD is justifiable on the basis of the results of extensive pre-clinical studies supported by the evidence that AS and CD

share similar and overlapping pathophysiological immunological mechanisms and clinical features.

As noted by the evaluator, initial data at least suggest that the effects of TNFα blockade on synovial inflammation are comparable in the different forms of autoimmune inflammatory arthritis. Furthermore, the similarity of efficacy of the various TNFα antagonists with very different structures in the different indications, particularly the rheumatological indications, does suggest the primacy of TNFα blockade in those different indications. The Delegate agrees that the data in this submission may be extrapolated to PsA. Please see the reviews by clinical units 1 and 4 (Attachment 2) for discussion on the other indications.

Safety

The total safety population in the clinical dossier consisted of 871 patients who were treated with at least 1 dose (full or partial) of either CT-P13 or Remicade during any dosing period. Of these, 621 patients had active RA (311 treated with CT-P13, and 309 received Remicade). A total of 250 patients with acute AS received infliximab in Study CT-P13 1.1, 128 were treated with CT-P13 and 122 received Remicade. Overall, 242 patients with RA and 106 patients with AS were exposed to CT-P13 for 54 weeks. The Delegate agrees with the clinical evaluator that the size of this safety population and the duration of exposure to the medication are acceptable and are in keeping with the relevant EMA guidelines for long term prescribing.[12] However, rare differences in the safety profile may not emerge until post-marketing.

Treatment related AEs

In the pivotal study in patients with RA, CT-P13 3.1, treatment emergent adverse events (TEAEs) that were considered by investigators to be drug related, were recorded in 131 (43.4% of 302) patients treated with CT-P13, and 134 (44.7% of 300) subjects treated with Remicade. The most frequently reported treatment related TEAEs for patients in the CT-P13 treatment group were latent TB (21 patients, 7.0%) followed by infusion related reactions, nasopharyngitis, increased serum alanine aminotransferase (ALT), and upper respiratory tract infection (all recorded in 10 patients, 3.3% each), and urinary tract infection (8 patients, 2.6%). The most frequently reported TEAEs considered to be related to Remicade were latent TB (19 patients, 6.3%) followed by infusion related reactions, increased serum ALT, and drug hypersensitivity (all recorded in 11 patients, 3.7% each), urinary tract infection (9 patients, 3.0%), and bronchitis, increased serum aspartate aminotransferase (AST), and headache (7 patients, 2.3% each). A similar pattern of treatment-related TEAEs was observed between the 2 treatment groups in the pivotal study.

In the supportive study in patients with AS, Study CT-P13 1.1, TEAEs that were considered to be drug related by investigators were reported in 62 (48.4%) patients in the CT-P13 group, and 63 (51.6%) subjects in the Remicade arm. There did not appear to be any significant treatment related differences in the number and pattern of drug related TEAEs observed. Latent TB was seen in 5.5% on CT-P13 versus 4.1% on Remicade.

Given the small numbers of drug related AEs and the small numbers in each treatment group in the pilot Phase I study in patients with RA, CT-P13 1.2, no robust conclusions can be drawn. However, there were no significant safety signals that could be identified.

Deaths and other serious adverse events, discontinuations

One sudden death was reported in the pivotal RA trial, CT-P13 3.1, in a patient who received Remicade. The cause of death was unknown but it was not considered related to treatment. In the supportive study in AS patients, CT-P13 1.1, there were two deaths reported, one in each group and each due to a motor vehicle accident. There were no deaths reported in the small study in RA patients, CT-P13 1.2.

In the pivotal study in patients with RA, CT-P13 3.1, more treatment emergent serious adverse events (TESAEs) were reported in the CT-P13 group (42 out of 302 patients, 13.9%) compared with the Remicade group (30 out of 300 patients, 10.0%) but no statistical analysis was provided comparing the difference. The numbers of each individual type of TESAE were small. The significance of this difference is not clear. There was a numerically lower number of TEAEs that led to discontinuation of treatment compared to the Remicade group in this study (33 out of 302 patients, 10.9% for CT-P13 versus. 45 out of 300 patients, 15.0% for Remicade). In the supportive study in AS patients, CT-P13 1.1, a total of 16 patients with AS experienced SAEs: 8 (6.3%) patients in the CT-P13 group reported 10 SAEs, and 8 (6.6%) patients in the Remicade arm recorded 11 SAEs. One patient in each treatment group in the small, pilot Phase I study, CT-P13 1.2, experienced SAEs. Similar numbers of patients in each treatment group discontinued in the supportive study in AS and in the small, pilot Phase I study.

Laboratory tests

There did not appear to be any significant differences, in either the rates or the types of abnormal laboratory tests in any of the three clinical studies in the dossier. One case of drug related serious neutropaenia and one of serious hepato-biliary disturbance were reported. There were no electrocardiogram (ECG) related safety concerns.

Adverse events of special interest

Infections

The overall number of TEAEs due to infections was comparable between the treatment groups receiving either formulation of infliximab. However when the safety results (up to Week 54) of the 3 studies were combined there was a higher number of serious infections in the CT-P13 treated subjects versus those who received Remicade. In total, 18 serious infections were reported across all studies in 16 patients treated with CT-P13 compared with 12 serious infections in 10 patients treated with Remicade. In particular, these serious infections included 5 cases of pneumonia in patients treated with CT-P13 versus no reports in those receiving Remicade. In addition, a total of 7 cases of active TB (including 3 cases of disseminated TB) occurred in patients treated with CT-P13 (1.6% of 437) compared with 1 case (0.2% of 431) in patients treated with Remicade. Infections including disseminated and extra-pulmonary cases of TB have been previously reported with Remicade and other TNFα inhibitors. Although the overall number of events was low and it is difficult to draw a clear conclusion from this observation, the clinical evaluator did ask the sponsor to provide further clarification on this issue.

There were no reports of hepatitis B reactivation from any of the studies.

Infusion-related reactions

Reactions related to infusion of study medication occurred in Study CT-P13 3.1 (both treatment groups), and Study CT-P13 1.1 (Remicade group only). None of the SAEs was indicative of a delayed hypersensitivity reaction. Drug related infections occurred at a similar rate in patients receiving CT-P13 and Remicade in all 3 studies. However, in Study CT-P 3.1 a higher number of subjects treated with CT-P13 (4 out of 302) were reported to have experienced anaphylactic reactions compared to Remicade (1 out of 300) and the significance of this observation remains unclear. The sponsor did respond to a question asked on this issue in the first set of questions.

Lymphoproliferative disorders

No patients in the CT-P13 clinical development program were diagnosed with lymphoproliferative disorder during the follow up periods, which extended to a maximum of 54 weeks. However, as noted by the clinical evaluator, the duration of follow up is possibly too short in duration for any potential safety signal to be identified.

Immunogenicity

There were no clear differences in the proportions of patients who developed anti-drug antibodies between the test and reference treatment groups in the total clinical dataset.

Safety conclusions

The Delegate would agree that the analysis of AEs reported during treatment with CT-P13 and the reference product Remicade has, for the most part, not revealed any significant differences in the incidence and type of AEs. However, there is a concern about the higher rates of both serious pneumonia and of TB with CT-P13 compared with Remicade. The clinical evaluator asked the sponsor for comment. The sponsor's response is discussed in the next section.

Questions raised by the TGA

There were two sets of questions raised by the TGA.

First set of questions from the clinical evaluator (2 May 2015)

There were 11 questions asked of the sponsor by the clinical evaluator. Presented below is the Delegate's review of the questions and assessment of the evaluation of the responses to those questions.

Question 1

Question 1 asked whether the evaluated PK dataset, with doses all in the range 3 to 5 mg/kg, could be extrapolated to higher doses such as up to 10 mg/kg sometimes given to patients with inflammatory bowel disease. Because historical data does show that Remicade exhibits linear pharmacokinetics in the dose range of 1 to 20 mg/kg in both RA and CD patients and because of the high degree of biosimilarity between the test and reference medicines, the sponsor asserts that the extrapolation is valid. The clinical evaluator concurred with the sponsor's assessment.

Question 2

Question 2 raised the issue of the lack of PK data in children in the submission. The sponsor confirmed the lack of such data and provided a detailed theoretical justification for not requiring such data. The clinical evaluator was of the opinion that the sponsor be requested to collect efficacy, safety and PK data in a group of paediatric patients as a condition of registration. The clinical unit responsible for inflammatory bowel diseases (clinical unit 1) has considered this (see below) and concluded that such a study is not required.

Question 3

Question 3 concerned the comparability of the EU and Australian sourced Remicade products. This has been resolved by the results of the bridging study undertaken by the sponsor and evaluated by the quality evaluator. The two are highly comparable.

Question 4

Question 4 concerned the limited information about the baseline RA disease characteristics of the subjects in the pivotal trial, Study CT-P13 3.1. The sponsor's response with additional data and analyses was able to satisfy the clinical evaluator. However, the evaluator was still concerned that the sponsor had not provided any information about the dose levels of MTX used by subjects prior to study inclusion or any information about the pattern of alternative conventional DMARD use. The sponsor addressed this matter in the 'Post TGA Meeting' response, which indicated that at the date of the first infusion on infliximab, the mean MTX dose was 15.6 mg/week for patients receiving CT-P13 and 15.61 mg/week for patients receiving Remicade. At the most recent

MTX dose, the mean values were 15.41 mg/week versus 15.54 mg/week. Patients were excluded from the trial's entry on the basis of DMARD use within 4 weeks prior to screening and DMARD use was prohibited during the trial, except for MTX. The sponsor has indicated that no patients deviated from the exclusion criteria based on DMARD use.

Question 5

Question 5 concerned the limited number of time assessment points for ACR response in the pivotal trial in RA patients, Study CT-P13 3.1, and the impact that this may have had on the secondary outcome measure of median time to the onset of ACR20 response. The Delegate agrees with the sponsor that this is a deficiency in the study and that no robust conclusions can be drawn about any differences between test and reference for the parameter.

Question 6

Question 6 concerned the lack of radiographic endpoint data beyond 54 weeks in the pivotal trial in RA patients, Study CT-P13 3.1. Additional data were provided. The overall mean (and median) joint damage scores at baseline were 98.4 and 86.0 units. At Week 54, both treatment groups achieved a similar mean (and median) decrease in joint damage progression; 30.7 units (32.0 units) for the CT-P13 group and 31.9 units (32.0 units) for Remicade. At Week 104, there was maintenance of the infliximab treatment effect in both the CT-P13 maintenance and CT-P13 treatment switch arms with the mean (and median) reduction in joint progression score being 30.9 units (30.0 units) in the maintenance group and 30.1 units (29.0 units) in the treatment switch arm. The data supports the maintenance of radiographic endpoint effect out to 2 years, sufficient to support the indication claim of inhibition of structural damage. Similarly, the proportions of patients achieving clinical response according to the ACR20, ACR50 and ACR70 criteria at Weeks 78 and 102 were similar in the CT-P13 maintenance and treatment switch groups. The sponsor was requested to clarify the joint scoring method and the sponsor has indicated in the 'Post TGA Meeting' response that the method was the van de Heijde modified Total Sharp Score. The sponsor realised after the Week 54 data that the results were not in line with the published joint damage progression score of Remicade in the ATTRACT study. This was due to the evaluation of joint damage scores being different to the method used in ATTRACT. The sponsor reanalysed the data and a summary of the results indicates comparable joint damage progression scores as shown in Table 15.

Table 15: Joint damage progression in Study CT-P13 3.1; All randomised population

Statistic	CT-P13 3 mg/kg (N=302)		Remicade® 3 mg/kg (N=304)		Difference between means (95% CI)	P-value [1]
	Result at each visit	Change From Baseline	Result at each visit	Change From Baseline		
Total Combined Score						
Week 0						
n	232	-	238	-	-	-
Mean (SD)	68.3 (58.88)	-	64.8 (62.46)	-		
Median (Min, Max)	52.0 (0, 307)	-	46.8 (0, 328)	-		
Week 54						
n	206	168	201	168	0.39 (-0.88, 1.66)	0.5463
Mean (SD)	66.0 (58.38)	1.0 (6.25)	63.7 (59.93)	0.6 (5.56)		
Median (Min, Max)	49.0 (0, 258)	0 (-18, 28)	45.5 (0, 353)	0 (-23, 23)		
Total JSN Score						
Week 0						
n	232	-	238	-	-	-
Mean (SD)	36.0 (30.11)	-	32.5 (30.25)	-		
Median (Min, Max)	27.0 (0, 135)	-	25.5 (0, 135)	-		
Week 54						
n	206	168	201	168	-0.31 (-1.19, 0.57)	0.4852
Mean (SD)	33.2 (27.47)	0.4 (4.19)	30.9 (27.89)	0.7 (4.01)		
Median (Min, Max)	24.5 (0, 114)	0 (-18, 15)	26.0 (0, 140)	0 (-16, 14)		
Total Erosions Score						
Week 0						
n	232	-	238	-	-	-
Mean (SD)	32.3 (31.97)	-	32.4 (34.38)	-		
Median (Min, Max)	23.0 (0, 173)	-	19.3 (0, 193)	-		
Week 54						
n	206	168	201	168	0.70 (-0.08, 1.49)	0.0795
Mean (SD)	32.7 (33.65)	0.7 (3.91)	32.8 (34.27)	0 (3.39)		
Median (Min, Max)	21.0 (0, 156)	0 (-10, 24)	21.0 (0, 213)	0 (-9, 18)		

[1] Differences in the mean change from baseline between the treatment groups were examined based on Student's t-tests with the significance level set at 5%.
Note: Summary statistics of actual result were only calculated if all X-rays were completed and all required joints were evaluated for a patient at that visit.
Summary statistics of change from baseline are only calculated if all X-rays were completed and all required joints were evaluated for a patient at that visit and also the baseline visit.

Question 7

Question 7 concerned further data available to 112 weeks in the pilot Phase I study in RA patients, Study CT-P13 1.2 (beyond the data to 54 weeks submitted). Submitted data demonstrated that, although the patient dataset was small in Study CT-P13 1.2, treatment with CT-P13 (either continuation of therapy or a treatment switch from Remicade) between Weeks 62 and 112 did not reveal any new safety concerns, particularly with respect to immunogenicity potential.

Question 8

Question 8 concerned the results of the extension studies of the pivotal study in RA patients and of the supportive study in AS patients, in particular with regard to any evidence of safety related concerns after patients were switched from Remicade to CT-P13. The clinical evaluator was satisfied that there were no new safety concerns.

Question 9

Question 9 concerned the reported higher rate of anaphylactic reactions in the CT-P13 group compared with the Remicade group. The sponsor conducted a review and re-evaluation of all cases of anaphylactic reactions and serious infusion related reactions in the CT-P13 clinical trial program. Upon review of Study CT-P13 3.1, the sponsor has now identified a total of 6 cases in the CT-P13 group (versus 4 events previously) and 4 patients in the Remicade (versus 1 event previously) as experiencing anaphylactic reactions or serious infusion related reactions. In Study CT-P13 1.1 (AS study), 1 patient in the CT-P13 treatment group and 3 subjects in the Remicade met the definition of experiencing anaphylactic or serious infusion related reactions. Therefore, the overall incidence of serious infusion related reactions in the CT-P13 clinical trial program is 1.6% (7 out of 430) in subjects who received CT-P13 and 1.7% (7 out of 422) in patients who were administered Remicade. The rates are now comparable in test and reference groups. It would appear that the discrepancies originally occurred because of limited reporting options on the case report form.

The sponsor was requested to provide further information on the following aspects of this matter:

1. Clarify in precise detail the differential rates of anaphylactic reactions and serious infusion related reactions in the CT-P13 clinical development programme. Firstly, please provide the comparative rates/incidences, that is CT-P13 versus Remicade, for both anaphylactic and/or anaphylactoid reactions in the entire clinical development programme for CT-P13. Please also provide these details broken down by individual study and if possible, broken down by division into anaphylactic and anaphylactoid types of reaction.
2. Secondly, please define precisely what is meant by the term 'serious infusion related reaction' and clarify whether or not there can be any overlap between the terms, 'anaphylactic reaction', 'anaphylactoid reaction' and the term 'serious infusion related reaction'.
3. Thirdly, please provide the comparative rates/incidences, that is, CT-P13 versus Remicade, for serious infusion related reactions in the entire clinical development programme for CT-P13. Please provide these details broken down by individual study. Please also indicate the degree of overlap, if any, between the occurrences of anaphylactic/anaphylactoid reaction and the occurrences of serious infusion related reaction in the entire clinical development programme of CT-P13.

The sponsor responded to this request in the 'Post TGA Meeting' response. Infusion related reactions were based on pre-specified definitions in the protocols. The sponsor conducted an expanded search for anaphylactic reactions using FDA advice and used definitions for infusion related reactions and anaphylactic reaction as listed in Tables 16 and 17. Using the expanded definitions, infusion reactions in the combined RA and AS populations occurred in 9.2% on CT-P13 and 13.4% on Remicade. Anaphylaxis using the expanded definition across the RA and AS populations occurred in 7 (1.6%) patients on CT-P13 and 7 (1.6%) patients on Remicade (see Table 18 below).

Table 16: Expanded definition of infusion related reactions as defined by the following algorithm

Algorithm for expanded definition of infusion related reactions	
A. Medical dictionary for regulatory activities (MeDRA) preferred term (PT) selection: The event should be defined by one of the PT terms listed below and also classed as possible probable or definite for relationship to study drug	
Preferred Term	Drug relationship

Algorithm for expanded definition of infusion related reactions	
Hypersensitivity	Possible Probable Definite
Drug hypersensitivity	
Anaphylactic shock	
Anaphylactic reaction	
Infusion related reaction	
B. AE term selection: The event should be defined by any word in Term 1 as well as one word in Term 2 to 8 groups. In addition the event must be classed as "possible, probable or definite' for relationship to study drug.	
AE Term 1 (mandatory)	Infusion, study drug reaction, _IP*_hypersensitivity, hypersensitivity, hypersensitiviti, postinfusion
PT Term 2	Pyrexia, body temperature increased, chills
PT Term 3	Pruritis, pruritis allergic, rash pruritic, rash, rash macular, rash macro-papular, rash generalised, urticaria, eye irritation, burning sensation, erythema, dermatitis allergic, angioedema, lip oedema
PT Term 4	Dyspnoea, non-cardiac chest pain, chest pain, chest discomfort, upper respiratory tract congestion, bronchospasm
PT Term 5	Hypotension, procedural hypotension, hypertension, procedural hypertension, blood pressure increased, supraventricular extrasystoles
PT Term 6	Brady cardia, sinus bradycardia, tachycardia, sinus tachycardia, palpitations, atrial fibrillation
PT Term 7	Vomiting, nausea, oropharyngeal pain, abdominal pain upper, abdominal pain
PT Term 8	Back pain, myalgia, arthralgia, headache, migraine
C. AE Term selection: The event should be defined by any term listed below for which the AE start date matches an infusion date and it must be classified as 'possible, probable or definite' relationship to study drug.	
Pyrexia, body temperature increased, chills, pruritus, pruritus allergic, rash pruritic, rash, rash macular, rash macro-papular, rash generalised, urticaria, eye irritation, burning sensation, erythema, dermatitis allergic, angioedema, lip oedema, dyspnoea, non-cardiac chest pain, chest pain, chest discomfort, upper respiratory tract congestion, bronchospasm, hypotension, procedural hypotension, hypertension, procedural hypertension, blood pressure increased, supraventricular extrasystoles, bradycardia, sinus bradycardia, tachycardia, sinus tachycardia, palpitations, atrial fibrillation, vomiting, nausea, oropharyngeal pain, abdominal pain upper, abdominal pain, back pain, myalgia, arthralgia, headache, migraine	

Table 17: Definition of anaphylactic reaction based on the criteria of Sampson et al., (2006)[31]

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled
A. Acute onset of an illness(minutes to several hours) with involvement of the skin mucosal tissue, or both (for example generalized hives, pruritis or flushing, swollen lips-tongue-uvula) and t least one of the following: a. Respiratory compromise(for example dyspnoea, wheeze-bronchospasm, stridor, reduced PEF (peak expiratory flow), hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (for example hypotonia (collapse), syncope, incontinence.
B. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): c. Involvement of the skin-mucosal tissue (for example generalised hives, itch-flush, swollen lips-tongue-uvula d. Respiratory compromise (for example dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) e. Reduced blood pressure or associated symptoms (for example hypotonia (collapse), syncope, incontinence) f. Persistent gastrointestinal symptoms (for example crampy abdominal pain, vomiting)
C .Reduced blood pressure (BP) after exposure to known allergen for that patient (minutes to several hours) g. Systolic BP of less than 90mm Hg or greater than 30% decrease from that person's baseline.
Management of anaphylaxis As with the treatment of any critically ill patient, the treatment of anaphylaxis begins with a rapid assessment and maintenance of airway, breathing and circulation. When a patient fulfils any of the 3 criteria of anaphylaxis outlined above, the patient should receive epinephrine immediately because epinephrine is the treatment of choice in anaphylaxis.

[31] Sampson H A et al.; Second symposium on the definition and management of anaphylaxis: Summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium *J Allergy Clin Immunol* 2006;117:391-397.

Table 18: Treatment emergent adverse events of infusion related reaction and anaphylaxis (Sampson's criteria) in controlled studies (Safety population)

Study	CT-P13				EU-Approved Remicade®			
	N	Infusion-related reaction	Serious or severe infusion-related reaction [1]	Anaphylaxis	N	Infusion-related reaction	Serious or severe infusion-related reaction [1]	Anaphylaxis
Controlled Studies								
CT-P13 1.1	128	11 (8.6)	1 (0.8)	1 (0.8)	122	15 (12.3)	3 (2.5)	3 (2.5)
CT-P13 1.2	10	0	0	0	9	1 (11.1)	0	0
CT-P13 3.1	302	30 (9.9)	8 (2.6)	6 (2.0)	300	43 (14.3)	6 (2.0)	4 (1.3)
CT-P13 3.3	6	0	0	0 (0)	9	0	0	0 (0)
Total	446	41 (9.2)	9 (2.0)	7 (1.6)	440	59 (13.4)	9 (2.0)	7 (1.6)

[1] Serious or severe cases in infusion-related reaction by expanded definition
[2] Anaphylaxis was defined using on Sampson *et al.*,(2006) in patients with serious or severe cases of infusion-related reaction (expanded definition)

The sponsor concluded that the incidence, pattern and severity of infusion related reactions were similar between the groups in the controlled studies, most adverse events reported as an anaphylactic reaction were considered to be a serious infusion related reaction and that overall the incidence of serious infusion related and anaphylactic reactions was similar between both groups in the controlled studies.

Question 10

Question 10 concerned the observation that the incidence of both TB and of serious pneumonia was higher with the test product, CT-P13, than it was with Remicade. As noted by the clinical evaluator, the CT-P13 clinical trial program showed a higher incidence of TB and serious pneumonia in subjects treated with CT-P13 versus Remicade. The overall reported incidence of TB was higher in the CT-P13 group (1.6%; 7 out of 440) compared with Remicade (0.2%; 1 out of 431). The 7 cases in patients on CT-P13 were from Philippines (3), Poland, Mexico, Korea and Latvia. The single case in a patient on Remicade was from Poland. There were apparently 3 cases of uncertain confirmation, the diagnosis of which was based on the local physician's judgement rather than on positive culture of the bacterium. Two of these 3 cases had abnormal chest X-rays (chronic upper lobe inflammatory changes) at enrolment, which represents a protocol violation. Even if these three cases are excluded from consideration the respective rates of developing TB in the clinical programme was 0.9% (4 out of 437) with CT-P13 and 0.2% (1 out of 431) with Remicade.

A total of 5 cases of pneumonia (1.1% of 440) were reported in the clinical programme in patients treated with CT-P13 versus no cases with Remicade. In the response to questions, the sponsor presented data suggesting that the observed incidence of each condition in the CT-P13 clinical programme is within the expected historical range for infliximab individuals.

The Delegate, like the clinical evaluator, remains concerned by the discrepancy in these adverse events. While the rates are small and the observed differences in rates may simply be a matter of chance, there is nevertheless a difference. Is there a possibility that the discrepancy may be reflective of some structural difference between CT-P13 and Remicade and, if so, could this alter the product's safety? The ACPM will be asked for its views on this matter.

The sponsor responded to these concerns in the 'Post TGA Meeting' response. For TB, the incidence rate across all controlled studies up to 54 weeks was 1.4% on CT-P13 versus 0.2% on Remicade (see Table 19 below).

Table 19: Summary of patient reporting active tuberculosis across CT-P13 studies; Safety population

Study	Indication	CT-P13	EU-approved Remicade®
CT-P13 1.1	AS	2/128 (1.6%)	1/122 (0.8%)
CT-P13 3.1	RA	3/302 (2.0%)	0/300 (0.0%)
CT-P13 1.2		2/10 (20.0%)	0/9 (0.0%)
CT-P13 3.3		0/6 (0.0%)	0/9 (0.0%)
B1P13101		0/51 (0.0%)	0/53 (0.0%)
RA + AS Total		7/497 (1.4%)	1/493 (0.2%)

AS: Ankylosing spondylitis, RA: Rheumatoid arthritis

The sponsor acknowledges there is a higher result for patients on CT-P13 however says the reasons for this imbalance are due to the following:

1. Some of the studies were conducted in regions where Remicade has not been previously approved or used and the background burden of TB is relatively high, for example Philippines.
2. Two of the three patients from the Philippines had abnormal chest X-ray findings at baseline and the decision to treat patients there was based on clinical findings rather than microbiological or molecular diagnostic criteria.
3. Patients reporting disseminated TB in study CT-P13 1.1 had an X-ray finding of pneumofibrosis at baseline and a history of previous TB.
4. Similar incidences were observed for seroconversion in the interferon gamma release assay (IGRA) test and for TEAEs of latent TB (CT-P13 8.3% versus Remicade 6.8%).
5. The incidence is broadly in line with previous Remicade studies at 0.9% for confirmed cases and 1.6% for all cases. Historical Remicade studies suggest an overall incidence of 0.80% for RA and 1.38% for AS.
6. The incidence of TB was in line with epidemiological ranking of high risk countries and therefore the imbalance has no relevance for low risk countries.
7. There was some asymmetry in randomisation at sites where active TB was reported with more on Inflectra than Remicade.

The sponsor provided a table of incidence based on ranks of epidemiological burden as shown below (Table 20).

Table 20: Incidence of active TB in CT-P13 studies categorised by ranks of epidemiological burden using WHO epidemiological criteria

Controlled studies			CT-P13			Remicade			Total
Indication	Study Number	TB Incidence Category	Events	Number of Subjects	Incidence Rate (Subjects/ 100PY)	Events	Number of Subjects	Incidence Rate (Subjects/ 100PY)	Incidence Rate (Subjects/ 100PY)
AS+RA	Total*	Low risk (<0.01)	0	0	0 (. , 5.73)	0	0	0 (. , 6.87)	0 (. , 3.12)
		Medium (>0.01 and <0.05)	3	2	1 (0.12 , 3.61)	1	1	0.49 (0.01 , 2.75)	0.74 (0.15 , 2.18)
		High (>0.05)	5	5	2.41 (0.78 , 5.62)	0	0	0 (. , 1.78)	1.2 (0.39 , 2.81)

Low risk: Australia, USA

The sponsor claims that the comprehensive analyses conducted have shown that CT-P13 is highly similar to Remicade on quality and nonclinical grounds and that minor differences seen have no clinically meaningful impact on safety, purity or potency. In conclusion, the sponsor states that the numerical imbalance represents a clinical finding of no relevance to overall biosimilarity and can be explained by epidemiological and patient related factors.

Registry studies are planned to be conducted in RA, CD, UC and AS in Europe and Korea. Safety will be assessed for up to five years, including for serious infections and TB. In addition, long term safety will be assessed in a post-market surveillance register in the UK for RA and a longitudinal observational study in RA in Germany. The sponsor has advised that they will report on TB and serious infections annually as part of the PSURs, will report on TB and other serious infections as part of an amalgamated report of registry data once 3,100 patients have been recruited and will continue dialogue with the TGA on risk management and minimisation activities.

In relation to pneumonia, in the controlled studies, serious pneumonia was reported in 7 (1.4%) patients on CT-P13 versus 3 (0.6%) patients on Remicade. A table summarising this is provided (Table 21).

Table 21: Summary of patient reporting serious pneumonia across CT-P13 studies. Safety population

Study	Indication	CT-P13	EU-approved Remicade®
CT-P13 1.1	AS	0/128 (0.0%)	0/122 (0.0%)
CT-P13 3.1	RA	4/302 (1.3%)	0/300 (0.0%)
CT-P13 1.2		1/10 (10.0%)	0/9 (0.0%)
CT-P13 3.3		0/6 (0.0%)	0/9 (0.0%)
B1P13101		2/51 (3.9%)	3/53 (5.7%)
RA + AS Total		7/497 (1.4%)	3/493 (0.6%)

AS: Ankylosing spondylitis, RA: Rheumatoid arthritis

The sponsor has suggested that the difference may be due to baseline risk factors with more patients on CT-P13 (5 out of 7) having risk factors than patients receiving Remicade (none out of three). The sponsor also states that the historical rate of serious pneumonia with Remicade in studies conducted over one year show the incidence to be 2.15 to 3.03% that is similar to the rate observed with CT-P13. All cases of pneumonia were successfully treated with antibiotics.

Question 11

Question 11 concerned the two small additional studies, Studies CT-P13 3.3 (Russia) and B1P13101 (Japan). In the response to questions, the sponsor provided an interim clinical study report up to Week 30 for the Russian study and data up to Week 54 for the Japanese study.

Study CT-P13 3.3 was a Phase III, 2 centre (in Russia), randomised, double-blind, parallel group study primarily designed to evaluate the efficacy of CT-P13 and Remicade in the treatment of adult patients with active RA receiving concomitant stable doses of MTX. The primary endpoint was the ACR20 response rate at Week 30. The secondary objectives were PK characteristics, efficacy beyond 30 weeks of treatment follow-up and safety outcomes. This study was a Russian substudy of the pivotal study CT-P13 3.3 and involved 15 patients. The proportion of patients achieving clinical response according to the ACR20 criteria at Week 30 was 5 (83.3%) patients and 5 (55.6%) patients in the CT-P13 and Remicade treatment groups, respectively. In Study CT-P13 3.3, no TESAEs were reported and only 1 (11.1%) patient in the Remicade treatment group discontinued due to AE (bronchitis of moderate severity).

Study B1P113101 was a Phase I, multicentre (21 sites in Japan), randomised, double blind, parallel group study primarily designed to evaluate the PK parameters of CT-P13 and Remicade in the treatment of 108 adult patients with active RA receiving concomitant stable doses of MTX. The primary endpoint was the C_{max} of CT-P13 compared to Remicade at Weeks 0, 2, and 6. The secondary endpoints were other PK characteristics, efficacy, and safety outcomes. The trial demonstrated that CT-P13 and Remicade produced a similar rate of ACR20, ACR50 and ACR70 response at Weeks 14, 30 and 54, as well as functional improvement (using HAQ-DI score changes). The safety profile of CT-P13 and Remicade in Study B1P13101 was comparable.

Second set of questions (21 August 2014)

In a second set of questions, the sponsor was asked a number of questions related to the differences observed in the comparability studies undertaken between Remicade and Inflectra. The comments of the quality evaluators and nonclinical evaluators have been discussed. The clinical evaluator also commented on these differences:

- The higher percentage of high molecular weight species with CT-P13 did not translate to a higher incidence or type of anti-infliximab antibodies with CT-P13
- The differences in IgG fragments present in CT-P13 did not result in significant differences in binding affinity or neutralisation activity for TNFα
- The differences in oxidation of methionine did not impact on the PK parameters in vivo
- The 4% higher protein content in CT-P13 did not affect the patient weight based exposure under the dosing regimens tested
- The minor differences in glycosylation and mannose content did not have clinical consequences in terms of PK, safety or immunogenicity.

The clinical evaluator was of the view that overall the differences were not clinically significant with respect to the rheumatological indications (RA, AS and PsA).

Next in this set of questions the sponsor was asked for comment on the precise role of TNFα compared to the role of other modes of action such as Fc-mediated effector functions particularly in relation to the six different indications proposed. In the opinion of the clinical evaluator, the information provided supports the key role of TNFα in the pathology of all six treatment indications. The clinical evaluator states that in each of these conditions, TNFα is a key cytokine involved in the inflammatory process, mediates structural damage and is found in high concentrations at the sites of tissue involvement as

well as in the blood of patients with moderately to severely active clinical disease. Furthermore, in the inflammatory arthritis conditions (RA, AS and PsA), infliximab exerts its beneficial effect through neutralisation of sTNFα. The Delegate is of the opinion that the clinical trial data in RA and AS may be applied more broadly across the rheumatological spectrum to include PsA also. Advice has been provided in the reports from clinical unit 1 and clinical unit 4 in relation to CD, UC and psoriasis (see Attachment 2).

The sponsor was next asked about planned or ongoing studies. In its response, the sponsor provided a list of planned or ongoing registry studies (UK and Germany) and post-marketing studies. Two of the latter are studies in CD and UC. The sponsor indicated that it has no plans to initiate any specific post-marketing studies or treatment registries in Australia.

The sponsor confirmed that the approval in the EU was a full marketing authorisation.

The sponsor confirmed that it is unclear why Health Canada only granted partial approval to CT-P13, that is did not grant approval for the inflammatory bowel disease indications and is currently in discussions with Health Canada about the decision.

Clinical evaluator's recommendation

The clinical evaluator has recommended approval of CT-P13, Inflectra for all treatment indications that were sought by the sponsor.

The clinical evaluator has recommended that the sponsor be required to give an undertaking to perform a post-marketing study in paediatric patients with inflammatory bowel disease. This recommendation was motivated in part by the fact that there is no data for the use of CT-P13 in children in the current clinical development programme. This matter is discussed in the advice from clinical unit 1 (Attachment 2).

The clinical evaluator has noted that the sponsor states that it plans to conduct a non-inferiority study in adult patients with CD comparing CT-P13 with Remicade (Study CT-P13 3.4). The clinical evaluator recommends that the study report should be submitted in a timely manner. The Delegate agrees that this study should be submitted to the TGA when completed.

Risk management plan

The RMP evaluator has accepted the EU Risk Management Plan Version 4.0 (dated May 2014, DLP 15 April 2013) and Australian Specific Annex Version 1.0 (dated 24 November 2014), and any future updates (where TGA approved) as a condition of registration.

The RMP evaluator also recommended the following conditions of registration:

- Provide interim reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan through PSURs/periodic benefit-risk evaluation reports (PBRERs)
- Provide final reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan, once available
- Implement additional risk minimisation activities, within 3 months of approval, where approved by the TGA Pharmacovigilance and Special Access Branch (PSAB).

Following the second round RMP advice to the sponsor, the sponsor provided a response to the outstanding issues. This has been reviewed by the RMP evaluator, who has advised that the responses are mostly acceptable except for the following outstanding matters that should be followed up with PSAB prior to finalisation of this submission and responded to in the Pre-ACPM Response:

1. The ASA should reflect the changes made in the EU-RMP with regard to 'skin cancer', 'off-label use' 'medication errors' (that is reclassification of 'skin cancer' and addition of 'off-label use' 'medication errors').
2. The sponsor should prepare additional risk minimisation activities to the satisfaction of the TGA, including the DHCPL. This should be submitted to PSAB post-ACPM. If Inflectra is not approved for all indications, then this will have implications for the discussion of 'off-label' use in the RMP and the information to be put into the proposed DHCPL.
3. Legionella infections associated with infliximab have been reported in the medical literature, a 2011 FDA safety communication and the current FDA label for Remicade. It is recommended to the Delegate to consider adding this information to the proposed PI. The sponsor has indicated that no cases of legionella pneumonia have been reported in the Inflectra clinical trials and no cases have been reported in the post-marketing data for Inflectra. The Delegate notes that this information is not included in the Remicade PI in Australia or Europe but the PI does mention opportunistic infections. The Delegate accepts the sponsor's assurance that if the Remicade PI is updated then the Inflectra PI will also be updated.

The sponsor made a number of commitments in the 'Post TGA Meeting' response document from 27 November 2014 and these should be addressed with the RMP section post-ACPM, for example educational materials, DHCPL, revised RMP, updated ASA.[32]

Risk-benefit analysis

Discussion; rheumatological indications

Quality

The overall quality of Inflectra infliximab (rmc) is considered acceptable. From a biosimilar perspective, the overall comparability of Inflectra, infliximab (rmc) with the reference product Remicade has been satisfactorily demonstrated. There are no quality objections to approval.

Nonclinical

There are no nonclinical objections to the registration of Inflectra. With regard to the relative contribution of various mechanisms of action, the nonclinical evaluator was of the opinion that:

- There are considerable overlaps between RA, AS and PsA in terms of tissues that are targeted by inflammation and the detrimental effects of TNFα on cartilage, synovium and bone
- The sponsor had provided thorough, detailed evidence to support the view that TNFα plays a pivotal role in the pathophysiological processes that are characteristic of these three indications and that neutralisation of TNFα is the primary mechanism of action
- The most compelling evidence is the fact that structurally very different anti TNFα agents, including those without Fc functionality (certolizumab pegol) or those incapable of reverse signalling (etanercept) are all effective treatments for these indications, suggesting that it is the shared ability of these compounds to neutralise TNFα via Fab-mediated and not Fc-mediated functions which underlines their clinical efficacy.

[32] These issues were resolved prior to registration

Pharmacology

The clinical evaluator was satisfied that PK comparability between the test and reference products had been established albeit over a limited dose range (3 to 5 mg/kg every 8 weeks). The sponsor stated in its response to questions that historical data does show that Remicade exhibits linear pharmacokinetics in the dose range of 1 to 20 mg/kg in both RA and CD patients. Furthermore, there is a high degree of bio-comparability between the two products. In so far as the rheumatological indications are concerned the Delegate is satisfied as to the PK comparability of the two products, however the Delegate notes the differences seen in the antibody positive population in patients with AS, in which the AUC 95 % confidence interval was outside the usual bioequivalence limits. The significance of this is uncertain given the availability of the clinical data however, efficacy was a non-powered secondary endpoint in this study. ACPMs view on this is requested. There was comparability with regard to the changes in mean PD parameter values.

Rheumatoid arthritis

In the pivotal study in subjects with RA, Study CT-P13 3.1, the proportion of subjects in the ITT dataset achieving an ACR20 response at Week 30 in the CT-P13 group was 60.9% (184 out of 302), which was similar to that observed in the Remicade arm (58.6%; 178 out of 304). Similar results were observed for the PP population. Comparable efficacy was also demonstrated for secondary efficacy endpoints. The radiographic data was also supportive of comparability.

In the small, supportive study in RA patients, Study CT-P13 1.2, there did not appear to be clear differences between the two treatment groups demonstrated however, the sample size is too small to draw conclusions.

Ankylosing spondylitis

In the study in subjects with AS, Study CT-P13 1.1, the proportions of patients achieving a clinical response satisfying the ASAS20 and ASAS40 criteria at Weeks 14, 30 and 54 were comparable in the test and reference treatment groups. There was also comparability of the results for other efficacy endpoints. However, the study was not powered for efficacy assessment as it was designed for PK assessment; therefore, it is not possible to conclude therapeutic equivalence or non inferiority from this trial. Nevertheless, it provides some supportive evidence of equivalence.

Psoriatic arthritis

There was no actual clinical trial in patients with PsA. However, because of the similar mechanism of action and related clinical features across the rheumatological indications, the similarity demonstrated from the clinical comparability studies in RA and AS, the supportive PK data and the acceptable comparability demonstrated in the quality and nonclinical assessment, then the Delegate is of the view that the data are satisfactory to extrapolate to the PsA indication.

Safety

The analysis of adverse events did not, for the most part, reveal any significant differences in either the rates or incidences when the test was compared with the reference. Infusions related reactions and anaphylactic reactions appeared to occur at a similar incidence. However, there is a concern about the higher rates of both serious pneumonia and TB with CT-P13 when compared with Remicade. The CT-P13 clinical trial program showed a higher incidence of TB and serious pneumonia in subjects treated with CT-P13 versus Remicade. The overall reported incidence of TB was higher in the CT-P13 group (1.6%; 7 out of 440) compared with Remicade (0.2%; 1 out of 431). Across all controlled studies it was 7 out of 497 (1.4%) versus 1 out of 493 (0.2%). There were apparently 3 cases of uncertain confirmation, the diagnosis of which was based on the local physician's judgement rather than on positive culture of the bacterium. Two of these 3 cases had

abnormal chest X-rays (chronic upper lobe inflammatory changes) at enrolment, which represents a protocol violation. Even if these three cases are excluded from consideration the respective rates of developing TB in the clinical programme was 0.9% (4 out of 437) with CT-P13 and 0.2% (1 out of 431) with Remicade.

A total of 5 cases of pneumonia (1.1% of 440) were reported in the clinical programme in patients treated with CT-P13 versus no cases with Remicade. Across all controlled studies it was 7 out of 497 (1.4%) on CT-P13 versus 3 out of 494 (0.6%) on Remicade.

In the response to questions and the 'Post TGA Meeting' response, the sponsor presented data suggesting that the observed incidence of each condition in the CT-P13 clinical programme is within the expected historical range for infliximab individuals and that there are other epidemiological and patient factor explanations for the difference. However, the Delegate, like the clinical evaluator, remains concerned by the discrepancy in each of the rates and that both adverse events were more frequent on Inflectra than Remicade.

Additional information requested by the US FDA

The sponsor provided the TGA on 4 March 2015 with a copy of the additional information requested by the US FDA on 4 February 2015 in relation to the application to register this biosimilar in the USA. The TGA has reviewed the FDA requests for sterility and chemistry information and has determined that they do no impact on the outcome of the TGA sterility evaluation or quality assessment. The statistical question from the FDA relates to verifying the numbers in a table. The information in this table is similar to the table included above on radiographic results (Table 15).

Summary

Overall the Delegate is inclined to recommend approval of Inflectra for the three proposed rheumatological indications of RA, AS and PsA.

The bio-comparability/biosimilarity of Inflectra to Remicade has been satisfactorily established. That is to say, the quality of the product has been satisfactorily established and the quality evaluator is recommending approval. There are also no nonclinical objections to approval.

The clinical evaluator has recommended approval for all indications. There is sufficient clinical trial evidence of efficacy and safety of Inflectra in comparison with Remicade in RA with supportive evidence in AS and the Delegate is of the view that there is reasonable evidence that a similar mechanism of action would be involved for the third rheumatological indication, namely PsA. Therefore, the results of the evaluated data may be extrapolated to the latter indication. There is however, a lack of evidence to detect rare differences in safety, especially immunogenicity, which could emerge as a result of this product being a biosimilar to Remicade; therefore, robust post-market monitoring is required. The data is also too limited to detect long term differences in safety that are known with TNFα inhibitors. An RMP has been agreed with the sponsor and the sponsor will be required to submit the results of the patient registries and ongoing clinical trials to the TGA.

One important issue to be resolved concerns the issue of the differential rates of both serious pneumonia and of TB between test and reference in the clinical trial programme. While the actual numbers are small and possibly due to other factors, it is the overall difference between test and reference, which is of concern. The sponsor addressed this matter in the 'Post TGA Meeting' response, the details of which are summarised above under Question 10 of the first set of questions. The Delegate notes the possible explanations for the differences but remains concerned in the context of this being a biosimilar and the rates for two infections being higher on Inflectra. The ACPM is asked for

its opinion on this matter. The Delegate notes the sponsor's post-market activities and commitments to provide information to the TGA to address these concerns, which are acceptable.

Naming of biosimilars

With regard to tradenames, biosimilars are required to have a clearly distinguishable tradename from all other products, including the reference product and other biosimilars. The Delegate considers the proposed tradenames acceptable and consistent with those approved in Europe and Canada.

The lack of any qualifier to the active ingredient name may give the impression that the biosimilar is a generic medicine, lead to confusion in both prescribing and dispensing and contribute to difficulties in traceability following adverse event reporting for pharmacovigilance purposes. Although the naming policy at present is not to require any specific identifier, the sponsor has provided an, '*assurance that this will be reviewed post-approval in light of any TGA and/or WHO policy changes*'.

PI, CMI and Labels

The sponsor was requested to consider how communication of Inflectra being a biosimilar would be undertaken in the PI, CMI, labels, DHCPL or any other educational activities. The sponsor has included statements in the PI but has not included statements in the CMI due to the sponsor's view that the term biosimilarity is a difficult concept for consumers to understand and it could lead to anxiety in patients and that it should be explained by the prescriber to the patient. No statements are proposed for the label. The sponsor has agreed to work with the TGA to develop an appropriate DHCPL post ACPM. The Delegate considers the PI changes acceptable, however does not consider it acceptable to not include information in the CMI. The CMI should be consistent with the PI and therefore the CMI should include mention of this product being a biosimilar medicine. The Delegate accepts the sponsor's position to not include a specific statement on the labels.

RMP

The sponsor has mostly addressed the outstanding RMP matters however there remain a few issues, along with commitments made by the sponsor, to address post ACPM once the approved indications are clear. The sponsor is requested to address these directly with PMSB prior to finalisation of this submission.

Data deficiencies and limitations

There is a lack of direct evidence in patients with psoriatic arthritis and limited data in patients with ankylosing spondylitis. The safety pool is not large enough to detect small differences in safety that may not become evident until a broader exposure occurs post-marketing.

Questions for the sponsor from the delegate

The sponsor was requested to address the following issues;

1. The sponsor is requested to provide an update on the status of the submission to the US FDA and the sponsor's response to the 'Statistics information request 5 Feb 2015'.
2. Given the antibody positive population with AS showed an AUC 95 % confidence interval comparing CT-P13 and Remicade of 85.25 to 137.54, was there a difference in efficacy or safety in this subgroup on CT-P13?
3. The sponsor is requested to provide a detailed commentary on the differential rates of serious pneumonia, TB, infusions reactions and anaphylaxis comparing CT-P13 and Remicade in the CT-P13 clinical development programme, as per the draft response provided on 24 November 2014 along with any additional information that the sponsor would like to provide.

4. Please provide an up to date list of all clinical studies and patient registries that are presently ongoing, completed or planned as per the draft response provided on 24 November 2014 along with any additional information that the sponsor would like to provide.
5. Please provide a summary of all post-marketing approval commitments entered into by the sponsor with both the EMA and Health Canada, as per the draft response provided on 24 November 2014 along with any additional information that the sponsor would like to provide.
6. The sponsor is invited to provide any further information that is available or any further response that the sponsor would like to provide in relation to the differences noted by the quality evaluator from the comparability studies between Remicade and Inflectra.
7. Please summarise for ACPM how the sponsor is informing prescribers and patients that Inflectra is a biosimilar product and how this is being communicated in the PI, CMI and any educational materials for example DHCPL.
8. Please provide the reasons from Health Canada on the decision to not approve the indications of Crohn's disease and ulcerative colitis for Inflectra.

Conditions of registration:

The following are proposed as conditions of registration and the ACPM and sponsor are invited to comment:

1. The implementation in Australia of the EU Risk Management Plan Version 4.0 (dated May 2014, DLP 15April 2013) and Australian Specific Annex Version 1.0 (dated 24 November 2014), and any future updates (where TGA approved).
2. Provide interim reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan through PSURs/PBRERs.
3. Provide final reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan, once available.
4. Implement additional risk minimisation activities, within 3 months of approval, where approved by the TGA PSAB.
5. Provide the amalgamated report from registry data that will report on tuberculosis and other serious infections when it is available.
6. The following study report must be submitted to the TGA, as soon as possible after completion, for evaluation. The final study report for study CT-P13 3.4 as listed in the sponsor's response to Question 9 of the 'Post TGA Meeting' response, dated 27 November 2014. The type of submission can be discussed with the TGA prior to submission.
7. Batch Release Testing by Laboratories Branch: It is a condition of registration that, as a minimum, the first five independent batches of Inflectra, Emisima, Flixceli, Inflectra infliximab (rmc) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Summary of issues

Summary of issues rheumatology indications

The primary issues with this submission for the rheumatology indications and in general are as follows:

1. The first major issue concerns the adequacy of the evidence in RA and AS and the ability to extrapolate this evidence and what is known about the pathophysiology of the diseases in the various indications and the mechanism of action of infliximab to the indications without specific clinical trial data, namely PsA, CD, UC and plaque psoriasis.
2. The second major issue concerns the differences observed in the rates of TB and serious pneumonia between Inflectra and Remicade.
3. The third major issue concerns the ways in which information about the biosimilarity to the reference product should be communicated in the PI, CMI and any educational materials including DHCPL.

Summary of issues inflammatory bowel disease

1. No studies of Inflectra in inflammatory bowel disease have been presented for evaluation. The sponsor is seeking approval for these indications based on extrapolation of indications. It is not clear whether this is appropriate. The mechanisms of action of Remicade in inflammatory bowel disease may be different from its mechanisms of action in other indications and may include ADCC.
2. Nonclinical testing has shown a difference in potential ADCC between Remicade, the innovator and Inflectra under specific circumstances.
3. The submission did not contain any pharmacokinetic data for children however, the inflammatory bowel disease indications include use in children aged from 6 years. It is not clear whether pharmacokinetic data in children, should be required.

Summary of issues psoriasis

No studies of Inflectra (the proposed biosimilar infliximab) in psoriasis (PsA) patients have been presented for evaluation. The sponsor is seeking approval for use of Inflectra in psoriasis on the basis of extrapolation of indications.

One issue is to what extent infliximab's mechanism of action varies by indication due to varying contributions of FcγRIIIA mediated effects. A view was put that ADCC was the key biological effect of infliximab that would be FcγRIIIa mediated. The sponsor argues against ADCC being of relevance in infliximab's action in psoriasis. It seems unlikely ADCC has a dominant role; also, it is an open question as to whether FcγRIIIa binding differences noted in the quality evaluation translate to differences in ADCC in patients. However, a degree of uncertainty remains.

A second broad issue is that while efficacy appeared similar for the two agents in RA and AS, this could be because those two models are insensitive, that is do not detect true differences that might be clinically relevant in other indications. The clinical unit 4 reviewer thinks the reasonably close match in efficacy outcomes in the main RA and AS studies, and the fact that efficacy was comparable across agents in two indications, offsets this risk sufficiently.

A third and critical issue is that the safety of the two agents was not similar in an important regard that is the incidence of active TB (including disseminated disease). There are grounds to argue that a difference of the magnitude seen cannot be offset sufficiently by post-marketing activities.

Proposed action

The Delegate had no reason to say, at this time, that the application for Inflectra should not be approved for registration for the indications involving RA, AS and PsA.

The clinical unit 1 reviewer has no objection to the registration of for the following indications:

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

Inflectra is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Inflectra is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Inflectra is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

On balance the clinical unit 4 reviewer would be prepared to recommend (to the TGA Delegate) approval of the psoriasis indication, if there is satisfactory evidence of efficacy and safety in the RA and AS target populations (for example if the imbalance in active TB can be shown to be unrelated to a differential impact on immunosuppression; also if the issue of model sensitivity is addressed sufficiently). The clinical unit 4 reviewer's recommendation is also contingent upon the views of the ACPM concerning the FcγRIIIa/ ADCC issue relating to psoriasis.

The clinical unit 4 reviewer is not in a position to say, at this time, that the product should be approved for treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. This is because approval in psoriasis depends upon approval in other indications.

Request for ACPM advice (April 2015 ACPM meeting)

The committee is requested to provide advice on the following specific issues. Please note that the committee is also requested to provide advice on the matters raised in the sections of advice from clinical evaluation unit 1 and clinical evaluation unit 4.

1. Is the difference in pharmacokinetic results for the antibody positive population in study CT-P13 1.1 in patients with ankylosing spondylitis of clinical concern?
2. Is there sufficient clinical trial evidence of similarity to support the indications relating to rheumatoid arthritis and ankylosing spondylitis for this biosimilar infliximab?
3. Is there sufficient evidence with regard to pathophysiology, mechanism of action of infliximab and from the similarity in clinical trial evidence in rheumatoid arthritis and ankylosing spondylitis to support extrapolation of the data to the indication of psoriatic arthritis?
4. What are ACPM's views regarding the differential rates of both serious pneumonia and TB in the CT-P13 clinical trial programme? Is the incidence of TB and serious pneumonia observed within the expected range? Are the findings acceptable to conclude similarity with the safety profile of Remicade? The reviewer (clinical evaluation unit 4) with regard to plaque psoriasis has also expressed concern over this issue.
5. What are the ACPM's views on how this product, which is a biosimilar medicine, should be communicated and reported in the PI, CMI and so on? Should there be anything further, for example educational material?

6. Has sufficient evidence and/or justification been presented to support extrapolation of the data to the indications of Crohn's disease and ulcerative colitis in both adults and children?
7. Has sufficient evidence and/or justification been presented to support extrapolation of the data to the indication of psoriasis?
8. The reviewer with regard to the indication for Crohn's disease and ulcerative colitis has asked a number of specific questions of the ACPM. These are above (in advice from clinical evaluation section 1).
9. The reviewer with regard to the indication for plaque psoriasis has asked a number of specific questions of the ACPM. These are located above (in advice from clinical evaluation unit 4).

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

The sponsor responded to questions, providing additional information for consideration by the Advisory Committee.

Advisory Committee Considerations April 2015 ACPM Meeting

The ACPM having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Inflectra, Emisima, Flixceli, Remsima lyophilised powder, containing 100 mg of infliximab to have an overall positive benefit–risk profile for the following indications:

Rheumatoid Arthritis in adults

Inflectra, in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:

Patients with active disease despite treatment with methotrexate

Patients with active disease who have not previously received methotrexate.

Inflectra should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis

Inflectra is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.

Psoriatic arthritis

Inflectra is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease-modifying anti-rheumatic drug (DMARD) therapy.

Inflectra may be administered in combination with methotrexate.

Psoriasis

Inflectra is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy considered Inflectra, Emisima, Flixceli, Inflectra lyophilised powder, containing 100 mg of infliximab has a negative benefit-risk profile for the proposed indications:

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

Inflectra is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Inflectra is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Inflectra is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

In making both these recommendations the ACPM:

- The ACPM was of the view that there are differences in the chemical qualities and purity of Inflectra and Remicade which could reasonably not be anticipated to result in clinically meaningful differences in efficacy, PK, immunogenicity and safety between the two medicines. However, non inferior efficacy of Inflectra has been established only for RA.
- The ACPM considered extrapolation is possible to AS, PsA and psoriasis.
- The ACPM noted the comparative data on PK, PD and immunogenicity are limited.
- The ACPM noted it has not been established that the role of TNFα in CD and UC is identical to that in RA.
- The ACPM noted the application proposes a dose of Inflectra in inflammatory bowel disease indications of 5 mg/kg, which may be increased to 10 mg under certain circumstances. However, the Inflectra clinical trial programme did not utilise doses over 5 mg/kg for any patients.
- In the absence of efficacy and safety data on the use of Inflectra, particularly in children and adolescents with inflammatory bowel disease, the ACPM considered the dossier does not contain sufficient data to extend Inflectra use to inflammatory bowel disease indications.
- The ACPM considered the properties of two anti-TNF agents, which are not intact immunoglobulin molecules. It was noted that certolizumab pegol is a PEGylated Fab′ fragment of humanised anti-TNF and thus cannot mediate Fc related functions and thus cannot mediate ADCC, complement mediated cytotoxicity or reverse signalling through cell bound TNFα. Certolizumab pegol has not been approved by TGA for use in inflammatory bowel disease but is considered to be effective in these disorders. This suggests that ADCC may not be important in the diseases in which certolizumab is effective. However, etanercept, derived from TNF receptor and which does not mediate reverse signalling or Fc related functions has not been shown to be effective in inflammatory bowel disease and is not licensed in any jurisdiction for inflammatory

bowel disease indications. It does therefore remain possible that these functions are important in the action of anti TNFα agents in inflammatory bowel disease. It is therefore difficult to extrapolate the efficacy of Inflectra from RA, in which reverse signalling and Fc related activities are not important, to inflammatory bowel disease where they may be.

- The ACPM noted that the 12 day half-life of Inflectra in AS is evidence of functional Fc but did not consider this sufficient clinical evidence that all Fc related functions of Remicade can be extrapolated to Inflectra.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Inclusion in the RMP for the sponsor to monitor the incidence of TB and serious pneumonia.
- Provision in the RMP to monitor for differences in efficacy between second line use in RA and use as first line therapy in RA and as therapy for AS, PsA and psoriasis.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- The consumer should be provided with a clear explanation of what a biosimilar product is
- Highlight in the PI and the relevant section of the CMI the importance of TB screening and prophylaxis of TB in those patients at risk of re-activation of the disease.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. *Is the difference in pharmacokinetic results for the antibody positive population in study CT-P13 1.1 in patients with ankylosing spondylitis of clinical concern?*

The ACPM noted that the equivalence criteria were not met because the upper bound of the CI for AUC was outside the pre-specified range. However, the ACPM advised that this is unlikely to impact efficacy (or safety).

2. *Is there sufficient clinical trial evidence of similarity to support the indications relating to RA and AS for this biosimilar infliximab?*

The ACPM advised that there is sufficient clinical trial evidence of similarity to support the indications relating to RA and AS for this biosimilar infliximab.

3. *Is there sufficient evidence with regard to pathophysiology, mechanism of action of infliximab and from the similarity in clinical trial evidence in RA and AS to support extrapolation of the data to the indication of PsA?*

The AS data come from study CT-P13 1.1 which was a Phase I safety, PK and PD study. The efficacy outcomes supported the extension of indication to AS since when ASAS scores were compared the odds ratio for % responders was close to 1.00 in each comparison with 95% CI straddling 1.00. However, the 95% CIs were wide and outside the range usually required in non-inferiority comparisons. The AS indication is thus dependent on extrapolation from RA and cannot be used for extrapolation of efficacy to other indications.

The ACPM accepted the evidence for RA was sufficient to conclude similarity between Inflectra and Remicade and that, given the similar mechanisms of action between RA and AS, that the data can be extrapolated to support the PsA indication.

4. *What are ACPM's views regarding the differential rates of both serious pneumonia and TB in the CT-P13 clinical trial programme? Is the incidence of TB and serious pneumonia observed within the expected range? Are the findings acceptable to conclude similarity with the safety profile of Remicade? The reviewer with regard to plaque psoriasis has also expressed concern over this issue.*

The ACPM noted that these are a cause for concern and cannot be easily dismissed as a randomisation problem or statistical aberration and noted that infection risk is a recognised feature of anti-TNF use. However, the ACPM was of the view that, the difference in diagnosis of TB disease may be explained by the higher prevalence of and deficiencies and/or variability in screening for TB infection in the countries where the trial programme was conducted. Nonetheless, the ACPM noted that there is insufficient evidence to discount the possibility that there are different rates of TB activation for this biosimilar product compared to the incidence with Remicade. The ACPM advised that this highlights the importance of high quality screening for TB as well as initiating TB prophylaxis in patients deemed to be at risk of TB reactivation prior to starting treatment with any infliximab product. The ACPM noted that such monitoring was included in the PI but wished to re-enforce the importance of such monitoring in the PI and in surveillance in the RMP.

Despite the differences, the ACPM advised that the findings are acceptable to conclude similarity with the safety profile of Remicade. For pneumonia, ACPM noted the imbalance but considered the finding acceptable to conclude similarity with Remicade.

5. *What are the ACPM's views on how this product, which is a biosimilar medicine, should be communicated and reported in the PI, CMI etcetera? Should there be anything further, for example educational material?*

The ACPM advised that there needs to be an explanation in the PI and CMI regarding what is a biosimilar product. An educational 'Dear Doctor' letter on the subject might also be useful.

6. *Has sufficient evidence and/or justification been presented to support extrapolation of the data to the indications of Crohn's disease and ulcerative colitis in both adults and children?*

The ACPM noted that it has not been established that the role of TNFα in CD and UC is identical to that in RA. The binding of sTNFα does not fully explain the mode of action of anti TNF agents in inflammatory bowel disease. The ACPM also noted that larger doses are required to treat inflammatory bowel disease and there also might be a different spectrum of activity of infliximab in these conditions. Therefore, the ACPM advised that the data are inadequate from the single pivotal trial in RA (where binding of sTNFα is thought to be the most important property of infliximab) to be reassured that the results presented can be extrapolated to CD and UC.

7. *Has sufficient evidence and/or justification been presented to support extrapolation of the data to the indication of psoriasis?*

The ACPM noted that, although there is differential target tissue, the ACPM advised there are sufficient data and similarities in conditions and treatment doses to support extrapolation of the data to the indication of psoriasis.

The reviewer (clinical unit 1) with regard to the GI indications has asked the following specific questions of the ACPM:

8. *Are there reasonable grounds for concern that the difference in FcγRIIIa binding between Inflectra and Remicade, and hence potential ADCC could result in differences in efficacy for the inflammatory bowel disease indications?*

The ACPM noted that Inflectra clearly binds to membrane associated TNFα but advised that the application is unsupported by clinical evidence that the binding imparts to Inflectra all the properties of Remicade.

9. *Are these grounds of sufficient concern that the inflammatory bowel disease indications for Remicade should not apply to Inflectra?*

The ACPM advised that there are grounds for concern that the inflammatory bowel disease indications should not apply to Inflectra (see question 6 above).

10. *Should consideration be deferred until further evidence of similarity is available?*

The ACPM advised that it is premature to recommend registration for the inflammatory bowel disease indications for Inflectra and that further clinical evidence should be submitted to reassure the ACPM before the inflammatory bowel disease indication is approved for Inflectra.

11. *Is there a need for comparison of the pharmacokinetics of Inflectra and Remicade in children aged from 6 years?*

The ACPM agreed with the Delegate that as Inflectra's pharmacokinetics in children is unlikely to be different to that of Remicade.

The reviewer (clinical unit 4) with regard to the plaque psoriasis indication asked the following specific questions of the ACPM:

12. *Is there concern that the observed imbalance in active tuberculosis could make it difficult to declare the two products biosimilar?*

See response to Question 4.

13. *Is there concern that studies showing comparability of efficacy in RA and AS are insufficiently sensitive to detect real differences in efficacy, which might be seen in psoriasis?*

The ACPM agreed that it is quite possible that the studies comparing efficacy in RA and AS are insufficiently sensitive to detect real differences in efficacy and therefore that differences in efficacy might exist in psoriasis. The ACPM did not consider this uncertainty precluded the psoriasis indication. However, monitoring of efficacy and safety in psoriasis should be incorporated into the RMP.

14. *Is there concern that the demonstrated difference in affinity to FcγRIIIa will translate, for example via differential capacity for the two products to leverage ADCC, into varying efficacy in psoriasis?*

The ACPM noted that the difference in FcγRIIIa was small. Further, the ACPM was not convinced that this demonstrated difference in Fc binding related activity was of clinical significance or that there is strong evidence of an important role for ADCC in RA or psoriasis.

15. *In relation to Question 14, if the ACPM considers that there is uncertainty about this issue; is the degree of uncertainty sufficient to invalidate the extrapolation of indications to psoriasis?*

The ACPM did not consider there was clinically significant uncertainty and that the results from RA can be extrapolated to psoriasis.

16. *Is the balance of efficacy and safety of Inflectra sufficiently established to approve the psoriasis indication?*

The ACPM advised that there is sufficient efficacy and safety data to approve the psoriasis indication.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Timeline: The application was resubmitted to the June 2015 ACPM for additional advice as additional information had become available.

Delegate's overview for June 2015 ACPM

Following the advice from the April ACPM Meeting, further advice was sought by the Delegate responsible for the inflammatory bowel disease indications (clinical unit 1). The request for advice summary and the sponsors Pre-ACPM response for the June 2015 ACPM are presented below.

Background

Previously the ACPM considered there were insufficient data on the use of Inflectra in inflammatory bowel disease indications. Additional information, particularly post-market efficacy and safety data in inflammatory bowel disease data have been made available.

The ACPM previously considered that in the absence of efficacy and safety data on the use of Inflectra in children was of concern. New information on paediatric use of Inflectra is now available.

At the ACPM meeting in April 2015 the ACPM provided advice on a submission to register Inflectra (also referred to as CT-P13) and the alternative tradenames as a biosimilar infliximab. The ACPM considered that the product had an overall positive benefit–risk profile for the current indications of infliximab (Remicade) other than the indications pertaining to inflammatory bowel disease. These indications are:

> *Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)*
>
> *Inflectra is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.*
>
> *Refractory Fistulising Crohn's Disease*
>
> *Inflectra is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.*
>
> *Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years).*
>
> *Inflectra is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.*

The sponsor has now responded to the advice in the ACPM's resolution #2339. Updated versions of the following previously submitted information were included with the sponsor's response:

- PK modelling report; was previously submitted as part of response to the first round of questions (June 2014)
- Korean post-marketing surveillance study; previously submitted as response to Question 4 of the second round of questions (September 2014)

- EU studies (Norway, Hungary, Czech); these studies were discussed during the face to face meeting held with TGA on 14th November 2014. The study reports were provided as follow up information
- A poster presentation on the use of Inflectra in 50 paediatric patients with inflammatory bowel disease in Poland.

The major points addressed by the sponsor are summarised below.

Regulatory considerations

The sponsor has noted that the TGA has adopted the EU Guideline.**Error! Bookmark not defined.** Regarding extrapolation of indication, the sponsor believes that it has met the criteria in that guideline for extrapolation to the inflammatory bowel disease indications for CT-P13 (Inflectra) based on an extensive body of evidence supporting structural and biological similarity between CT-P13 and Remicade in conjunction with demonstrated clinical comparability between the two products in RA and AS. The sponsor has noted that other regulators including the EMA and the Japanese Ministry of Health, Labour and Welfare have approved Inflectra for all the indications currently approved for Remicade, including the inflammatory bowel disease indications. The TGA's clinical evaluator also recommended approval of all those indications.

The ACPM was advised at the April 2015 meeting that Health Canada has not approved Inflectra for the inflammatory bowel disease indications. The sponsor has noted that there were scientific and regulatory reasons for Health Canada not approving those indications, for example; procedural constraints for the review of the totality of the evidence, lack of the external scientific expert input, lack of the opportunity for applicants to submit additional data or engage in open dialogue.

Health Canada in a meeting held in February 2015 with [information redacted] (the sponsor in Canada). The Biologics and Genetic Therapies Directorate (BGTD) of Health Canada have provided an update on the current situation in Canada, which is included in the papers for the June 2015 ACPM.

Extrapolation of therapeutic similarity

The EU Guideline;[33]**Error! Bookmark not defined.** states the following in regard to the extrapolation of clinical data for medicinal products with multiple indications:

> '*In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications. In certain cases, it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product. Justification will depend on for example, clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications. Possible safety issues in different subpopulations should also be addressed.'*

The above recommendation does not specify the extent or nature of the justification for extrapolation of indications where the originally authorised product has multiple indications. This requires case by case consideration, which allows the possibility of regulatory agencies reaching different conclusion when presented with the same dataset.

[33] EMEA/CHMP/BMWP/42832/2005: Guideline on similar biological medicinal products Containing Biotechnology-Derived Proteins as Active Substances: Non-Clinical and Clinical Issues

The ACPM noted that it has not been established that the role of TNFα in CD and UC is identical to that in RA and that the binding of sTNFα does not fully explain the mode of action of anti TNF agents in inflammatory bowel disease.

The sponsor has noted that the role of TNFα might not be identical across indications but in all indications, for which licensure is sought TNFα is a key factor in inflammation, and structural damage, and is found at high concentrations at the sites of inflammation and in the serum of these patients. Published papers were submitted to support the following statements regarding the mechanisms of action of TNFα; in patients with CD, high levels of TNFα are found in the deeper layers of the lamina propria and submucosa; and in patients with UC high levels of TNFα are observed in the sub epithelium and upper layers of the lamina propria. Thus anti TNFα therapy is an important option in the management of these inflammatory diseases.

Ten published papers identifying mechanisms of action of sTNFα and a further 7 papers discussing the action and/ or inhibition of tmTNFα in inflammatory bowel disease were then described.

The above papers provided details on the multiple mechanisms of action of TNFα. Assurance that structural and nonclinical findings translate to similarity can only be extrapolated to indications where the mechanism of action of infliximab is the same as the mechanism of action in clinical study indications. This was the basis of concern that the inflammatory bowel disease indications of Remicade could not be approved for Inflectra but that the remaining indications for Remicade could be approved.

The sponsor has previously provided data that it considered sufficiently characterised all mechanisms of action using physiologically relevant models and has demonstrated similarity of Inflectra (CT-P13) with Remicade in:

- binding and neutralisation of sTNFα
- binding to tmTNFα
- induction of reverse signalling and resulting suppression of cytokines and induction of apoptosis
- induction of regulatory macrophages.

The ACPM has expressed concern that reverse signalling, Fc relative activities and ADCC may be important in the action of anti TNFα agents in inflammatory bowel disease and that it was difficult to extrapolate efficacy of Inflectra in RA, in which reverse signalling and Fc related activities are not important, to inflammatory bowel disease where those mechanisms may be important. The sponsor has provided in vitro comparative tests for these mechanisms of action and contends that an efficacy comparison in the indications with likely varying mechanisms of action is not needed. A document submitted by the sponsor summarised the assays that have been performed. The Delegate noted the nonclinical evaluator did not consider that this product should be rejected due to insufficient evidence of comparability of the mechanism of action between Inflectra and Remicade.

Dose required to treat inflammatory bowel disease is higher than the rheumatoid arthritis dose and there might be a different spectrum of activity of infliximab in these conditions

The ACPM previously noted that the dose of Inflectra in inflammatory bowel disease indications is 5 mg/kg, which may be increased to 10 mg under certain circumstances. However, the Inflectra clinical trial programme did not utilise doses over 5 mg/kg for any patients. The infliximab dose regimen for patients with RA is 3 mg/kg at Weeks 0, 2 and 6 then every 8 weeks thereafter. For the inflammatory bowel disease indications the recommended doses are for an initial dose regimen of 5 mg/kg at weeks 0, 2 and 6 and

then maintenance doses of 5 mg/kg every 8 weeks thereafter. For patients with CD indications the maintenance doses may be increased to 10 mg/kg for patients who have an incomplete response during maintenance treatment. This higher dose applies to children as young as 6 years.

The sponsor performed Study CT-P13 3.1 in patients with AS who received the 5 mg/kg dose regimen. This was a randomised, double blind, multicentre, parallel group Phase I study designed to compare the pharmacokinetics and safety of multiple doses of CT-P13 (5 mg/kg) with the reference product, Remicade (5 mg/kg) administered by a 2 hour IV infusion per dose in patients with active AS. Patients were randomly assigned in a 1:1 ratio to receive either CT-P13 or Remicade as a single dose of study treatment on the first day of each dosing period. The total duration of the study was up to 68 weeks. The dosing interval in the maintenance phase was 8 weeks.

The sponsor submitted a dose proportionality of CT-P13 extrapolated from a population pharmacokinetic analysis. While this analysis demonstrated linearity within the 3 to 5 mg/kg dose range it did not address whether there could be loss of linearity with doses of 10 mg/kg. The pharmacokinetic parameters of Remicade are known to be proportional to the doses given (5 and 10 mg/kg in patients with CD, 5, 10, and 20 mg/kg in patients with RA) in previous reports of pharmacokinetics of Remicade and as stated in the PI for Remicade. It is therefore reasonable to assume that dose proportionality for Inflectra at doses up to 20 mg/kg would also occur.

Post-market studies

Updates from four post-market studies were presented.

Czech Republic Cohort Assessment

Comment: No response or remission results were provided for patients who had switched from other therapies. For patients commencing therapy, particularly those with CD the results appear extremely good, though this is based on very low patient numbers. Cross study comparisons with Remicade are limited due to the use of different methods of assessment of clinical response/ remission, as well as the size and design of the assessment.

Hungarian Cohort Assessment

Comment: While cross study comparison with Remicade efficacy and antibody positivity rates is limited by the use of differing definitions of remission, assessment time points and study design it is clear that Inflectra has some efficacy. The ADA levels are difficult to interpret due to the small numbers of patients assessed and the pre-existing antibody in patients who were anti TNF naïve. Antibody positivity in anti TNF experienced patients at baseline was also quite high.

Korean Surveillance Study

Comment: The above data allow some comparison with the studies of Remicade described in the PI for Remicade because the same definition of clinical remission and response for CD was used and there are some efficacy data for the Weeks 14 and 30 assessments. Differences in study size, design and patient selection still limit the comparison however, the efficacy results for Inflectra appear broadly comparable to those of Remicade.

Norwegian Cohort Assessment

Comment: The definitions of clinical remission and response for CD in this cohort assessment have allowed for reporting of higher rates of remission than for response. Nevertheless, the results are similar to those of other post-market

studies of Inflectra and broadly consistent with results for Remicade in both CD and UC.

Paediatric data in inflammatory bowel disease

The ACPM previously considered there were insufficient data to extend Inflectra use to inflammatory bowel disease indications. Limited information on the use of Inflectra in a cohort of children with inflammatory bowel disease was presented in 2 posters from D. Jarzebicka et al. These posters presented preliminary efficacy data from 32 paediatric CD patients and 6 paediatric UC patients. The posters were presented at the 10th Congress of European Crohn's and Colitis Organisation (ECCO) in Spain. Another poster, by J. Sieczkowska et al., presented efficacy data from 12 children with CD treated in Poland. It was not possible to determine whether these children were a subset of the 32 children included in the cohort described in the poster by D. Jarzebicka et al., though the sponsor has stated these were independent groups in Poland and the data were from 50 children.

Efficacy assessment was primarily by Paediatric Crohn's Disease Activity Index (PCDAI) for the induction period only. In all 3 posters, there was a reduction from baseline in mean PCDAI in these children.

Safety information from the post-market studies

The post-market data presented are generally from small, non randomised, uncontrolled, open studies of short duration data. Among these studies from a total of 518 patients with inflammatory bowel disease there was only one new case of TB (in a Korean patient). Infusion reactions were reported in none of the Czech patients, 6 Hungarian patients, 9 Korean patients and at least 2 Norwegian patients. Two Norwegian patients discontinued due to infusion reactions, one of which was considered to be severe.

Discussion

The issues of concern to the ACPM regarding the benefits and risks from the use of Inflectra in patients with inflammatory bowel disease have been further assessed. The additional information comprised further scientific justification for extrapolation of the indications to include inflammatory bowel disease indications and additional post-market data. The Delegate previously had no objection to the inclusion of inflammatory bowel disease indications for Inflectra and continues to consider that inclusion of these indications is acceptable based on the data submitted.

The sponsor has presented more recent safety and efficacy data on the use of Inflectra in inflammatory bowel disease indications. These are post-market case series and one open study and do not provide a direct comparison of either the safety or efficacy of Inflectra with the innovator infliximab product, Remicade. They are open, uncontrolled, and non-randomised. Varying methods were used to assess efficacy, the duration of assessment included the induction period only in the majority of cases and only broad cross study comparisons with the efficacy of Remicade is possible. Nevertheless, the Delegate does not consider that a comprehensive development program to examine the efficacy and safety of Inflectra in inflammatory bowel disease indications is necessary given the comparative data on structure and function previously considered acceptable for the other indications of infliximab.

The major issue of concern currently is the exposure of children to Inflectra. Data are available only from poster presentations from the 10th ECCO, held in February 2015. While efficacy of Inflectra was shown in these cohorts of children no information on the ages of the children treated or the severity of initial disease was provided, nor were safety data presented. However, data on use of a product in paediatric subgroups is not a requirement in any of the adopted EU guidelines concerning biosimilars. The Australian specific guideline is under review. Given this, the Delegate is inclined to consider the limited information provided to be acceptable.

Proposed action

The Delegate had no reason to say, at this time, that the application for Inflectra should not be approved for registration.

Advice sought (for the June 2015 ACPM meeting)

The committee is requested to provide advice on the following specific issues:

1. The ACPM has previously considered Inflectra to have an overall positive benefit–risk profile for the indications of Remicade (infliximab) other than the inflammatory bowel disease indications. Having considered the additional justifications and post-market data concerning the safety and efficacy of Inflectra in inflammatory bowel disease indications, does the committee continue to consider that the benefit–risk profile for Inflectra is negative?
2. The ACPM previously considered that efficacy and safety data on the use of Inflectra, particularly in children and adolescents with inflammatory bowel disease was required. Does the committee now consider the additional information on the use of Inflectra in inflammatory bowel disease and specifically in paediatric patients with inflammatory bowel disease adequately addresses their concerns?

Sponsor response to the delegate's overview for the June 2015 ACPM meeting

The sponsor responded to questions, providing additional information for consideration by the Advisory Committee.

June 2015 ACPM Meeting

The ACPM, taking into account the additional submitted evidence of efficacy and safety considered Inflectra, lyophilised powder, containing 100 mg of infliximab (rmc) to have an overall positive benefit–risk profile for the following indications:

> *Crohn's Disease in Adults and in Children and adolescents (6 to 17 years):*
>
> *Inflectra, Emisima, Flixceli, Remsima is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.*
>
> *Refractory Fistulising Crohn's Disease:*
>
> *Inflectra, Emisima, Flixceli, Remsima is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.*
>
> *Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years):*
>
> *Inflectra, Emisima, Flixceli, Remsima is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.*

Specific advice

The ACPM advised the following in response to the specific Delegate's questions on this submission:

1. The ACPM has previously considered Inflectra to have an overall positive benefit–risk profile for the indications of Remicade (infliximab) other than the inflammatory bowel disease indications. Having considered the additional justifications and post-market data concerning the safety and efficacy of Inflectra in inflammatory bowel disease

indications, does the committee continue to consider that the benefit–risk profile for Inflectra is negative?

The ACPM advised that after consideration of the additional justifications and post-market data concerning the safety and efficacy of Inflectra in inflammatory bowel disease indications that the committee no longer considers the benefit-risk profile for those indications to be negative.

2. *The ACPM previously considered that efficacy and safety data on the use of Inflectra, particularly in children and adolescents with inflammatory bowel disease was required. Does the committee now consider the additional information on the use of Inflectra in inflammatory bowel disease and specifically in paediatric patients with inflammatory bowel disease adequately addresses their concerns?*

The ACPM advised that in considering the additional information on the use of Inflectra in inflammatory bowel disease and specifically in paediatric patients with inflammatory bowel disease, that their concerns regarding the use of Inflectra in children and adolescent's with inflammatory bowel disease have been adequately addressed.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Remsima/ Emisima/ Flixceli/ Inflectra (infliximab (rmc)) 100 mg powder for injection vial indicated for:

Rheumatoid Arthritis in adults

Remsima or Emisima or Flixceli or Inflectra in combination with methotrexate, is indicated for the reduction of signs and symptoms and prevention of structural joint damage (erosions and joint space narrowing) in:

-patients with active disease despite treatment with methotrexate

-patients with active disease who have not previously received methotrexate.

Remsima or Emisima or Flixceli or Inflectra should be given in combination with methotrexate. Efficacy and safety in Rheumatoid Arthritis have been demonstrated only in combination with methotrexate.

Ankylosing Spondylitis

Remsima or Emisima or Flixceli or Inflectra is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease

Psoriatic arthritis

Remsima or Emisima or Flixceli or Inflectra is indicated for the treatment of the signs and symptoms, as well as for the improvement in physical function in adult patients with active and progressive psoriatic arthritis who have responded inadequately to disease modifying anti-rheumatic drug (DMARD) therapy.

Remsima or Emisima or Flixceli or Inflectra may be administered in combination with methotrexate.

Psoriasis

Remsima or Emisima or Flixceli or Inflectra is indicated for the treatment of adult patients with moderate to severe plaque psoriasis for whom phototherapy or conventional systemic treatments have been inadequate or are inappropriate. Safety and efficacy beyond 12 months have not been established.

Crohn's Disease in Adults and in Children and adolescents (6 to 17 years)

Remsima or Emisima or Flixceli or Inflectra is indicated for the treatment of moderate to severe Crohn's disease, to reduce the signs and symptoms and to induce and maintain clinical remission in patients who have an inadequate response to conventional therapies.

Refractory Fistulising Crohn's Disease

Remsima or Emisima or Flixceli or Inflectra is indicated for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients.

Ulcerative colitis in Adults and in Children and adolescents (6 to 17 years)

Remsima or Emisima or Flixceli or Inflectra is indicated for the treatment of moderately severe to severe active ulcerative colitis in patients who have had an inadequate response to conventional therapy.

Specific conditions of registration applying to these goods

1. Implement EU Risk Management Plan Version 4.0 (dated May 2014, DLP 15 April 2013) and Australian Specific Annex Version 2.0 (dated 31 July 2015), and any future updates (where TGA approved) as a condition of registration.
2. Provide interim reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan through PSURs/PBRERs.
3. Provide final reports of the additional pharmacovigilance activities referenced in the pharmacovigilance plan, once available.
4. Implement additional risk minimisation activities, within 3 months of approval, where approved by the TGA PSAB.
5. Provide the amalgamated report from registry data that will report on TB and other serious infections when it is available.
6. The final study report for study CT-PI33.4 must be submitted to the TGA, within 3 months of completion for evaluation as a minor variation Category I submission:
7. Batch release testing by TGA Laboratories Branch: It is a condition of registration that, as a minimum, the first five independent batches of Remsima, Emisima, Flixceli, Inflectra; infliximab (rmc) imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

Final outcome

The PI approved at the time of the initial decision to approve the registration of Remsima/ Emisima/ Flixceli/ Inflectra (infliximab (rmc)) 100 mg powder for injection vial is at Attachment 1.

Following the initial decision described above and subsequent to the entry of the product into the ARTG, a third party sought a review under the provisions of Section 60 of the Therapeutics Goods Act of the decision by a Delegate of the Minister to approve the PI for the product.

The appeal was not seeking to review the decision to approve the product, but was seeking amendments to the specific wording of the approved PI.

Outcome of s60 appeal

The s60 Delegate decided to set aside the decision to approve the current PI and substitute in its place a decision to approve an amended version in order to be satisfied that the PI reflects the basis on which the Secretary decided under subsection 25(3) of the Act to register the goods.

The s60 Delegate's decision was the subject of an appeal to the Administrative Appeals Tribunal (AAT) as provided for in section 60 (6) (b) of the Act. The s60 Delegate's decision was stayed until the AAT has determined the matter. Therefore, the current approved PI is the PI approved by the Secretary's Delegate.

Outcome of AAT appeal

The Administrative Appeals Tribunal decided that the Product Information approved by the Secretary's Delegate should be the approved Product Information for the product. This decision was implemented by the TGA on 12 February 2018.

The approved Product Information is at Attachment 1.

Attachment 1. Product Information

The PI for Inflectra approved with the submission which is described in this AusPAR is at Attachment 1.[34] For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>[35]. The PI for Emisima, Flixceli, and Remsima, Inflectra is identical except for the product name (also attached).

Attachment 2. Reports from Clinical Units 1 and 4

[34] Please note that the sponsor has changed subsequent to registration. At the time of publication of this AusPAR Pfizer Australia Pty Ltd is the current sponsor for Inflectra and Celltrion Healthcare Australia Pty ltd for Remsima, Emisima, and Flixceli

[35] The currently approved PI is the subject of the s60 appeal described above. The outcome of that appeal is currently the subject of an AAT appeal.

Therapeutic Goods Administration

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