Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Delegate's reports from clinical units 1 and 4

Proprietary Product Name: Remsima, Emisima, Flixceli, Inflectra

Sponsor: Pharmbio Pty Ltd[1]

TGA Health Safety Regulation

[1] The sponsorship for the products has changed subsequent to registration. For details please see 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.
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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

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List of 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

Abbreviation	Meaning
CS	Corticosteroids
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
EOS	End-of-Study
ESR	Erythrocyte Sedimentation Ratio
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBI	Harvey-Bradshaw index
IFX	Infliximab
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	MTX
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
PBRERs	periodic benefit-risk evaluation reports
PBMC	Peripheral blood mononuclear cells
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

Abbreviation	Meaning
SLE	Systemic lupus erythematosus
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

1. Discussion of indications pertaining to inflammatory bowel disease; advice from clinical unit 1

This review has taken into consideration the clinical and nonclinical evaluation reports, the sponsor's response to evaluation reports, a second round of questions, a nonclinical evaluator evaluation of responses to those questions, information submitted at a meeting with the sponsor on 14 November 2014 and a Pre-ACPM response document intended for the December 2014 ACPM.

Remsima (CT-P13) was granted full marketing authorisation for all the indications that apply to Remicade (infliximab) in the EU and Japan. There was no condition applied to conduct additional studies in Crohn's disease (CD). In Canada marketing authorisation for indications applicable to ulcerative colitis (UC) or CD were not approved. The degree of afucosylation is known to have a potential impact on Fcγ receptor binding. Chile has also not approved the inflammatory bowel disease indications. The sponsor has stated that the biosimilar legislation and guideline in Chile does not provide an option for extrapolation.

Differences in NK cell mediated antibody-dependent cell-mediated cytotoxicity (ADCC) were reported between Remicade and Remsima. These differences have been discussed in other documentation presented to the committee and are further discussed below.

1.1. Nonclinical evaluation

The nonclinical evaluator had concluded in their second round evaluation report that 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 Remsima for all the proposed indications. The nonclinical evaluator also noted that the mechanism of action of infliximab is complex, it is currently widely accepted that neutralisation of soluble tumour necrosis factor (sTNF) and transmembrane tumour necrosis factor (tmTNF) is responsible for the efficacy in rheumatoid arthritis (RA) by preventing tumour necrosis factor (TNF) from binding to its receptor and mediating downstream cellular functions. However, other mechanisms are likely to be involved in inflammatory bowel diseases, which 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 difference identified between Remsima (CT-P13) and Remicade is the affinity of FcγRIIIa binding (CT-P13 = 102% versus Remicade = 130% ($p < 0.0001$).

To explore the clinical implications of the above difference between the innovator and proposed biosimilar infliximab additional questions were presented to the nonclinical evaluator who provided the following opinion regarding the activity of infliximab via ADCC for the inflammatory bowel disease indications:

> '*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 disease *conditions. The fact that ADCC mediated processes are associated with* inflammatory bowel disease *patient populations more responsive to infliximab through an Fc receptor mechanism also adds weight to their relevance in the actions of infliximab. Notwithstanding uncertainties on whether the new studies used a pharmacologically responsive cell type to assess ADCC, it is also uncertain whether these new findings can be extrapolated to in vivo mechanism of infliximab in* inflammatory bowel disease *patients. Based on these uncertainties, a contributing role for Fc dependent*

mechanisms in the actions of infliximab in inflammatory bowel disease *indications cannot be explicitly ruled out.'*

The sponsor has performed an in vitro study that suggested that that expression of tmTNFα by native monocytes was too low to evoke ADCC compared with Jurkat T-cells. However, most studies invoking a role for ADCC in the effects of infliximab have relied on Jurkat T-cell line to make this point, including those previously submitted to support registration of CT-P13 (Remsima). The sponsor did not confirm if the ADCC study was performed using cells with the FcγIIIa-158V polymorphism that are more responsive to infliximab and evoke ADCC8.

The nonclinical evaluator has noted that Fc dependent interaction with infliximab also activates ADCC by an action on FcγRIIIa receptors on NK cells. Polymorphisms of this receptor generate allotypes with variable affinity for the Fc region of IgG: allotypes with a valine residue at amino acid position 158 (FcγRIIIa-158V) have higher affinity for IgG than allotypes with a phenylalanine residue (FcγRIIIa-158F). Of relevance to inflammatory bowel disease conditions, in the early phase of infliximab treatment CD patients with V/V allotype responded to infliximab compared to V/F or F/F, while ADCC activity of PBMCs from either the V/V or V/F allotypes elicited a strong lytic response to tmTNFα expressing Jurkat cells compared to F/F.

Following consideration of the issues above, the nonclinical evaluator was requested to comment further in relation to the differences in responses between CT-P13 and Remicade. Additionally the sponsor provided a Pre ACPM response intended for the December 2014 ACPM meeting. The submission required further assessment and presentation to the ACPM was deferred to allow thorough assessment of that response. The major points concerning differences in ADCC test results between CT-P13 and Remicade are summarised in the responses to the questions below.

1. *Is the FcyIIIa-158V polymorphism in the cell line used in the ADCC study likely to make a difference to the study outcome?*

Nonclinical evaluator response:

Using peripheral blood mononuclear cells (PBMC) (NK cell populations) from FcγRIIIa-158 V/V allotypes would have ensured that optimal (maximal?) conditions for ADCC were used since NK cells of the FcγRIIIa V/V allotype have a higher affinity for Fc and evoke a more potent ADCC reaction at much lower antibody concentrations than other allotypes.[2]

It is unclear whether potential qualitative differences between Remicade and Remsima would manifest as different binding for the different allotypes in CD patients. The link between FcγRIIIa polymorphism and CD is indirect and based on the observation that CD patients with the FcγRIIIa-158 V/V allotype have a more favourable response to infliximab compared with other allotypes. The implication is that, since the polymorphism concerns FcγRIIIa, a corresponding difference in the function of this receptor (that is induction of ADCC by NK cells expressing this receptor) may partly explain the difference in responsiveness. Of the many possible actions of infliximab (for example neutralisation of sTNFα, inhibition/induction of apoptosis, reverse signalling, induction of regulatory macrophages, ADCC/CDC), only ADCC is associated with FcγRIIIa function.

Sponsor response:

FcγRIIIa V/V allotype have a higher affinity for Fc and evoke a more potent ADCC reaction. However, at sites of inflammation in vivo, multiple cell types, immune complexes, soluble serum factors and endogenous IgG will be present and impact binding of infliximab to binding to Fc receptors. It is for this reason the sponsor considers PBMC and whole blood ADCC assay data to

[2] Wu J et al. A novel polymorphism of FcγRIIIa (CD16) alters receptor function and predisposes to autoimmune disease. *J. Clin. Invest.* 19971000, 1059-1070.

be more representative of physiological conditions. Comparable ADCC activity to Remicade was shown under these conditions.

2. *Is there information on the proportion of CD patients who have the responsive FcγRIIIa-158 variant (V/V) and the extent of difference in response rate for those CD patients who have the variant?*

Nonclinical evaluator response:

Information on the proportion of CD patients with this variant was limited to two studies that specifically assessed response to infliximab in FcγRIIIa variants as described below:

Louis et al., (2006);[3] presented findings that examined clinical (as CDAI calculation) and biological responses (as CRP levels) to infliximab according to FcγRIIIa allotypes and graded the responses as either, complete, partial or non responding. To summarise for all patient clinical responses:

- V/V allotypes: 60% complete, 23% partial, 17% non-responding
- V/F allotypes: 51% complete, 22% partial, 27% non-responding
- F/F allotypes: 52% complete, 20% partial, 28% non-responding.

For biological responses:

- V/V: 45% complete, 55% partial, 0% non-responding
- V/F 38% complete, 34% partial, 28% non-responding
- F/F: 27% complete, 40% partial, 33% non-responding.

Proportions for each genotype were as follows (total n = 200): V/V 18%, V/F 50%, F/F 33%.

Moroi et al., (2013);[4] also demonstrated a biological response with infliximab in V/V allotypes but up until 8 weeks of treatment, and clinical responses did not differ between the allotypes. Group sizes were smaller in this study (n = 102) with proportion of genotypes used as: V/V 11.7%, V/F 37.3%, F/F 51%.

Sponsor response:

The available literature;[3,4,5,] suggest that there is no significant difference in clinical response in CD patients of different FcγRIIIa genotypes following infliximab treatment. These data include data obtained in the pivotal CD study (ACCENT I trial) with Remicade. The authors suggest some marginal difference in CRP response between patients of different genotype but the effect on CRP was dependent on the choice of mean or median at baseline for normalisation. CRP response is impacted by other factors such as mediated by IL-1 and IL-6;[6] and bacterially mediated release of these cytokines;[7] and is not fully predictive of the extent of inflammation or clinical disease activity in inflammatory bowel disease patients and responsiveness to infliximab.

The sponsor provided published information on errors in the Moroi paper;[4] that bear on the conclusion regarding the biological response with infliximab. The calculations of ΔCDAI,

[3] Louis E et al Polymorphism in IgG Fc receptor gene FCGR3A and response to infliximab in Crohn's disease: a subanalysis of the ACCENT I study. *Pharmacogenetics and Genomics*. 2006;16 :911-914.
[4] Moroi Ret al. FCGR3A-158 polymorphism influences the biological response to infliximab in Crohn's disease the affecting ADECC activity Immunogeneitcs 2013; 65: 265-271.
[5] Louis E et al Association between polymorphism in IgG Fc receptor IIIa coding gene and biological response to infliximab in Crohn's disease. *Aliment Pharmacol Ther* 2004; 19: 511-519.
[6] Mazlam and Hodgson Interrelations between interleukin-6, interleukin-1 beta, plasma C-reactive protein values, and in vitro C-reactive protein generation in patients with inflammatory bowel disease. Gut 1994; 35: 77-83.
7 Haider D G et al., 2006 C-reactive protein is expressed and secreted by peripheral blood mononuclear cells *Clin Exp Immunol* 2006; 146: 533-539

ΔCDAI%, ΔCRP, ΔCRP% in Table 2 of the paper were incorrect based on the values of CDAI and CRP provided in that table and using the stated method of calculation 'ΔCDAI% = ((CDAI of Week 0) – (CDAI of Week 8))×100/(CDAI of Week 0) and ΔCRP% = ((CRP of Week 0) – (CRP of Week 8))×100/(CRP of Week 0)'.

When calculated correctly, there is no difference in ΔCRP% between the genotype groups at Week 8.

3. *Is this difference in immune system response between Remicade and Remsima likely to result in any difference in efficacy for patients with ulcerative colitis?*

Nonclinical evaluator response:

The role of TNFα in UC is less well characterised than CD and for this reason, literature on ADCC and infliximab has focused on CD. That infliximab, adalimumab and golimumab are indicated for use in UC suggests that their Fc region can potentially participate in FcγRIIIa-dependent interactions. In the sponsor's studies where inflammatory bowel disease patient biopsies were used to prepare lamina propria monocytes, 3 out of 5 were from UC patients, which were found to have very low tmTNFα expression levels (relative to the tmTNFα overexpressing Jurkat T-cell line). On consideration of the available published data, the evidence for ADCC in UC is less compelling.

Having considered the above issues the nonclinical evaluator's conclusion was not changed in that the evaluator did not think a contributing role for Fc-dependent ADCC in the actions of infliximab has been explicitly excluded by the sponsor's additional studies. There is an association between CD and FcγRIIIa (and by extension ADCC) in the actions of infliximab and for this reason the possibility of a contributing role for ADCC should not be dismissed. Evidence for UC is less compelling.

Sponsor response:

Simponi is a humanized version of Remicade and has similar TNFα binding affinity with efficacy in UC. Simponi has lower afucosylation ratio (0.85 to 2.70%), compared to that of Remicade (4.7 to 11.0%) and Remsima (4.3 to 6.3%) based on the sponsor's data. Simponi has lower FcγRIIIa binding and lower ADCC activity based on published data and the sponsor's data. Simponi has lower ADCC activity than infliximab;[8] (and the sponsor's data) but is approved for UC in Australia. This implies that low ADCC does not result in low efficacy in UC.

A detailed discussion of the mechanisms of action of TNFα blockade was included in the meeting notes and in the Pre-ACPM response intended for the December 2014 ACPM meeting. Central to the discussion, the sponsor noted that in evaluating the importance to attach to ADCC assay formation, the critical preliminary question is whether ADCC assays have any predictive value in ascertaining efficacy in inflammatory bowel disease. If not, reliance on these assays to draw any conclusion is arbitrary.

The sponsor noted that in the comparability tests between CT-P13 and Remicade in respect of ADCC, only in one variant of one non-physiologically representative assay could any difference be observed. Purified human NK effector cells had to be taken outside of their natural environment and paired in a particular ratio with genetically engineered Jurkat target cells that do not exist in nature in the absence of serum. The Jurkat cells (used in the assay that showed a difference in ADCC between CT-P13 and Infliximab) express 20 to 25 times more transmembrane TNFα on their surface than LPS stimulated monocytes and as a result, the assay is 20 to 25 times more sensitive than using more physiologically relevant cells. With that test, the ADCC difference was approximately 15 %. This result was seen only when the ratio of NK

[8] Shealy D Characterisation of golimumab, a human monoclonal antibody specific for human tumor necrosis factor α. mAbs 2010; 2: 428-439.

cells to Jurkat cells was 2:1 and at a dose below any concentration on the dose response curve for CT-P13 or Remicade. No difference was observed using other doses or ratios.

The sponsor also claims that ADCC is of no clinical relevance and is of unsubstantiated predictive value in the inflammatory bowel disease indications. In physiologically representative assay conditions, using the normal array of effector and target cells seen in humans, no differences were observed between CT-P13 and Remicade regardless of the ratio of effector to target cells and regardless of dose.

The sponsor noted that many in vitro studies reported in the literature, have found that infliximab can induce ADCC but all these studies employ engineered TNFα overexpressing cell lines as target cells. Infliximab is not observed to induce ADCC in a system comprised of naturally derived cells. Specifically, when LPS stimulated human monocytes are used as target cells and PBMC as a source of effector cells no observable ADCC is seen in response to infliximab or golimumab;[8] these findings have been replicated by the sponsor for CT-P13 and EU sourced Remicade both with PBMC and purified NK cells as source of effector cells. Since LPS stimulated human monocytes are considered representative of the target cells encountered in vivo, these results suggest that ADCC is not likely to play a significant role in mediating the therapeutic effect of anti-TNF therapies.

The sponsor noted that applying the exact same experimental system but replacing activated monocytes as the target with genetically engineered Jurkat cells that overexpress TNFα on their surface cell by approximately 25 fold does induce measurable ADCC activity using both infliximab and golimumab. Also noted is that golimumab was considerably less potent than infliximab in inducing ADCC in these studies with the transformed Jurkat cells, yet is considered effective in UC as well as in RA, PsA and AS.

1.2. Clinical evaluation

The clinical evaluator concluded that there is sufficient evidence to approve this biosimilar infliximab product for all indications that the innovator product, Remicade is currently approved for in Australia. The evaluator stated in their report that the preclinical development program showed that the medicine is comparable with Remicade for the binding of soluble and tmTNF. However, that conclusion was subject to evaluation of the preclinical data.

The clinical evaluator also noted that the submission did not contain any pharmacokinetic data from children, though these indications had been proposed by the sponsor for the inflammatory bowel disease indications. The sponsor was requested to provide any pharmacokinetic data in children and adolescents, or if none exists comment on whether or not there is likely to be any significant PK differences between Remicade and CT-P13 (Remsima) in this population.

The clinical evaluator noted that the sponsor provided a detailed response to this question (based on a mechanistic approach and extrapolation of the observed adult patient data to the paediatric inflammatory bowel disease setting), but without any directly collected data in this target population. In addition, the sponsor reported experience with CT-P13 in treating 92 adult Korean patients with active inflammatory bowel disease as demonstrating similar efficacy and safety compared with historical data from inflammatory bowel disease patients treated in the Remicade registration studies. Furthermore, the sponsor believed there are scientific and ethical reasons for not conducting prospective comparative clinical studies with biosimilar medicines in paediatric patients but to utilise adult patients for an appropriate comparability development program.

The clinical evaluator did not entirely concur with the sponsor's opinion and suggested that the sponsor be requested to collect clinical (efficacy and safety) and PK data in a group of paediatric patients as a condition of registration.

1.3. RMP evaluation

The sponsor was requested to provide a list of ongoing and planned clinical studies. This list was provided and included the following studies pertaining to inflammatory bowel disease. An additional 92 patients with inflammatory bowel disease indications have been enrolled in Korean post-market studies. No post-market studies are proposed to be conducted in Australia. The sponsor has undertaken to report to the TGA on completion of EU and Korean registries and to notify any unexpected safety signals or findings from ongoing and planned registries.

The sponsor advised that Study CT-P13 3.4 in CD patients has not been requested by any authority and has not been designed to fulfil any regulatory obligations or commitments. The sponsor further advised that, it opted to proactively propose and include observational post marketing study in Korea and interventional randomised controlled Study CT-P13 3.4 in inflammatory bowel disease patients. The objectives of these studies were to obtain to evaluate the similarity of CT-P13 against Remicade in terms of efficacy in CD patients, evaluate safety and immunogenicity and address the switch associated safety and immunogenicity in CD patients. Study CT-P13 3.4 has been proposed solely by the sponsor (and Hospira) following CHMP approval and added into RMP. CHMP and pharmacovigilance risk assessment committee (PRAC) did not regard necessary this study and declined to assess or comment on the synopsis of the study as it was considered that inflammatory bowel disease clinical data are useful but essentially redundant from extrapolation scientific perspective.

1.4. Discussion

The evidence regarding ADCC appears not to be clinically relevant. It is apparent only in a laboratory test that is not consistent with the conditions in the body. Furthermore, it has not been established that ADCC has a clinically significant role in the mechanism of action of infliximab, or TNFα antagonists in general. The clinical unit 1 reviewer is of the opinion that the difference in the FcγRIIIa binding assay is not of concern however, the clinical unit 1 reviewer seeks the ACPM's advice on this issue.

The clinical evaluator was also concerned about the need for additional PK data in children. PK data in population subgroups are not routinely requested for generic medicines and clinical unit 1 reviewer sees no issues specific to the PK for infliximab that would require additional PK data in any sub group, including children. For this reason, clinical unit 1 reviewer does not propose that the submission of PK data for Remsima be a condition of registration.

No specific amendments to the proposed PI are requested by clinical unit 1.

1.5. Conclusion and proposed recommendation

1.5.1. Summary of issues

1. No studies of Remsima 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 Remsima under specific circumstances.

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.

1.6. Recommendation

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)

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

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)

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.

1.7. Advice sought by clinical evaluation unit 1

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

1. Are there reasonable grounds for concern that the difference in FcγRIIIa binding between Remsima and Remicade, and hence potential ADCC could result in differences in efficacy for the inflammatory bowel disease indications?
2. Are these grounds of sufficient concern that Remsima the inflammatory bowel disease indications for Remicade should not apply to Remsima?
3. Should consideration be deferred until further evidence of similarity is available?
4. Is there a need for comparison of the pharmacokinetics of Remsima and Remicade in children aged from 6 years?

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

2. Discussion of psoriasis indications; advice from clinical unit 4

2.1. Background

2.1.1. Plaque psoriasis

Psoriasis affects 2.6% of Australians and 85 to 90% of psoriasis patients have chronic plaque psoriasis. Around 10% of these have severe chronic plaque psoriasis (although the sponsor proposes an indication in moderate to severe disease).

'Treatment modalities are chosen on the basis of disease severity, relevant comorbidities, patient preference (including cost and convenience), efficacy, and evaluation of individual patient response.'[9] Disease severity takes into account extent of body surface involvement, involvement of face/palm/sole, and disability.

[9] Up-To-Date; 'Treatment of Psoriasis'; accessed 28.10.2014

Various topical agents are used for psoriasis (topical corticosteroids; emollients; etcetera). Severe disease requires ultraviolet light (for example phototherapy; PUVA[10]) or systemic therapies. The following systemic agents are approved for psoriasis:

- Cyclosporin (for example Neoral: In patients with severe psoriasis in whom conventional therapy is ineffective or inappropriate and the disease has caused a significant interference with quality of life.)
- Methotrexate (for example Methoblastin: Because of the high risk attending to its use, Methoblastin is only indicated in the symptomatic control of severe, recalcitrant, disabling psoriasis which is not adequately responsive to other forms of therapy, but only when the diagnosis has been established, as by biopsy and/or after dermatologic consultations.)
- Acitretin (Severe intractable psoriasis in all its forms)
- Infliximab (TNFα inhibitor): Remicade 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.
- Etanercept (TNFα inhibitor): Adult patients with moderate to severe chronic plaque psoriasis, who are candidates for phototherapy or systemic therapy.
- Adalimumab (TNFα inhibitor): Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
- Ustekinumab (anti-IL12/IL-23): Stelara is indicated for the treatment of adult patients (18 years or older) with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.
- Golimumab and certolizumab pegol are not indicated for psoriasis.
- Apremilast (a phosphodiesterase 4 inhibitor) has been approved by the US FDA for treatment of moderate to severe plaque psoriasis in candidates for phototherapy or systemic therapy.

2.1.2. Regulation

The TGA has published guidance on the evaluation of biosimilars.[11] A key EU guideline adopted by the TGA is the Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues.[12] It is important to acknowledge from within that guideline:

> *The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, pharmacokinetic/ pharmacodynamic (PK / PD) studies for demonstrating clinical comparability.*

The clinical unit 4 reviewer notes the existence of an EU document 'Guideline on similar biological medicinal products containing monoclonal antibodies – nonclinical and clinical issues.[13] This is not formally adopted by the TGA but it contains useful concepts, for example:

[10] PUVA or photo chemotherapy is a type of ultraviolet radiation treatment (phototherapy) used for severe skin diseases. PUVA is a combination treatment which consists of Psoralens (P) and then exposing the skin to UVA (long wave ultraviolet radiation).
[11] TGA Guidance Evaluation of Biosimilars (2013)
[12] EMEA/CHMP/42832/05/ Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues
[13] EMA/CHMP/BMWP/403543/2010 Guideline on similar biological medicinal products containing monoclonal antibodies; nonclinical and clinical issues

> *Populations and study models should be chosen for their sensitivity (that is ability to reveal relevant differences) – this is to increase confidence in study findings that 'do not show any difference' and reduce the risk that such study findings are falsely negative.*
>
> *It may at the current stage of knowledge be difficult to interpret the relevance of minor quality differences in the physicochemical and biological characterisation when comparing a biosimilar mAb to a reference mAb.*

Regarding extrapolation of indications, the published TGA position is as follows:

> *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 TGA has adopted the EU 'Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis'.[14] The TGA has added: '*Section 5.2.5 on this guideline suggests that regulatory approval requires a comparison with an active comparator (for example cyclosporine, MTX etcetera). Placebo controlled studies may also be acceptable in Australia*'.

2.1.3. Targets and mechanism of action

Infliximab is a TNFα inhibitor that is a monoclonal antibody that binds with high affinity to TNFα.

The sponsor's response (dated 22 September 2014) details the role of TNFα in the pathology of psoriasis and other proposed indications. By way of introduction, it was noted that TNFα can bind two receptors, TNFR1 (TNF receptor type 1; CD120a) and TNFR2 (TNF receptor type 2; CD120b). TNFR1 is expressed in most tissues, and can be activated by both the membrane bound and soluble trimeric forms of TNFα. TNFR2 is found in cells of the immune system, and responds to the membrane bound form of the TNFα homotrimer.

Monoclonal antibodies exert biological effects not only through their variable portion (here, binding TNFα) but also through their constant region, that is Fc, which specifically binds to FcRs. These receptors are expressed on many immune cells. On binding with the IgG Fc portion, FcγRs trigger different cell functions, such as cytokine release, induction of apoptosis, antibody dependent cellular cytotoxicity, and macrophage mediated clearance of immune complexes. These effects may be partially responsible for the efficacy and safety of a given mAb.

Binding to FcγRIIIa of CT-P13 (Remsima) was assayed at 102% compared with 130% for Remicade, suggesting Remsima has lower affinity for the receptor than does Remicade.

FcγRIIIa is expressed mainly on macrophages and NK cells. Polymorphism in the gene for this receptor has been shown to influence clinical efficacy of biological therapies in neoplastic and autoimmune disorders.[15] If polymorphism at FcγRIIIa can influence efficacy, it is at least plausible that variation from the reference to biosimilar in binding affinity for FcγRIIIa could also influence efficacy. However, there is not a solid body of literature supporting the view that polymorphisms at FcγRIIIa can influence efficacy of TNFα blockers in psoriasis.

[14] CHMP/EWP/2454/02 corr. Guideline on clinical investigation of medicinal products indicated for the treatment of Psoriasis'

[15] Julia M et al. The role of Fcγ Receptor Polymorphisms in the Response to Anti-Tumor Necrosis Factor Therapy in Psoriasis. *JAMA Dermatol* 2013; 149: 1033-1039

It is relevant that drug clearance may be mediated by FcγR binding; but differences in clearance should be assessable by PK studies.

The sponsor comments that a range of structurally different anti TNFα therapies capable of neutralizing TNFα including etanercept and certolizumab (lacking Fc region) as well as monoclonal antibodies such as infliximab have been utilized in the treatment of psoriasis and have been shown to be effective in the management of this disease.

This is not a strong argument in favour of the applicant. Etanercept may not have the same degree of efficacy as infliximab. Certolizumab pegol is not indicated in treatment of psoriasis in Australia.

2.1.4. Overseas status

The product is approved in the EU for psoriasis (amongst other indications). An European Public Assessment Report (EPAR) is available.[16] The indication for psoriasis in the EU for Remsima is:

> *Remsima is indicated for treatment of moderate to severe plaque psoriasis in adult patients who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or PUVA.*

While this varies from the indication proposed in Australia, it aligns with the psoriasis indication approved for Remicade in Europe. The EPAR states that:

> *'Based on the robust comparisons of the physicochemical and in vitro and ex vivo biological analyses, Remsima was considered biosimilar to the reference product Remicade. These data, in combination with clinical data demonstrating pharmacokinetic and therapeutic equivalence in rheumatology conditions, allow for extrapolation to all other indications of Remicade. In addition, the Applicant will conduct a randomised, double blind, parallel group comparative study between Remsima and Remicade in patients with active Crohn's disease.'*

[Information redacted] applied to the FDA on 8 August 2014 for approval for Remsima.[17] The news source with this information also stated:

> *'After prior consultation with the US FDA, [information redacted] conducted additional clinical trials (starting on October 2013 and lasting 6 months) to determine the bioequivalency of the originator products with Remsima. Specifically, [information redacted] tested for Pharmacokinetic /Pharmacodynamic (PK/PD) equivalency and safety equivalency for the three distinct products, the originator products sold in the US, the originator products sold in Europe, and Remsima.'*[18]

In Canada, Remsima has been approved as a 'subsequent entry biologic' for use in RA, AS, PsA and psoriasis (but not other indications); a Summary Basis of Decision is available.[19] Essentially, inflammatory bowel disease indications were not granted because of concern that the biosimilar might have a different ability to induce antibody dependent cell mediated cytotoxicity, and the linked concern that ADCC cannot be ruled out as a mechanism of infliximab's action in inflammatory bowel disease. It was stated that:

> *'The differences observed in the FcγRIIIa binding and, subsequently, ADCC, do not preclude extrapolation from the settings of RA and AS to the other requested indications of PsA and plaque psoriasis. In these diseases, it is likely that ADCC is not an important mechanism for generating a response to infliximab.'*

[16] EMA/CHMP/589317/2013 Assessment report: Remsima
[17] http://www.fiercebiotech.com/press-releases/celltrion-files-us-fda-approval-remsima
[18] FDA approved Inflectra on 4 April 2016
[19] Health Canada; Summary basis of decision(SBD) for Remsima

2.2. Quality data evaluation

A broad conclusion from the quality evaluation was that most physicochemical comparisons between the two agents indicated similarity. An important divergent result related to FcγRIIIa binding, discussed elsewhere. The result is plausible; several studies have demonstrated that differences in the glycosylation of the Fc fragment modulate the effector function of IgG; this has established the Fc associated glycan as a critical regulatory determinant for antibody activity.[20]

2.3. Nonclinical evaluation

Endorsement was given to the sponsor's view that TNFα plays a pivotal role in the pathophysiological processes of psoriasis and that neutralisation of TNFα is the primary mechanism of action for infliximab for the treatment of psoriasis.

2.4. Clinical evaluation

There were three studies in the initially presented dataset:

1. Studies initially presented in the dataset

Name	Objectives	Population
CT-P13 1.1	Pharmacokinetics, efficacy, safety	Active ankylosing spondylitis; n = 125 per arm; n = 110 to 113 per arm for PK
CT-P13 1.2	Pharmacokinetics, pharmacodynamics	Active RA, with MTX; n = 9 to 10 per arm
CT-P13 3.1	Efficacy and safety, pharmacokinetics, pharmacodynamics	Active RA with MTX; n=300 to 302 per arm; n = 254 to 256 per arm for PK

With regard to efficacy in psoriasis, the clinical evaluator notes:

> *There are no efficacy studies for CT-P13 in psoriasis. The sponsor's justification for approval is extrapolated from the collected PK data, mechanism of action and a single non inferiority study performed in patients with RA.*

The clinical evaluator accepted the sponsor's arguments regarding extrapolation to all other indications, including psoriasis.

Basic aspects of the clinical dataset are summarised below.

2.4.1. Pharmacokinetics

In CT-P13 1.1, bioequivalence of Remsima and Remicade was established. The ratio of geometric means for AUC Dose 5 to Dose 6 was 104.4% (90% CIs 94.2 to 115.7) and for C_{max} was 101.5 (90% CI 94.7 to 108.9). These estimates were well within the established range of 80 to 125%. Secondary PK parameters were broadly similar across treatments.

In CT-P13 3.1, measured PK parameters were broadly similar across treatments. Study CT-P13 1.2 was too small to contribute useful PK data.

Another study in active RA (51 to 53 patients per arm), provided in the response to questions, and titled Study B1P113101, suggested possibly higher exposure with Remsima than with

[20] Pincetic A et al Type I and type II Fc receptors regulate innate and adaptive immunity. *Nature Immunology* 2014; 15: 707-716.

Remicade. The ratio of geometric means was 112% (90% CI 100 to 124%) for AUC_τ but the upper limit of the 90% CI remained less than 125%.

The two products Remsima and Remicade appear to have similar PK. Study B1P113101 hints at the possibility of higher systemic exposure with Remsima; the larger Study CT-P13 1.1 found close similarity in exposure across the two agents.

2.4.2. Pharmacodynamics

PD outcomes were evaluated only in the two RA studies. Some PD endpoints in Study CT-P13 3.1 (for example CRP, ESR) are summarised. Outcomes were similar across arms. Study CT-P13 1.2 was too small to contribute useful PD data.

2.4.3. Efficacy

In Study CT-P13 3.1, efficacy was compared between Remsima and Remicade in adult active RA patients with an inadequate response to MTX. Dosing was concomitant with a stable dose of MTX in the range 12.5 to 25 mg/week (oral or parenteral). Patients could receive oral steroids equivalent to prednisolone 10 mg/day or less, if dose was stable. Dosing of infliximab was 3 mg/kg IV over 2 hours at Weeks 0, 2 and 6, then every 8 weeks to Week 54. Efficacy variables are discussed, but the primary outcome was the proportion of patients with an ACR20 at Week 30.

Mean age of patients was 48.8 years; 82.7% were female; 72.9% were Caucasian; mean BMI was 26.4 kg/m^2. In psoriasis, the gender imbalance is typically in the opposite direction. There was an imbalance in use of corticosteroids (71% for CT-P13; 62% for Remicade).

Based on the primary endpoint, the two treatment arms were similar (61% in the CT-P13 arm achieved ACR20, versus 59% for Remicade). The 95% CI around the difference was -6 % to 10%, so equivalence can be claimed rather securely. Other endpoints were also similar across arms.

Study CT-P13 1.2 did not add to understanding of therapeutic equivalence, because of small sample size.

In Study CT-P13 1.1, efficacy was compared between Remsima and Remicade in adult active ankylosing spondylitis. Efficacy assessment was discussed; it relied on reporting of symptoms and functionality, though the BASMI also gauged spinal mobility using clinical examination.

Dosing was 5 mg/kg IV over 2 hours, at Weeks 0, 2, 6, then every 8 weeks to Week 54. Mean age was 49 years; 81% were male; 76% were White; and mean BMI was 25.6 kg/m^2. Disease activity was similar across arms at baseline. There were no substantial differences across arms in efficacy.

The clinical evaluator considers justifications from the sponsor for extrapolation of indications. Most relevant in this section was an argument that other anti TNF therapies have an efficacy spectrum similar to infliximab, despite in some cases significant structural differences. However, the similar efficacy of the listed agents can be contested, in psoriasis. There are few head to head studies; some listed agents are not routinely used in psoriasis; and cross study comparison suggests some variation in efficacy (for example etanercept seems to have lower efficacy, at least in the early months of treatment).

2.4.4. Safety

Some 242 RA patients and 106 AS patients have been exposed to CT-P13 for 54 weeks.

There were some disparities across arms in the overview of safety; for example in Study CT-P13 3.1 (RA), serious AEs were more frequent with CT-P13 than with Remicade; discontinuations due to AEs were more frequent with Remicade than with CT-P13. In the AS study, these patterns were not replicated.

The clinical evaluator notes that:

> *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.*
>
> This remains an important finding despite further information provided by the sponsor and discussed in the clinical evaluation report. It is relevant that AEs of latent TB were reported at similar rates across agents. Presumably the finding regarding active disease is not due to imbalances in treatment of latent disease.

The evaluator also writes:

> *It is of potential concern in Study CT-P13 3.1 that anaphylactic reactions were more common in the CT-P13 group (4 out of 302) compared to the Remicade arm (1 out of 300)*

This concern was allayed by the sponsor's subsequent information that overall incidence of serious infusion reactions (including anaphylaxis) in the clinical programme was 1.6 to 1.7% across arms.

2.5. Risk management plan

In the second round advice, the RMP evaluator notes, of relevance to psoriasis:

> *In the 'Precautions' section, the PI should include a statement that psoriasis patients should be monitored for non-melanoma skin cancers (NMSCs), in particular those exposed to prior prolonged phototherapy treatment (or a statement to that effect).*

One comment about such a statement is that prior UV therapy may be a risk factor for melanoma (published papers draw different conclusions on that subject). The safety review conducted by the TGA may have concluded that infliximab poses a clinically relevant additive risk only of NMSC; this would need to be confirmed by the PSAB. Also, presumably the precaution is not restricted to this infliximab biosimilar.

2.6. Extrapolation to psoriasis

No studies of Remsima in psoriasis patients have been presented for evaluation.

The sponsor seeks approval for use of Remsima in psoriasis via extrapolation (arguing that comparability has been demonstrated sufficiently in RA and AS, and that there is no reason; for example differences in mechanism of action across indications, to think Remsima's efficacy and safety are not comparable to Remicade's efficacy and safety in psoriasis).

One assumption in writing about the psoriasis component of the application is that the TGA Delegate does consider comparability has been shown sufficiently in RA and AS. Without re-arguing this issue, the clinical unit 4 reviewer does note that Remsima use was linked with active TB in 1.6% of patients; Remicade use was linked with active TB in 0.2% of patients. While any differential immunosuppressant effect should not on the face of it be further exaggerated in psoriasis, a true difference in risk of active TB of this magnitude is of concern. For such an important AE, it is difficult to disregard this as a 'chance finding' even if a plausible mechanism is not transparent. Differential Fc mediated biological actions of the mAb could provide a mechanism to explain this finding. Enrolment of some patients from high prevalence areas is not a deficiency in this regard, assuming reasonably balanced enrolment across arms by region; in fact, this increases 'sensitivity' of the trials to detect imbalances in active TB.

A second issue is that while efficacy appeared similar for the two agents in RA and AS, this could be because those disease models are insensitive, that is cannot easily detect differences that

might be clinically relevant in other indications.[21] The clinical unit 4 reviewer thinks the close match in efficacy of the agents in studies in two indications offsets this risk.

Regarding extrapolation to psoriasis, a stepwise approach requires consideration of physicochemical, nonclinical and clinical data. As noted above, extrapolation is not possible without establishment of efficacy and safety ('biosimilarity') in those groups where there is direct clinical evidence (that is RA and AS).

Physicochemical comparisons revealed some subtle distinctions between Remsima and Remicade, chiefly a difference in affinity with FcγRIIIa. Evaluation documents cite 102% binding for Remsima, 130% binding for Remicade. The clinical unit 4 reviewer assumes this means higher affinity binding to this Fc receptor for Remicade.

This focused attention on the potential for infliximab's mechanism of action to vary by indication due to varying involvement of FcγRIIIa mediated effects. There was consensus ADCC was the key biological effect of infliximab that would be FcγRIIIa mediated. The sponsor argues against ADCC being relevant in infliximab's mode of action against psoriasis.

The clinical unit 4 reviewer's concern is that knowledge in this area is evolving, and that it is difficult to rule out ADCC as an important mechanism in infliximab's mechanism of action in the treatment of psoriasis. There is low level evidence ADCC might have a role, for example in a study of the effect of polymorphisms of FcγRIIIa on efficacy of anti-TNF agents in psoriasis.[15] In the clinical unit 4 reviewer's opinion, it is unlikely the role is dominant; it is an open question also as to whether the FcγRIIIa binding differences observed would translate to ADCC differences in patients treated with the two agents (for example, in in vitro Study GR2-RD-11-099 an assay of relative ADCC bioactivity did not reveal relevant differences across agents, in tm hTNFα Jurkat target cells;[22] using PBMCs as effector cells; sensitivity of the assay is open to debate). The issue does introduce further uncertainty about extrapolation of indications to include psoriasis.

2.6.1. Product Information

The following comments refer to the PI proposed at the response to questions stage of the TGA evaluation.

It should be clearer that trials emphasised in the clinical trials section were of the reference drug, Remicade. The same applies to the adverse effects section.

More detailed information should be provided about the imbalance in frequency of active TB across agents in the clinical comparability studies. This might extend to additional precautionary text, for example a need for closer monitoring for active TB if patients are switched to Remsima. Compatibility of such statements with the principles of 'biosimilarity' is a consideration.

2.7. Summary of Issues

No studies of Remsima (the proposed biosimilar infliximab) in psoriasis patients have been presented for evaluation. The sponsor is seeking approval for use of Remsima 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

[21] Feagan B et al. The challenge of indication extrapolation for infliximab biosimilars. *Biologicals* 2014;42: 177-183
[22] Transmembrane human TNFα over-expressing cell line obtained from Kyushu University

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.

2.8. Proposed action

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.

2.9. Advice sought from the ACPM by clinical unit 4 reviewer

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

1. Is there concern that the observed imbalance in active tuberculosis could make it difficult to declare the two produces biosimilar?
2. 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?
3. 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?
4. In relation to Question 3, 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?
5. Is the balance of efficacy and safety of Remsima sufficiently established to approve the psoriasis indication?

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.

2.10. Addendum to review by clinical unit 4 dated 27 February 2015

2.10.1. Introduction

This addendum takes into account the sponsor's further information submitted with a cover letter dated 27 November 2014. It focuses on material that has a bearing on the key issues identified above.

2.10.2. Psoriasis and ADCC

It is unlikely that infliximab's mechanism of action in psoriasis is mediated to any significant extent by ADCC. It is also unlikely that the in vitro signal of a difference in ADCC activity between Remicade and CT-P13 will be relevant to clinical efficacy in psoriasis.

The questions to ACPM should remain, to ensure ACPM is also satisfied there is no likely impact of this in vitro difference between CT-P13 and Remicade on efficacy.

2.10.3. Clinical assay sensitivity

Assay sensitivity appears acceptable in the studies in RA and AS.

The question to ACPM should remain, to ensure ACPM is also satisfied about this.

2.10.4. Serious pneumonia and active TB

With regard to risk of serious pneumonia and/ or active tuberculosis with CT-P13 relative to Remicade, the following observations are made.

Question 3 for the sponsor by the Delegate ('*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*') relates to serious pneumonia and active TB.

2.10.4.1. Serious pneumonia

In discussion of serious pneumonia, the sponsor argued that there was an imbalance in predisposing risk factors amongst those with serious pneumonia (5 out of 7 treated with CT-P13 had such risk factors, yet 0 out of 3 on Remicade had such risk factors). A more relevant consideration is any imbalance in baseline risk amongst all patients in each group (CT-P13, Remicade). This is because consideration only of imbalances in baseline risk factors amongst those who developed pneumonia is unable to take into account those patients with baseline risk factors who do not go on to develop pneumonia.

In Study CT-P13 3.1 (the major study accounting for an imbalance in pneumonia), basic baseline characteristics were addressed, and the CT-P13 arm had a higher rate of 'history of GI disorders' and a modestly higher rate of concomitant systemic corticosteroid use. The analysis of baseline characteristics was not in the clinical unit 4 reviewer's opinion deep enough to determine whether there was any baseline imbalance across arms in all key risk factors for serious pneumonia.

Across studies, there was not a consistent pattern of more serious pneumonia with CT-P13 than with Remicade; this was the case in one of the three largest studies (Study CT-P13 3.1), while in another (Study B1P13101), the opposite pattern was observed, and in Study CT-P13 1.1, there were no reports of serious pneumonia in either arm.

The clinical unit 4 reviewer did not think there was a significant signal that CT-P13 predisposes to pneumonia (more than Remicade).

The sponsor's argument that all 10 cases were successfully treated with antibiotics and that clinical findings did not indicate active TB were noted.

2.10.4.2. Active TB

In discussion of active TB, the sponsor argued that studies were in some regions with a high background rate of TB. With randomisation, this should not bias towards a higher frequency of active TB with CT-P13 than with Remicade.

Having a relatively high background incidence of TB may increase assay sensitivity (that is draw out a difference that would not have become apparent in a small clinical trial programme if studies had been restricted to countries with a relatively low TB burden). It is not a strong argument to note, as the sponsor did, that 2 to 3 fold more patients were enrolled in the CT-P13 group than the Remicade group at study sites that reported cases of active TB.

The incidence of latent TB reported as an AE was similar (for example in Study CT-P13 3.1) across arms. If site was a confounder, it might be expected that latent as well as active TB would be seen at higher rates with CT-P13 than with Remicade.

The sponsor argued that in 3 patients treated with CT-P13 from the Philippines, the diagnosis of active TB was on clinical grounds in the absence of microbiological or molecular diagnosis. The sponsor noted later that in previous Remicade studies, there had been a distinction between confirmed cases and all cases. Although it is sensible to distinguish between confirmed and other cases of TB, it is relevant that there was an imbalance in both confirmed and other cases of TB across arms.

Across studies, there was a fairly consistent pattern of more active TB with CT-P13 than with Remicade. This was the case in two of the three largest studies (Study CT-P13 1.1, and CT-P13 3.1) while in the other (Study B1P13101) there were no reports of active TB as shown in Table 19 of AusPAR (note; the calculated frequency in the CT-P13 arm of 3.1 should be 1.0%.).

Such studies are not powered to detect with statistical significance any differences in the frequency of rare AEs. Differences may provide important signals, despite the lack of statistical significance. The fair reproducibility of effect across studies is an important consideration. Interestingly, for at least one other AE, leukopenia, an even more consistent trend across the larger studies was evident (in Study CT-P13 1.1, 0% in the CT-P13 arm versus 1.6% in the Remicade arm; in Study CT-P13 3.1, 0.3% versus 1.7%; and in B1P13101, 0% versus 1.9%). However, at least in Study CT-P13 3.1, laboratory evaluation was not concordant with this (Grade 3 low WBCs were reported in 0.7% for CT-P13 and 0% for Remicade).

The sponsor argued that mechanistically, there is no known reason to suppose CT-P13 should increase susceptibility to active TB, over and above the susceptibility conferred by Remicade. Understanding of the mechanism behind infliximab's link to active TB may be incomplete, and despite the 'finger-print-like algorithm' used to assess biosimilarity of CT-P13 and Remicade, relevant differences may not have been detected. It would be unsafe to discount observed differences in safety on the basis that such differences cannot be explained mechanistically. The clinical unit 4 reviewer acknowledges, on the same point, that if an obvious mechanism were known to explain such findings, this would add to the argument for causality.

The sponsor argued that monitoring for infections in the post-market period may address the issue of an observed imbalance in active TB. An advantage of post-market studies is that by virtue of their size (often large) and duration (often long) they can detect safety signals not detectable in the clinical study programme. This circumstance is different: a safety signal has been found in the clinical programme.

The sponsor is arguing (it seems) that the imbalance in active TB '*observed*' in the clinical programme is not robust and that post-marketing studies are better placed to show '*no difference*' between CT-P13 and Remicade. It would be conservative to assume a safety difference has been found in the clinical programme, and to decide whether post-market activities can mitigate the observed risk to the extent that CT-P13 and Remicade can be considered to have a '*similar*' safety profile, prior to decision-making. For example, a

requirement for a suitable patient alert card may mitigate risk (compare RMP evaluation, second round; dossier, 'Educational material' includes a mock-up of an 'infusion card' that includes a warning about infections).

2.10.5. Summary

The observed imbalance in incidence of active TB between CT-P13 and Remicade cannot confidently be ascribed to chance, despite the lack of a clear cut mechanistic explanation for this imbalance.

Risk minimisation activities, if implemented, might offset concern about the observed imbalance in active TB. These activities might include appropriate communication of safety findings in the PI, and appropriate educational material aimed at patients (for example an alert card) and physicians (for example educational booklets) approved by the RMP Evaluation Section.

The ACPM's views on the observed imbalance in active TB between CT-P13 and Remicade would be valuable.

2.11. The clinical unit 4 reviewer's recommendations to the Delegate

After considering the sponsor's response document dated 27 November 2014, the clinical unit 4 reviewer's 'proposed actions' are unchanged from above.

Specifically, questions to the ACPM above are still relevant, and would help inform the Delegate's decision about the application.

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