Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for certolizumab pegol

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

August 2014

TGA Health Safety Regulation

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: http://www.tga.gov.au

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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

List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ACR	American College of Rheumatology
AE	Adverse Event
ARTG	Australian Register of Therapeutic Goods
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CER	Clinical Evaluation Report
CI	Confidence interval
CRP	C-Reactive Protein
CS	Corticosteroids
CV	Coefficient of Variation
CZP	Certolizumab Pegol
DMARD	Disease Modifying Anti-Rheumatic Drug
ES	Erosion Score
ESR	Erythrocyte Sedimentation Ratio

Abbreviation	Meaning
EU	European Union
FAS	Full Analysis Set
Fc	Fragment crystallisable
Gab	Fragment antigen binding
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCQ	Hydroxychloroquine
JSN	Joint Space Narrowing
LEF	Leflunomide
LS	Least Square
MCID	Minimal Clinically Important Difference
mTSS	modified Total Sharp Score
MTX	Methotrexate
NRS	Numerical Rating Scale
nr-SpA	non-radiographic axial Spondyloarthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
NY	New York
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamic
PEG	Polyethylene glycol
PGA	Psoriasis Global Assessment
PhGADA	Physician Global Assessment of Disease Activity
PK	Pharmacokinetic
PPS	Per Protocol Set

Abbreviation	Meaning
PsA	Psoriatic Arthritis
PtGADA	Patient Global Assessment of Disease Activity
PY	Patient-Years
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RS	Randomized Set
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine
TGA	Therapeutic Goods Administration
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal
US	United States

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	1 May 2014
Active ingredient:	Certolizumab
Product name:	Cimzia
Sponsor's name and address:	UCB Australia Pty Ltd T/A UCB Pharma Division of UCB Australia Level 1, 1155 Malvern Road Malvern VIC 3144
Dose form:	Solution for injecton
Strength:	200 mg/mL
Container:	Pre-filled syringe
Pack size:	Two
Approved therapeutic use:	New indications: *Psoriatic arthritis: Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease-modifying anti-rheumatic drug therapy (DMARDs) has been inadequate. Cimzia has been shown to improve physical function.* *Ankylosing Spondylitis: Cimzia is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).*
Route of administration:	Subcutaneous
Dosage:	The same loading and maintenance dosage regimen used for RA is proposed for the additional indications of psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).
ARTG number :	154726

Product background

This AusPAR describes the application by the sponsor to register Cimzia for the following indication;

> *Psoriatic arthritis:*
>
> *Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease-modifying anti-rheumatic drug therapy (DMARDs) has been inadequate. Cimzia has been shown to improve physical function.*
>
> *Ankylosing Spondylitis:*
>
> *Cimzia is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).*

Certolizumab pegol is a member of the Tumour Necrosis Factor alpha (TNFα) inhibitor drug class (ATC code: L04AB05). It is a recombinant, humanised antibody fragment antigen binding (Fab') fragment that is expressed in an Escherichia coli bacterial expression system, subsequently purified and conjugated to polyethylene glycol (PEG). It has a high affinity for human TNFα and neutralises membrane associated and soluble human TNFα in a dose dependent manner. It does not neutralise lymphotoxin, or TNFβ. Certolizumab does not contain a fragment crystallisable (Fc) region, which is normally present in the complete antibody, and therefore does not fix complement or cause antibody-dependent, cell mediated cytotoxicity in vitro. It does not induce apoptosis in vitro in human peripheral blood monocytes or lymphocytes. The pegylation of the Fab' fragment increases its half-life and may also decrease its immunogenicity, without affecting the affinity and specificity of the antibody in binding to human TNFα *in vivo*.

TNF-α is a key pro-inflammatory cytokine in the pathogenesis of inflammatory conditions. It is present in significantly elevated concentrations serum and synovial fluid in patients with PsA. It affects a variety of pathophysiological processes including activation of T-cells, induction of acute phase proteins, and stimulation of haemopoietic precursor cell growth and differentiation.

Axial Spondyloarthritis is a relatively new term that was developed by the Assessment of SpondyloArthritis international Society (ASAS). It comprises 2 subgroups: Ankylosing Spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). Historically, AS has been classified and diagnosed according to the modified NY criteria, a key component of which is evidence of sacroiliitis on plain X-ray. However, as radiographic evidence of sacroiliitis develops late in the disease process, diagnosis and treatment can be delayed. The recently established ASAS criteria allow for classification of axial SpA using modern imaging techniques (MRI, as well as plain X-rays), permitting earlier diagnosis of axial SpA. The term nr-axSpA is used to define the earlier stage of axial SpA where there may be little or no changes seen on plain radiographs.

Current approved treatment options in Australia for moderately to severely active PsA include NSAIDs, corticosteroids (CS), and non-biological DMARDs (mainly methotrexate (MTX), sulfasalazine [SSZ] and leflunomide [LEF]). Specific pharmaceutical treatments (TNF-α inhibitors) registered for the treatment of PsA includes adalimumab (Humira), infliximab (Remicade), etanercept (Enbrel), and golimumab (Simponi).

Current approved treatment options in Australia for active ankylosing spondylitis (AS) include NSAIDs and TNF-α inhibitors (adalimumab, infliximab, etanercept, and golimumab). There are no specific pharmaceutical treatments registered for the treatment of nr-axSpA.

The currently approved PsA and AS indications (at the time of this evaluation) for the TNF-α inhibitors are as follows:

Adalimumab:

> *Humira is indicated for the treatment of signs and symptoms, as well as inhibiting the progression of structural damage, of moderate to severely active psoriatic arthritis in adult patients where response to previous DMARDs has been inadequate.*
>
> *Humira is indicated for reducing signs and symptoms in patients with active ankylosing spondylitis.*

Infliximab:

> *Remicade 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.*
>
> *Remicade may be administered in combination with methotrexate.*
>
> *Ankylosing Spondylitis: Remicade is indicated for the reduction of signs and symptoms and improvement in physical function in patients with active disease.*

Etanercept:

> *Enbrel is indicated for the treatment of:*
>
> *The signs and symptoms of active and progressive psoriatic arthritis in adults, when the response to previous disease-modifying antirheumatic therapy has been inadequate. Enbrel has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function.*
>
> *The signs and symptoms of active ankylosing spondylitis in adults.*

Golimumab:

> *Simponi, alone or in combination with methotrexate, is indicated for:*
>
> *The treatment of active and progressive psoriatic arthritis in adult patients when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Simponi has also been shown to inhibit the progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease, and improve physical function.*
>
> *Simponi is indicated for:*
>
> *The treatment of active ankylosing spondylitis in adult patients.*

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 20 January 2010.

Certolizumab was considered by Advisory Committee on Prescription Medicines (ACPM) (previously ADEC) at the 266th meeting (October 2009), leading to its approval in 2010 for rheumatoid arthritis.

At the time the TGA considered this application, a similar application had been approved in the United States (US), Canada and had been submitted in the European Union (EU). Applications had not been submitted in Switzerland or New Zealand.

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The main treatment options available for axial SpA are NSAIDs and physiotherapy. Non-biologic DMARDs such as MTX, SSZ and CS may be tried, but the supporting evidence of efficacy is very limited to non-existent. Four anti-TNF drugs (infliximab, etanercept, adalimumab and golimumab) are currently registered in Australia, Europe and the USA for the treatment of AS in terms of improving the signs and symptoms of spinal and peripheral arthritis, physical functioning and health related quality of life. Based on the similarities between AS and nr-SpA as they are likely to represent a disease spectrum continuum, it is anticipated that anti-TNF drugs may be effective in patients with nr-SpA. Initial small MRI studies of the nr-SpA subset using anti-TNF therapies (for example adalimumab) have shown efficacy, but currently no anti-TNF treatment is registered for the nr-SpA indication as the original licensing studies restricted patient entry to those with confirmed AS. Hence, there is an unmet need for effective and safe therapies in patients with active nr-SpA.

Guidance

Contents of the clinical dossier

The submission contained the following clinical information:

- All 4 of the efficacy/safety studies collected pharmacokinetic data.
- No population pharmacokinetic analyses.
- 2 pivotal efficacy/safety studies – Study PsA001 for the proposed PsA indication; and Study AS001 for the proposed SpA indication.
- No dose-finding studies.
- 2 other efficacy/safety studies – Studies C87040 and C87044 were conducted in patients with moderate to severe plaque psoriasis as supportive evidence in the PsA indication.

- No pooled analysis, or meta-analysis was provided.
- The sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

The 2 pivotal trials (Study PsA001, and Study AS001) which evaluated the use of Certolizumab Pegol (CZP) in adults with active PsA and axial SpA were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met.

Pharmacokinetics

Studies providing pharmacokinetic data

All 4 clinical studies collected a limited quantity of Pharmacokinetic (PK) data in the target populations of PsA, axial SpA and skin psoriasis. Discussion is contained within the CER extract (Attachment 2).

Evaluator's conclusions on pharmacokinetics

The PK properties of CZP in adult patients with active RA have been previously assessed. The sponsor has provided a limited quantity of new PK data (trough CZP concentrations collected every 2-4 weeks over 24 weeks of treatment) in this submission for patients with the additional treatment indications of active PsA and axial SpA. The sponsor is not proposing any changes to the PK section of the current PI to include the new PK data.

The key PK findings for CZP use in patients with active PsA or axial SpA are:

- Plasma trough CZP concentrations were highest at weeks 2 and 4 of both pivotal studies when subjects received a loading regimen of CZP 400 mg at weeks 0, 2 and 4;
- Trough CZP concentrations at weeks 12, 16 and 24 (maintenance phase) were lower in subjects treated with CZP 400 mg Q4W versus CZP 200 mg Q2W, which is consistent with the extended dosing interval approach;

Subjects who developed anti-CZP antibodies had significantly lower trough CZP concentrations indicating increased plasma clearance of CZP; and

Plasma levels of CZP are similar during the first and re-treatment periods for those subjects who remain persistently negative for anti-CZP antibodies.

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic (PD) data was provided in this submission, apart from changes in CRP levels with treatment (considered in efficacy section of this report).

Evaluator's conclusions on pharmacodynamics

The PD properties of CZP when used in adult patients with active RA have been previously assessed. No new PD data, apart from changes in CRP levels, was presented in this submission for patients with active PsA or axial SpA, and the sponsor is not proposing any changes to the PD section of the current PI.

Dosage selection for the pivotal studies

No specific dose-finding studies have been performed for patients with PsA and axial SpA. The dose and administration frequency of CZP used in the 2 pivotal studies (PsA001 and AS001), and proposed by the sponsor for licensing, have been extrapolated from the posology approved for use in adult patients with active RA. Previous submissions in patients with RA have justified the dose selected for that indication. The additional inflammatory arthritis indications (PsA and axial SpA) have similar demographic and disease characteristics to RA to believe the selected dose used in the 2 pivotal studies has been reasonably justified by extrapolation.

The sponsor is proposing that CZP be administered in the maintenance phase of treatment by SC injection at either a fortnightly dose of 200 mg, or 400 mg given every 4 weeks. A loading dose regimen of CZP 400 mg at Week 0, 2 and 4 is proposed for all of the inflammatory arthritis indications. The doses of background treatment with conventional DMARDs (mainly, MTX), CS and NSAID when used by patients in the pivotal studies (PsA001 and AS001) were appropriate, and consistent with contemporary clinical practice in Australia.

Efficacy

Studies providing efficacy data

Indication 1: The treatment of adult patients with active psoriatic arthritis.

- Studies PsA001,C87040, C87044

Indication 2: The treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis and patients with non-radiographic axial spondyloarthritis.

- Study AS001

Evaluator's conclusions on efficacy

Indication 1: The treatment of adult patients with active psoriatic arthritis

This submission contains a single pivotal trial (Study PsA001) in subjects with PsA, and 2 non-pivotal trials (Studies C87040 and C87044) in patients with chronic plaque psoriasis, to support the extension of indication to include the treatment of active PsA. The pivotal study is ongoing with an interim study report to 24 weeks of treatment follow-up being included in this submission. Study PsA001 recruited patients according to the CASPAR criteria. The 2 non-pivotal studies were each of 12 weeks duration, and have been finalised with complete study reports in this submission.

This submission is seeking an indication in active PsA, and in general is consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EMEA guideline CPMP/EWP/438/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis" (effective 5 February 2008). In addition, the single pivotal study (PsA001) had a design that met the criteria for single pivotal study

applications. For Study PsA001, the choice of clinical and functional efficacy endpoints and statistical analysis were appropriately performed. However, although the radiographic endpoints were appropriate, the statistical analysis plan was modified post-hoc to demonstrate statistical significance in favour of CZP as the primary statistical analysis was observed to be erroneous. This is a major deficiency of the current submission for the additional claim of reducing the rate of radiographic progression in patients with PsA.

The baseline demographic and disease related characteristics of patients in Study PsA001 are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. However, there are some caveats to the generalizability of the treatment population. For example, Study PsA001 excluded patients who were at a significant risk of infection, or who had various abnormal laboratory results at baseline (for example abnormal haematology or liver function tests).

The pivotal trial enrolled patients with moderately active axial SpA, and demonstrated that CZP is an effective treatment in those who have either failed to respond to conventional treatment options, such as DMARDs (mainly MTX), as well as other anti-TNF drugs. One of the 2 co-primary efficacy endpoints of Study PsA001 was the proportion of subjects who achieved an ACR 20 response at 12 weeks (that is clinical response criteria), and this was reached. Overall, 58.0% (80/138) of patients treated with CZP 200 mg Q2W and 51.9% (70/135) of subjects treated with CZP 400 mg Q4W achieved this outcome versus 24.3% (33/136) of patients in the placebo group. Many secondary efficacy measures examining clinical outcomes and functional endpoints also demonstrated clinically significant changes with CZP such as various rates of ACR response (20, 50, and 70) at 12-24 weeks, DAS 28 and PsARC response, as well as the mean change from baseline in HAQ-DI score. Additionally, improvements in measures of skin disease activity (PASI response) and health related quality of life were also attained with CZP therapy. The 2 supporting psoriasis studies (C87040 and C87044) supported the observation that CZP therapy results in clinically meaningful improvements in skin disease activity in patients with chronic, moderately severe plaque psoriasis.

The second co-primary efficacy endpoint in Study PsA001 was the mean change from baseline to Week 24 in the modified Total Sharp Score (mTSS). The study's protocol-defined imputation rules led to physiologically implausible changes in the mTSS, and this endpoint was not achieved in the primary (pre-defined) statistical analysis. However, when different post-hoc imputation rules along with a specified window between radiographs (minimum 8-week window) were applied to the dataset a statistically significant outcome in favour of CZP versus placebo was demonstrated for the primary radiographic endpoint (mean change from baseline to 24 weeks in mTSS), as well as several supporting X-ray endpoints (such as, the proportion of mTSS responders at Week 24).

Overall, the data in this submission supports the efficacy of CZP in the treatment of active PsA from a clinical perspective (that is in beneficially treating the symptoms and signs of peripheral arthritis, as well as improving physical functioning), in those with moderate-severely active disease at baseline, with or without concurrent DMARD and/or NSAID. However, the current submission does not provide a sufficiently robust dataset for the claimed additional feature of reducing the rate of radiographic progression of peripheral joint damage as measured by X-ray. Further longitudinal X-ray follow-up with a pre-defined statistical analysis plan would be required before that additional claim can be made. At this stage, a statistically significant inhibition of structural damage progression after 24 weeks of treatment with CZP in subjects with active PsA has only been observed when post-hoc imputation rules and related sensitivity analyses have been applied to the dataset.

Indication 2: The treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis and patients with non-radiographic axial spondyloarthritis.

Historically, AS has been classified and diagnosed according to the modified NY criteria, a key component of which is evidence of sacroiliitis on plain X-ray. However, radiographic evidence of sacroiliitis develops late in the disease process, thereby delaying diagnosis and treatment. The recently established ASAS criteria allow for classification of axial SpA using modern imaging techniques (MRI, as well as plain X-rays). This permits earlier diagnosis of axial SpA, and the term nr-SpA is used to define the earlier stage of axial SpA.

This submission contains a single pivotal trial (Study AS001) to support the extension of indication to include axial SpA. The study is ongoing with an interim study report to 24 weeks of treatment follow-up being included in this submission. Study AS001 recruited patients according to the ASAS criteria. All subjects had to meet the ASAS diagnostic criteria, and in addition 50% of the enrolled patients had to fulfil the modified NY criteria for definitive AS.

This submission is seeking an indication in active axial SpA, and is consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EU guideline CPMP/EWP/4891/03 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Ankylosing Spondylitis" (effective 23 February 2010). In addition the single pivotal study (AS001) had a design that met the criteria for single pivotal study applications. For Study AS001, the choice of efficacy endpoints and statistical analysis were appropriately performed; and strategies to maintain blinding and randomisation procedures were considered.

The baseline demographic and disease related characteristics of patients in Study AS001 are similar to those in the anticipated Australian patient cohort, and therefore generalisation of these results to the Australian context is expected. The majority of patients were male, of Caucasian ethnicity, and within the expected age range of 25 and 54 years. However, there are some caveats to the generalizability of the treatment population. For example, Study AS001 excluded patients who were at a significant risk of infection, or who had various abnormal laboratory results at baseline (for example abnormal haematology or liver function tests).

The pivotal trial enrolled patients with moderately active axial SpA, and demonstrated that CZP is an effective treatment in those who have either failed to respond to conventional treatment options, such as NSAIDs and/or DMARDs (SSZ or MTX). The primary efficacy endpoint of Study AS001 was the proportion of subjects who achieved an ASAS 20 response at 12 weeks, and this was reached. Overall, 63.6% (68/107) of patients treated with CZP 400 mg Q4W and 57.7% (64/111) of subjects treated with CZP 200 mg Q2W achieved this outcome versus 38.3% (41/107) of patients in the placebo group. Many secondary efficacy measures of clinical relevance such as various rates of ASAS response (20, 40, 5/6 and partial remission) at 12-24 weeks, as well as BASDAI response confirmed that CZP is effective in treating the symptoms and signs of active axial SpA. Improvements in measures of inflammation (CRP), imaging (MRI parameters), physical functioning (BASFI), spinal mobility (BASMI), and health related quality of life were also attained with CZP therapy. Clinically meaningful improvements with CZP compared with placebo were observed in the overall axial SpA population, as well as the 2 subpopulations (AS and nr-SpA), with no significant differences between the 2 CZP dosing regimens.

Overall, the data in this submission supports the efficacy of CZP in the treatment of axial SpA (as per the ASAS criteria), in those with moderate-severely active disease at baseline, with or without concurrent NSAID or DMARD.

Safety

Studies providing safety data

Studies PsA001, AS001 and, two supporting, non-pivotal efficacy studies (C87040 and C87044).

Patient exposure

Study PsA001

In Study PsA001, a total of 138 subjects received CZP 200 mg Q2W, 135 subjects received CZP 400 mg Q4W, and 61 subjects exclusively received placebo throughout the 24-week, double-blind treatment period. At Week 16, 59 placebo subjects escaped to CZP therapy and were re-randomized to CZP 200 mg Q2W (30 subjects) or CZP 400 mg Q4W (29 subjects). The median number of doses received was 12.0 for the CZP 200 mg Q2W group and 7.0 for the CZP 400 mg Q4W group, as expected per the injection schedule. The median number of doses received in the placebo group was 8, which was less than planned per the injection schedule but reflects the fact that 43.4% (59/136) of placebo subjects escaped to CZP at Week 16. The median duration of exposure was 24 weeks for both CZP dose groups. The median duration of exposure was 16.4 weeks for the placebo group, which was the time at which placebo subjects could escape to CZP. This corresponds to 65.3-67.4 PY of exposure for each of the CZP dose groups, and 51.1 PY of exposure for the placebo arm. Of note, 4 placebo subjects inadvertently received a CZP injection at some time during the trial (3 of which did so at Week 0 or 2).

Study AS001

In Study AS001, a total of 111 subjects received CZP 200 mg Q2W, 107 subjects received CZP 400 mg Q4W, and 51 subjects exclusively received placebo throughout the 24-week, double-blind treatment period. At Week 16, 56 placebo subjects escaped to CZP therapy and were re-randomized to CZP 200 mg Q2W (27 subjects) or CZP 400 mg Q4W (29 subjects). The median number of CZP doses received was 12.0 for the CZP 200 mg Q2W group, and 7.0 for the CZP 400 mg Q4W group. The median number of doses received in the placebo group was 8.0, which was less than planned per the injection schedule but reflects that 52.3% (56/107) of placebo subjects escaped to CZP at Week 16. The median duration of exposure was 23.3 weeks for the CZP 200 mg Q2W group, 23.3 weeks for the CZP 400 mg Q4W arm, and 16.1 weeks for the placebo group. This corresponds to 53.3-55.5 PY of exposure for each of the CZP dose groups, and 38.0 PY of exposure for the placebo arm.

Study C87040

The mean exposure to study treatment was the same for both CZP dose groups in this trial (mean of 11.6 injections out of a possible maximum of 12 injections). However, because of a higher discontinuation rate in the placebo group, a mean of 10.2 injections occurred for this cohort. Ninety percent of subjects in both CZP groups received all 12 injections during the 12-week trial compared to 67.2% (39/58) in the control group.

Study C87044

The majority of subjects in each group received all 12 injections during this 12-week re-treatment study: 94.1% (32/34) were given CZP 200 mg Q2W, and 94.6% (35/37) received CZP 400 mg Q2W.

Safety issues with the potential for major regulatory impact

Risk of Infection, including opportunistic infection

CZP has been identified to be associated with an increased risk of infection, including tuberculosis and other serious opportunistic infections. Screening for tuberculosis was an entry requirement of both pivotal studies in this submission. One patient treated with CZP in Study C87040 developed disseminated tuberculosis, and another subject was a screen failure for the follow-on re-treatment study (C87044) because of latent tuberculosis. Herpetic infections were reported at a very low frequency in both pivotal studies, with no treatment related association being apparent. Nonetheless, the overall rate of infection related SAEs was slightly higher in CZP treated subjects versus placebo patients in both pivotal studies.

Malignancies, including lymphoma and melanoma

All 4 clinical studies had insufficient reported treatment follow-up periods (ranging from 12-24 weeks) in this submission to assess the malignancy potential of CZP in the target populations of PsA and axial SpA. Updated data from the RA population experience, which is significantly larger, does not indicate an increased overall risk of malignancy (excluding non-melanoma skin cancer) when using CZP, however, this issue will require ongoing surveillance in the target populations if approval is granted.

Injection Site and Hypersensitivity reactions

This has already been addressed in this report.

Cardiovascular safety, including heart failure and ischaemic events

Similar to the issue of malignancy, all 4 clinical studies in this submission had insufficient treatment follow-up periods to assess the long-term cardiovascular safety of CZP in the target populations. Like patients with RA, those with active PsA have an increased risk of cardiovascular morbidity and mortality. Currently, CZP does not appear to be associated with an increased risk of adverse cardiovascular events in patients with RA, but the issue will require ongoing pharmcovigilance in the requested target populations (particularly, PsA) if approval is granted.

Unwanted Immunological events

The rate and consequences of developing anti-CZP antibodies has already been discussed. The formation of anti-drug antibodies does not appear to be associated with experiencing AEs, but results in increased plasma clearance of the drug, which potentially may affect efficacy.

In this submission, no subjects developed clinical consequences consistent with systemic autoimmune disease such as systemic lupus erythematosus. One subject (64-year-old female) developed subacute cutaneous lupus 45 days after starting CZP 200 mg Q2W in Study PsA001. In addition, a 32-year-old female in Study AS001 reported pustular psoriasis 7 days after starting treatment with CZP 200 mg Q2W.

Post marketing data

As CZP has not been approved anywhere in the world at the time of submission for the treatment indications of active PsA and axial SpA, there is no post-marketing experience specific to the requested target populations in this submission. The sponsor has provided an updated report (data collected up to 14 November 2012) regarding its experience in patients with RA. The most recent update does not indicate any newly identified or potential safety concerns with CZP.

Evaluator's conclusions on safety

In this submission, the total clinical safety dataset for the use of CZP in adult patients with active PsA (n = 332) or axial Spa (n = 274) consists of 606 patients in 2 pivotal studies, all of whom received maintenance CZP by SC injection either at a dose of 200 mg Q2W or 400 mg Q4W. Most of the patients in the dataset received concurrent MTX and/or NSAID, and approximately 17-25% were taking concurrent low dose oral CS. In the pivotal PsA study, the overall exposure to CZP was 132.7 patient-years, and the total exposure to CZP in the pivotal SpA trial was 108.8 patient-years. In the 2 supporting skin psoriasis studies (C87040 and C87044) more than 90% of patients (n = 71) received CZP for 24 weeks in total (as part of a first, and then re-treatment period study design). Overall, there is sufficient volume of data to make a meaningful assessment of safety for up to 24 weeks of treatment in newly proposed treatment indications of active PsA and axial SpA.

Infection was the most common AE recognised in the CZP inflammatory arthritis studies with approximately 35.3% of patients (214/606) in both pivotal studies experiencing an infection related AE. The majority of infections were mild in severity, self-limiting, and predominately involved either the upper respiratory tract or gastrointestinal system. However, serious infection related AEs were reported in 2.8% (17/606) of CZP-treated patients in both pivotal trials. In addition, 1 patient in the supporting psoriasis study (C87040) developed disseminated tuberculosis. It is unclear if the use of concurrent DMARD and/or CS, as well as age increases the risk of infection associated with CZP.

Injection site reactions were a common type of AE reported in patients receiving CZP. In both pivotal studies, 6.6% (40/606) of subjects experienced an ISR. The majority of injection site reactions were mild, resolved without specific intervention and did not result in discontinuation from CZP therapy. Acute systemic hypersensitivity reactions were rare with CZP in all of the trials, as was the new onset of autoimmune diseases such as lupus (1 case each of cutaneous lupus and pustular psoriasis in CZP treated subjects in the 2 pivotal studies).

Two deaths (cardiac arrest and sudden cardiac death) were reported in the pivotal PsA study (PsA001), but both were considered to be unrelated to CZP. Another fatality (cerebral haemorrhage) was recorded 18 weeks following the last dose of CZP in the supporting psoriasis trial (C87044), and this was also considered to be unrelated to CZP. Two malignancies were identified in Study PsA001 but the 12-24 week follow-up periods of each trial are of insufficient duration to identify any potential safety signal on this topic of interest. Cardiovascular AEs occurred at a low and similar incidence to control therapy in the pivotal trials, but would require longer periods of treatment follow-up to be adequately evaluated.

Elevations in hepatic transaminases (AST and ALT) were recorded in up to 19.6% of patients treated with CZP in the pivotal study (PsA001). The majority of these changes in liver function tests were mild and without associated clinical implications. The same observation, but at a lower frequency, was seen in Study AS001.

The incidence of PsA or axial SpA subjects developing anti-CZP antibodies is low (5.9% - using the combined incidence observed in Studies PsA001 and AS001), and their clinical relevance for safety outcomes is yet to be defined with no discernible link to the risk of infection, or infusion related reactions. However, the development of anti-CZP antibodies may be associated with a lack or loss of efficacy.

In summary, the safety data indicates that CZP has an acceptable overall short-term safety profile in the treatment of adult patients with moderately to severely active PsA and axial SpA. There is insufficient long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events, which will require longitudinal safety follow-up. There are some significant identified safety concerns including the risk of serious infection, opportunistic infection, injection site reactions, and

abnormal liver function tests. These safety concerns are consistent with known profile of CZP in other approved indications, mainly active RA. Significant pharmacovigilance would be required if approval is granted for extension of treatment indications. This would include vigilance for opportunistic infections, adverse cardiovascular events and malignancy.

First round benefit-risk assessment

First round assessment of benefits

The benefits of CZP in the proposed usage are:

- PsA indication – improvement in the signs and symptoms of peripheral arthritis (as per the ACR clinical response criteria), and improvement in physical functioning (as evidenced by treatment related improvements in the HAQ-DI scale).
- Axial SpA indication (for both subjects with confirmed AS and nr-SpA) – improvement in the symptoms and signs of axial disease (as per improvements in back pain and stiffness), improvement in physical functioning (as per changes in BASDAI and BASFI), and slowing of structural damage (as evidenced by treatment related improvements in MRI parameters).

First round assessment of risks

The risks of CZP in the proposed usage (both treatment indications) are:

- Increased risk of infection, including tuberculosis and other serious opportunistic infections
- Local injection site reactions, which are generally mild and transient, and do not result in permanent discontinuation from CZP
- Increased incidence of abnormal liver function tests, in particular, raised serum transaminases
- Potential increased risk of malignancy and adverse cardiovascular events requiring long-term surveillance
- Formation of anti-CZP antibodies which results in increased plasma clearance of CZP and possible loss, or lack of efficacy

First round assessment of benefit-risk balance

The short-term (up to 24 weeks), benefit-risk balance of CZP in the target populations of adult subjects with active PsA and axial SpA is favourable.

First round recommendation regarding authorisation

This evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for CZP to include the treatment of active PsA and axial SpA. The proposed wording of treatment extension in patients with PsA has 2 additional elements: reducing the rate of progression of peripheral joint damage by X-ray, and improving physical functioning. The current submission provides robust evidence of improving physical functioning in patients with active PsA, however, the radiographic claim has not been sufficiently proven at this stage, and requires further evidence of justification before licensing is approved. In particular, the current X-ray data is limited to 24 weeks of assessment which is an insufficient time frame to evaluate such a claim. Furthermore, the

current X-ray data only shows a positive effect with CZP at 24 weeks when post-hoc imputation rules with a specified minimum 8-week period between X-ray assessments was applied. A robust treatment effect requires at least 12 months (ideally 2 years) of follow-up (as per regulatory guideline advice in RA), and the statistical analysis plan should be pre-specified.

It is also recommended that approval of the sponsor's proposed extension of indication be subject to:

Satisfactory response to the questions in this report,

- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study reports for Studies PsA001 and AS001.

Clinical questions

Pharmacokinetics

Cytokines have the potential to alter the expression of Cytochrome P450 enzymes. Could the sponsor comment on whether Cimzia has the potential for drug-drug interactions on the basis of an alteration in cytokine levels and/or activity.

Pharmacodynamics

This submission did not contain any new pharmacodynamic information (apart from changes in CRP values) in patients with psoriatic arthritis or axial spondyloarthritis. Could the sponsor provide information to support that pharmacodynamic response with Cimzia in patients with psoriatic arthritis and axial spondyloarthritis is similar to what has been observed in adult patients with rheumatoid arthritis.

Efficacy

The claim of radiographic benefit with Cimzia in patients with active PsA is based on assessments performed up to 24 weeks after the commencement of Cimzia. A statistically significant benefit with Cimzia was observed when post-hoc imputation rules were applied to the radiographic endpoint analysis. Could the sponsor comment on the robustness of the claim of reducing the rate of radiographic progression given the above limitations of the current dataset, and that regulatory guidelines in RA recommend a longer period of follow-up (at least 12 months) before a radiographic claim can be made.

Safety

Could the sponsor present information regarding an assessment of risk of AE by subgroups of special interest, such as those aged > 65 years, increased BMI, concomitant treatment (for example corticosteroid use), concurrent co-morbidities or gender.

Second round evaluation of clinical data submitted in response to questions

The sponsor's response dated 1 November 2013 addresses questions that were raised in the first round clinical assessment. Each of these responses will be assessed in order.

Pharmacokinetics

The sponsor states that the only in vivo drug-drug interaction study (PHA-001) performed in the CZP clinical development involved the concurrent administration of MTX in subjects with RA. This study showed that CZP did not have a statistically or clinically meaningful effect on the overall extent of exposure (AUC) or peak plasma concentration (Cmax) of MTX and 7-hydroxy MTX. However, the contribution of cytochrome P450 enzymes to MTX metabolism is small.

The sponsor also states the recent literature showing that the expression of cytochrome P450 enzymes may be down-regulated by increased levels of pro-inflammatory cytokines (for example TNF) during chronic active inflammation. Therefore, when chronic inflammation is successfully reduced this may impact upon the relative expression of cytochrome P450 enzymes. The sponsor has made no specific comment about how the "normalisation" of P450 enzyme expression (with effective anti-TNF treatment) may affect the PK of medications metabolised by this system. For example, the exposure to concurrent HMG Co-A reductase inhibitors may be increased once chronic inflammation is reduced. Patients with PsA and AS have an increased risk of cardiovascular disease and hyperlipidaemia requiring treatment.[1] The evaluator concurs with the sponsor opinion but recommends post-marketing pharmacovigilance of this potential issue if registration in Australia is granted.

Pharmacodynamics

The sponsor states that at the time of study development in the CZP program, consideration was given to PD data collection in patients with active PsA and axial SpA, however, in reviewing the European regulatory approvals for 4 other anti-TNF drugs (etanercept, adalimumab, infliximab and golimumab), no additional PD studies were performed to support their respective approvals in active PsA and AS. The evaluator concurs with the sponsor in that the collection of CRP and clinical outcome data in the 2 pivotal studies (PsA001 and AS001) provides some insight into the PD effect of CZP in patients with PsA and axial SpA.

In addition, the sponsor has provided 2 tables in the response which provide an indirect data comparison of the clinical endpoints between the 5 anti-TNF medicines in patients with PsA (Table 1 of the response) and AS/axial SpA (Table 2 of the response). With respect to the PsA studies, there were similar rates of ACR 20 (50-60%), ACR 50 (32-42%) and ACR 70 response (19-27%) at 24 weeks between the various anti-TNF drugs. The corresponding rates of ACR response in the control groups with PsA were slightly higher in the CZP study (PsA001) compared to the trials assessing other anti-TNF drugs, but within expectations. With respect to the AS/axial SpA studies, there were similar rates of ASAS 20 (51-68%), ASAS 40 (44-52%) and ASAS 5/6 response (42-49%) at 24 weeks between the various anti-TNF drugs. However, the study populations were heterogeneous in the SpA trials, ranging from only including patients with confirmed AS (for example infliximab and golimumab) compared to a broader cohort of subjects with AS and axial SpA (CZP).

Efficacy

In the sponsor's response, the sponsor has provided the radiographic data up to Week 48 (that is the end of the dose-blind treatment period) in Study PsA001 to support the claim of radiographic benefit with CZP in patients with active PsA. The original submission contained X-ray data obtained up to the Week 24 evaluation. A full description of the pre-

[1] Han C, et al. (2006) Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol.* 33: 2167-2172.

defined statistical analysis plan and post-hoc imputation methods were provided in the original submission. The sponsor states that in written advice received 9 February 2010, the FDA requested the primary efficacy analysis (including for X-ray endpoints) in Study PsA001 use the Randomized Set (RS) versus the Full Analysis Set (FAS) of subjects. The RS includes all subjects randomised with an intention-to-treat, whether or not valid assessments are available. In contrast, the FAS requires subjects to have at least 1 valid baseline and 1 valid post-baseline assessment. This cohort approach allows for the possibility of applying linear extrapolation when results are missing.

The primary radiographic endpoint of the change from baseline to Week 24 in mTSS was not achieved using the pre-specified analysis plan. The imputation rules applied in the primary analysis resulted in implausibly high Least Square (LS) mean changes from baseline in the mTSS across all treatment groups (ranging from 11.52 to 28.92 points). Hence, post-hoc imputation rules (8 potential cases with different combinations) were applied to the data along with a minimum 8-week window between X-rays. The sponsor states these rules are consistent with those accepted by regulatory authorities for another anti-TNF drug evaluated in patients with PsA (EPAR for golimumab). However, the S31 response did not include this document as a reference and this evaluator was unable to locate the above mentioned statement for review. Using the post-hoc imputation method, less progression of X-ray changes was observed at Week 24 (as measured by the LS mean change from baseline in mTSS) in the combined CZP treatment group compared with the placebo arm (0.06 versus 0.28 points, respectively). The difference between CZP (combined) and placebo was -0.22 points (95% CI -0.38, -0.06; p = 0.007). The LS mean change in mTSS from baseline to Week 24 was smaller (that is , less progression of radiographic changes) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group (0.01 versus 0.11 points). However, both CZP treatment regimens appeared to be better compared with placebo (treatment difference of -0.27 and -0.17 points, respectively). The difference between CZP 200 mg Q2W and placebo was statistically significant at -0.27 points (95% CI -0.45, -0.08; p = 0.004). However, the difference between CZP 400 mg Q4W and placebo was not statistically significant at -0.17 points (95% CI -0.35, 0.02; p = 0.072). Post-hoc sensitivity analyses (that is with imputation of missing values using mean change or worst change from baseline in the entire study population, and also the same treatment group) showed the same results in that CZP 400 mg Q4W was not statistically superior to placebo but CZP 200 mg Q2W and the combined CZP group were consistently better. This evaluator would not regard this observation as a consistently robust outcome in demonstrating radiographic benefit with CZP as this evaluator would expect both CZP dose regimens (either alone or combined in a dataset) to be statistically significant versus placebo. The LS mean change from baseline to Week 48 in mTSS was 0.13 points (95% CI -0.05, 0.31) in the combined CZP group versus 0.32 points (95% CI 0.10, 0.55) in the placebo arm. Although the data suggested a trend for less progression with CZP, the observation did not reach statistical significance (p = 0.127). For each CZP dose group compared with placebo, the Week 48 data for LS mean change in mTSS did not reach statistical significance. The sponsor opines that this observation may have occurred because there were lower levels of radiographic progression over 48 weeks of observation in Study PsA001 compared with historical progression rates.

In the S31 response, the sponsor has also presented a post-hoc subgroup analysis for the LS mean change from baseline to weeks 24 and 48 on subjects with or without structural damage at baseline. A cut-off mTSS score of 6 was used to define subjects with structural damage at baseline. No supporting literature was provided to justify the choice of this cut-off score, although the sponsor refers to the same methodology being used in the golimumab EPAR assessment. In patients with baseline mTSS > 6 points, very little radiographic progression was observed, independent of the treatment group. Nonetheless, the comparison between the CZP combined group (and each CZP dose regimen) versus

placebo was statistically significant at 24 weeks, but not 48 weeks.[2] In patients with baseline mTSS < 6 points, less than 10% of patients (regardless of treatment allocation) showed any X-ray progression.

In summary, the radiographic data collected in Study PsA001 at up to 48 weeks of follow-up does not demonstrate a consistent and clinically meaningful beneficial effect with CZP on X-ray progression in patients with active PsA. The positive results seen at 24 weeks in patients treated with CZP 200 Q2W (and the combined CZP treatment dataset) suggest there may be some effect of CZP in reducing X-ray progression, especially in high risk patients (that is those with evidence of structural damage at baseline – mTSS > 6 points). However, this finding was observed when post-hoc imputation rules were applied to the analysis. In general, post-hoc analyses, particularly of patient subgroups, are a relatively poor method of demonstrating a clinically meaningful effect with scientific rigor and validity. The best test for validity of subgroup-treatment effect interactions is reproducibility in other clinical trials. As such, this evaluator would not recommend acceptance of the sponsor proposal to add the element of reducing the rate of progression of peripheral joint damage as measured by X-ray to the PsA treatment indication.

Safety

The sponsor has provided 18 tables of data presenting the risk of AE and SAE by subgroups of special interest for PsA (Tables 1-9) and axial SpA.

With respect to Study PsA001, the incidence of AEs (overall and drug related) were similar between CZP and placebo regardless of subgroup factor of interest (gender, age, BMI and concurrent CS use). Female subjects (regardless of treatment allocation) had a higher incidence of AEs and treatment related AEs compared to male patients, but the rates of serious or severe AEs and discontinuations due to AEs were similar between male and female subjects. The same pattern of relatively increased AE frequency (overall and treatment-related) was observed in those with BMI > 30 kg/m^2 compared to non-obese subjects. The dataset also shows the very small number of subjects (22 in total – 7 in the placebo arm and 15 given either dose of CZP) in Study PsA001 who were aged > 65 years.

With respect to Study AS001, the incidence of AEs (overall and drug related) were similar between CZP and placebo regardless of subgroup factor of interest (gender, age, BMI and concurrent CS use). Female subjects (regardless of treatment allocation) had a higher incidence of AEs and treatment related AEs compared to male patients. The rate of SAEs was higher in female subjects receiving placebo, but comparable between males and female subjects treated with CZP. The dataset also shows the very small number of subjects (8 in total – 5 in the placebo arm and 3 given either dose of CZP) in Study PsA001 who were aged > 65 years.

The analysis of AE information by subgroups of special interest does not reveal any clinically significant risk factors for safety concerns with CZP therapy in patients with active PsA and axial SpA. Expectedly, the majority of subjects in both treatment studies were young to middle aged, and there is limited AE information regarding the safety of CZP in patients with PsA and axial SpA who are aged > 65 years.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of CZP in the proposed usage are unchanged from those identified.

[2] Further discussion of the evaluator's statement can be found in the sponsor's response.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of CZP in the proposed usage are unchanged from those identified.

Second round assessment of benefit-risk balance

The benefit-risk balance of CZP, given the proposed usage, is favourable.

Second round recommendation regarding authorisation

This evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for CZP to include the treatment of active PsA and axial SpA. The proposed wording of treatment extension in patients with PsA has 2 additional elements: reducing the rate of progression of peripheral joint damage by X-ray, and improving physical functioning. The current submission provides sufficient evidence of improving physical functioning in patients with active PsA and this evaluator supports its acceptance. However, the claim of radiographic benefit in patients with active PsA has not been adequately justified at this stage, as the evidence is not consistently observed in a scientifically robust manner. Therefore, the evaluator would not recommend acceptance of the proposed claim of radiographic benefit in patients with active PsA.

Should approval of the sponsor's proposed extension of indication be granted the evaluator would recommend 2 conditions of registration: - regular periodic safety update reports; and the provision by the sponsor to the TGA of the final clinical study reports for Studies PsA001 and AS001.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RA EU-RMP Version 8.0 dated 14 November 2012, PsA EU-RMP Version 1.0 dated 14 November 2012, axSpA EU-RMP Version 1.0 dated 14 November 2012) which was reviewed by the TGA.

Contents of the submission

The sponsor has submitted three separate EU-RMP's with this application, specifically a rheumatoid arthritis EU-RMP (RA EU-RMP), a psoriatic arthritis EU-RMP (PsA EU-RMP) and an axial spondyloarthritis EU-RMP (axSpA EU-RMP). The PsA EU-RMP and the axSpA EU-RMP both refer to the RA EU-RMP for their pharmacovigilance plan, which proposes routine and additional pharmacovigilance activities. The sponsor also proposes routine and additional risk minimisation activities in each EU-RMP

The presentation of the written submission contained a number of major issues, including.

- The sponsor has submitted three separate RMP's with this application corresponding to each indication. This is not the usual practice for drugs with multiple indications. Furthermore, the RMP's are all poorly indexed and numbered with mislabelled RA Annexes that are out of order. These documents have numerous internal inconsistencies and refer regularly to the "RA EU-RMP". The RMPs have incorrect section titles, references and refer to data tables that have not been submitted as part of the RMP. As per the EU Guideline on Good Pharmacovigilance Practices (GVP 22 June 2012 EMA/838713/2011), a Risk Management Plan should be a "stand alone" document and not refer to other RMP's or data that is not provided with the RMP. It is

recommended that the sponsor combine these separate documents into one RMP and improve the consistency of the RMP.

- The RMPs are labelled as a "Risk Management Plan for Australia", however they are actually EU-RMPs. The names of the documents should be corrected, as this is not an Australian RMP. Furthermore, no Australian Specific Annex has been submitted. In this case, one is required as the EU-RMP does not adequately discuss Australian specific issues, such as distribution of education materials, training on the education materials the Australian epidemiology of each condition and the application history.

Table 1. Ongoing safety concerns as specified by the sponsor.

Important identified risks	Infections including TB and serious opportunistic infections
Important potential risks	Malignancies including lymphoma and melanoma Congestive heart failure and ischemic cardiac events Demyelinating-like disorders Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia Serious bleeding events Lupus and lupus-like illness Immunogenicity including sarcoidosis Hepatitis B virus reactivation
Important missing information	Pregnancy and lactation Children and adolescents Elderly Patients with renal or hepatic impairment Potential for overdose Potential for medication errors Off-label use Concomitant use with DMARDs other than MTX Use by patients with prior anti-TNF use

Evaluator comments

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, this is not acceptable as a complete list of the ongoing safety concerns for certolizumab. The TGA will be seeking advice from the clinical evaluator and the ACSOM committee, to assist the delegate with advice regarding the completeness of the list of ongoing safety concerns associated with certolizumab.

The following risks should be added to the list of ongoing safety concerns, unless the sponsor can provide compelling justification for their exclusion:

- Hepatosplenic T-Cell Lymphoma (HSTCL):
  - The FDA has previously made statements about the incidence of HSTCL in patients treated with anti-TNFα medications. The majority of cases were in patients being treated for CD or UC, but also included a patient being treated for psoriasis and two patients being treated for rheumatoid arthritis (FDA statement 14 April 2011).
  - On the 25/4/2013 the EMA issued an opinion/notification regarding the addition of HSTCL to the SmPC.

- HSTCL is part of the proposed Australian product Information submitted with this application.
- This is a known Anti-TNFα pharmacological class effect.

· Merkel Cell Carcinoma:

- On 7 May 2012, the EMA requested that UCB perform a review of cumulative cases of Merkel Cell Carcinoma as a class effect could not be excluded. On the 18 October 2012, the CHMP adopted the conclusion that the prescribing information to indicate the risk of Merkel Cell Carcinoma should be updated and the Cimzia RMP should be updated accordingly.
- On 21 March 2013 the EMA issued an opinion/notification regarding the addition of Merkel Cell Carcinoma (MCC) to the SmPC as a new adverse event with unknown frequency.
- This is a known Anti-TNFα pharmacological class effect.
- Other drugs in this class are updating the product information to include this risk. For example, the United States FDA released a safety label update in March 2013 regarding Merkel Cell Carcinoma and infliximab.

· Under "demyelinating disorders", the following should be specifically listed: Guillain-Barre syndrome; demyelinating polyneuropathy; and multifocal motor neuropathy:

- The United States FDA released a letter dated 20 April, 2010, under Section 505(o)(4) of the Federal Food, Drug, Cosmetic Act (FDCA) notifying that new safety information should be included in the labelling for TNF blockers. This information specifically pertains to the risk of peripheral demyelinating disorders, including Guillain-Barre syndrome, demyelinating polyneuropathy, and multifocal motor neuropathy, associated with the use of the class of TNF blockers including Cimzia (certolizumab Pegol). (STN 125160/111).

· Under "Infections including TB and serious opportunistic infections", the sponsor should specifically list Legionella and Listeria:

- This is a known anti-TNFα pharmacological class effect.
- On the 9 July 2011, the United States FDA updated the boxed warnings for the entire class of Tumour Necrosis Factor-alpha blockers to include the risk of infection from Legionella and Listeria.

· Under 'Infections including TB and serious opportunistic infections", the sponsor should specifically list Invasive fungal infections:

· Drug specific antibody formation

- This is a known anti-TNFα pharmacological class effect.
- Listed in the Cimzia RA EU-RMP.

· Injection site reactions and infusion reactions:

- A known anti-TNFα pharmacological class effect, as stated in the Cimzia RA EU-RMP discussing class effects: '*Other AEs such as injection site reactions (etanercept and adalimumab) and infusion reactions (infliximab) have also been reported.*'

· Cranial nerve inflammation:

- The RA EU-RMP discusses cranial nerve inflammation, summarising the period covered by the PSUR 1, 07 September 2009 to 06 March 2010. The sponsor gives reasoning for the inclusion of this term in the SmPC: '*As cranial nerve inflammation may not always be due to demyelinating disease, UCB proposed the broader term*

"cranial nerve inflammation" instead of optic neuritis, acoustic neuritis, and trigeminal neuralgia that have been described with CZP in the setting of RA.'

- This is an important ongoing safety concern that should continue to be reported on through the PSUR process.

· Septic shock

- This is discussed in the RA EU-RMP in regards to inclusion of septic shock in the SmPC. This is an important ongoing safety concern that should continue to be reported on through the PSUR process.

· Hypersensitivity reactions:

- As stated by the sponsor in the Australian Product Information: '*The following symptoms that could be compatible with hypersensitivity reactions have been reported rarely following Cimzia administration to patients: angioedema, dyspnea, hypotension, rash, serum sickness, and urticaria. Some of these reactions occurred after the first administration.*'
- This is an important ongoing safety concern that should continue to be reported on through the PSUR process.
- Change in morphology/severity of psoriasis:
- A known anti-TNFα pharmacological class effect.
- This is an important risk that should be reported through the PSUR process, especially in light of the current application regarding the use of Cimzia in the treatment of psoriatic arthritis.

The following should be added to the list of important missing information:

· Certolizumab use in patients with HIV or hepatitis C.

- This has not been part of the studies involving certolizumab.
- Listed as important missing information for other TNFα antagonists (such as Golimumab).

· Long term safety

- This has not been included part of the studies involving certolizumab use in Psoriatic arthritis or Axial spondyloarthritis.
- Listed as important missing information for other TNFα antagonists (such as Golimumab).

Furthermore, the sponsor should correct the formatting error in the table of ongoing safety concerns.[3]

Reconciliation of issues outlined in the RMP report

Table 2 summarises the TGA's first round evaluation of the RMP, the sponsor's responses to issues raised and the TGA's evaluation of the sponsor's responses.

[3] The reconciliation of issues outlined above is discussed in Table 2.

Table 2. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
The following risks should be added to the list of ongoing safety concerns, unless the sponsor can provide compelling justification for their exclusion: · Hepatosplenic T-cell lymphoma (HSTCL) · Merkel Cell Carcinoma · Under "demyelinating disorders", the following should be specifically listed: Guillain-Barre syndrome, demyelinating polyneuropathy and multifocal motor neuropathy · Under "infections including TB and serious opportunistic infections" the sponsor should specifically list Legionella and Listeria · Under "infections including TB and serious opportunistic infections" the sponsor should specifically list Invasive fungal infections · Drug specific antibody	1. *UCB has now added hepatosplenic T-cell lymphoma, Merkel Cell carcinoma, hypersensitivity reactions, changes in morphology or severity of psoriasis to the list of ongoing safety concerns – important identified risks (see Cimzia EU-RMP version 9.3 pp 165).* 2. *Long term safety is added to the list of ongoing safety concerns – important missing information (see Cimzia EU-RMP version 9.3 pp 166).* 3. *The evaluator's comments are noted in regards to:* – *Under "infections including TB and serious opportunistic infections" the sponsor should specifically list Legionella and Listeria* – *Under "infections including TB and serious opportunistic infections" the sponsor should specifically list Invasive fungal infections* – *Under "demyelinating disorders", the following should be specifically listed: Guillain-Barre syndrome, demyelinating polyneuropathy and multifocal motor neuropathy* · *Cranial nerve inflammation* *UCB S.A. advises that the additional specific terms listed in the first two bullets are part of the general safety concern, that is Legionella, Listeria and invasive fungal infections are a part of "infections including TB and*	The Sponsor has added some safety concerns to the list. However, the Sponsor has not provided compelling justification for the exclusion of the following safety concerns from the list: (please refer to the Round 1 RMP Evaluation report for further details of the importance of including these recommendations): · Under "infections including TB and serious opportunistic infections" the sponsor should specifically list Legionella and Listeria · Under "infections including TB and serious opportunistic infections" the sponsor should specifically list Invasive fungal infections · Under "demyelinating disorders", the following should be specifically listed: Guillain-Barre syndrome, demyelinating polyneuropathy and multifocal motor neuropathy

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
formation · Injection site reactions · Hypersensitivity reactions · Change in morphology / severity of psoriasis The following should be added to the list of important missing information: · Long term safety	*serious opportunistic infections". UCB S.A. will assess all four bullet points mentioned in TGA proposals for the next version of the EU-RMP, once the next dataset for the PSUR is available (Mar 2014).* 4. *The evaluator's comments are noted in regards to:* – *HIV or hepatitis C* *UCB S.A. advises that this will be evaluated at the next major update of the EU RMP for inclusion. It is clinically prudent that HIV and hepatitis C status are investigated prior to initiation of TNF antagonists.* 5. *The evaluator's comments are noted in regards to:* – *Septic shock* *UCB S.A. considers septic shock a likely outcome of some serious infections (known and well characterized product risk). UCB S.A. respectfully advises that this will not be incorporated as an additional safety concern.*	· Injection site reactions · HIV or hepatitis C (important missing information) The Sponsor should add the above risks to the list of ongoing safety concerns. It is important to note that the ACSOM committee supported the inclusion of all the recommended additional safety concerns made by the evaluator.
It is recommended that the sponsor justify the exclusion of the ongoing studies from the pharmacovigilance plan relating to PsA and AxSpA	*UCB has now updated Cimzia EU-RMP to version 9.3; studies are now included in the PV Plan (see page 194).*	This is acceptable.
The sponsor should clarify the exact number of studies included within the pharmacovigilance plan, for example are studies included? Furthermore the milestones for the	*UCB has now updated Cimzia EU-RMP to version 9.3. The pharmacovigilance plan as summarised on p 193 contains: 4 registries (o Pregnancy data collections (ongoing studies, post-marketing reports and ARTIS and RABBIT)* *o*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
studies in the pharmacovigilance plan should be clarified.	*o Targeted follow-up with reporters with TB questionnaire* *o Targeted malignancy questionnaire sent to HCP* · *RA has now been completed and is now under table 5-2: Completed studies/activities from the Pharmacovigilance plan* · *The Status (planned /started) and Date for submission of interim or final reports (planned or actual) for all ongoing and planned additional PhV studies / activities in the Pharmacovigilance Plan are provided in table 5-1 on page 193.*	
Targeted follow-up questionnaires have not been submitted with the current application. It is recommended that the sponsor submit these for review by the TGA It is recommended to the sponsor that additional questionnaires regarding serious infection and hepatitis B reactivation be added Furthermore the method of supplying these questionnaires only after a spontaneous report has been made seems questionable. The sponsor should also consider including these questionnaires in	*UCB has now updated Cimzia EU-RMP to version 9.3. The targeted follow-up questionnaires are now in Part VII Annex 7:* · *Targeted follow-up with reporter with TB questionnaire* · *Targeted malignancy questionnaire in paediatric, adolescent and young adult patients (< 30 years of age)* · *Targeted follow-up with pregnancy questionnaire* *UCB will evaluate the TGA request regarding questionnaires for serious infection and hepatitis B reactivation.* *UCB will evaluate the request to include questionnaires (TB, malignancy, pregnancy) in any physician education material that will be supplied.*	The Sponsor remains unclear regarding the inclusion of these additional questionnaires, the current distribution methods, post-marketing data regarding RA and inclusion of these questionnaires in the educational material (please note that the Sponsor has also not yet clarified if an education programme will occur in Australia). The additional questionnaires suggested by the evaluator should be developed by the Sponsor and submitted to the TGA for review.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
the physician education material to prompt reporting and improve the quality of data collected.		
The protocols for the ongoing registry studies have not been reviewed as part of this evaluation. Should this application be approved it is recommended that the sponsor consider completing an Australian Specific Registry study including patients diagnosed with RA, PsA and AxSpA.	*An Australian Specific Registry study for patients diagnosed with RA, PsA and AxSpA is already established in Australia. The registry is known as the Australian Rheumatology Association Database (ARAD). ARAD is a national Australian database, which is supported by the Australian Rheumatology Association, and which collects important health information from individuals with inflammatory arthritis including rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis. The aim of ARAD is to determine the short and long term effectiveness and safety of new biological drugs, including certolizumab pegol, used to treat inflammatory arthritis conditions. The registry captures information on patient's anti-rheumatic medications, including reasons for stopping or switching, current symptoms, and suspected adverse effects. Information about intercurrent infections, new comorbidities including malignancy, joint surgery, and hospitalizations, are also collected. Patients and rheumatologists across Australia contribute to ARAD.* *In addition, registries exist in the EU with a much larger cohort of patients. Examples of these non-RA specific registries include DANBIO.*	It is recommended that the Sponsor report on both the ARAD and DANBIO studies within the PSUR. It is also important to note that the Sponsor makes the following statement regarding the DANBIO registry within the EU-RMP page 22: "*DANBIO is not a safety registry and does not look for specific adverse events. All adverse events are received as spontaneous adverse events".*
The sponsor should justify why the	*Medication error*	This is acceptable.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
important missing information of "Potential for medication errors" will not be further elucidated via additional pharmacovigilance.	*Potential medication errors are listed as missing information for Cimzia in the UCB Risk Management Plan (RMP). Medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient, or consumer.* *[information has been redacted]*	It is important to note that the Sponsor discusses the risk of medication error within the EU-RMP and makes the following statement regarding the importance of additional risk minimisation for this risk: "*The product packaging, labelling, and supporting CZP educational program are designed to minimize the potential for medication errors in the administration of the product.*" Therefore, the Sponsor should also apply additional risk minimisation activities in Australia.
The sponsor should clarify the status of the auto-injector and update the RMP accordingly. The sponsor should also comment on the number and types of medication errors that have occurred during post-market experience.	[information redacted]	[information redacted] Therefore, the Sponsor should apply additional risk minimisation activities in Australia.
It is recommended that the sponsor summarise all reports of overdose from post-market experience with RA. The sponsor does	*UCB directs the evaluator to page 95 of the Cimzia RMP Version 9.3, additionally:* *[information redacted]. This concern is considered addressed as part of the overall enhancement in product label as*	The potential for harm from overdose has not been adequately addressed in the EU-RMP Version 9.3 Part II Section 1.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
not discuss the risk of overdose in the PsA EU-RMP or the AxSpA EU-RMP and simply refers to the comments within the RA-RMP	*previously discussed.*	This section should be updated to include the cumulative post-marketing data regarding overdose that the Sponsor has provided in the adjacent comment.
The sponsor should clarify from post-marketing experience the number of spontaneous reports of off-label use.	*Off-label use of Cimzia is listed as missing information for Cimzia in the UCB Risk Management Plan (RMP). Off-label use is the use of pharmaceutical drugs for an unapproved indication or in an unapproved age group, unapproved dosage, or unapproved form of administration. It is worth noting that there are always geographical dimension to discussions regarding off-label use of a product. The premise is that what is considered off- label in one region may be entirely appropriate in another geographical region/country.* *[information redacted]* *It is generally understood that health authorities (regulators) do not prescribe the practice of medicine. This suggests that clinicians have the right to use an approved product in any manner they choose provided they have educated themselves of the risks and can manage such risks appropriately. Therefore off-label use of any approved product (including Cimzia) may not be entirely controlled. In an effort to assure a favourable benefit risk balance, it is an inherent interest of MAHs that their products are used for the approved indication, population and dose. The presumption is that the population studied, is the one for*	The potential for off-label use has not been adequately addressed in the EU-RMP Version 9.3 Part II Section 5. This section should be updated to include the cumulative post-marketing data regarding off-label use that the Sponsor has provided in the adjacent comment.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
	whom maximum benefit have been demonstrated. Specific to Cimzia, the product is appropriately labelled relative to indication, dose and age in all geographical regions. The patient education materials also note the product indications and conditions for use. A review of cases of off label use is a routine aspect of pharmacovigilance activity of Cimzia. Based on the cumulative review of data, the safety profile of Cimzia has been consistent. This statement is tempered by the fact that the doses for children have not been established. Overall, it is argued that the benefit/risk profile of Cimzia remains favourable given that off-label use represents very small fraction of the cumulative case volume of Cimzia.	
According to the sponsor, the patient alert card is distributed to patients as "*a detachable front-page of the patient guide, and it is also available in electronic form*" (RA EU-RMP page 364). The sponsor should clarify if this "patient guide" is in fact the "medication guide" listed in table 4 above or if there is an additional document.	*European Medicines Authority requested that, for the Cimzia RMP in the new format, only the Patient Alert Card (which is now a stand-alone document), and the Prescriber Guide are used. All the other documents (HCP Guide, Patient Medication Guide) have not been maintained since version 9.0 of the RMP as they are no longer required by EMA. The new educational material is product-specific and no longer indication-specific; therefore the same document can be used for all three indications (RA, PsA, AxSpA).* *UCB Australia confirms that if UCB decide to roll-out educational material in Australia, a Patient Alert Card will be adapted and produced to the local requirements in Australia.*	The Sponsor remains unclear regarding their risk minimisation plan proposed for Australia. The Sponsor initially submitted three "EMP's for Australia" which included additional risk minimisation activities. However, the Sponsor's initial S31 response with ASA Version 1.0 stated that no activities would be applied. This was then further confused by the current subsequent S31 response where the Sponsor uses the term "*if UCB decide to roll-out*

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
		educational material in Australia.". Due to the potential for serious adverse events with certolizumab treatment, in addition to the ongoing safety concerns associated with the product, additional risk minimisation activities, as applied in the EU, are required in Australia.
The sponsor should clarify if this Alert card will be supplied in Australia. If this is the case, the card should be updated for the Australian population, for example changing referenced to the SMPC.	*UCB confirm that, if UCB decide to roll-out educational material in Australia, the Patient Alert Card will be adapted to the local requirements in Australia.*	The Sponsor remains unclear regarding their risk minimisation plan proposed for Australia. Due to the potential for serious adverse events with certolizumab treatment, in addition to the ongoing safety concerns associated with the product, additional risk minimisation activities, as applied in the EU, are required in Australia.
It is recommended that the sponsor amend the following: · This document should be updated for the Australia population, for example changing	*UCB Australia currently have a how to prescribe brochure, which includes dosing instructions, a copy of which is attached. This can be expanded upon to address the comments above. UCB confirm that, if UCB decide to roll-out additional educational material in Australia, the material will be*	This response appears inconsistent with those provided below and with the content of the ASA. The Sponsor remains unclear regarding their risk minimisation plan

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
references to the SmPC. · The steps describing the injection preparation and administrated should be numbered. · Each administration picture should be placed with the corresponding administration step. · The three pages regarding *"clinical efficacy of Cimzia"* should be removed and a reference made to the prescriber guide, or placed at the back of the document to ensure that the most relevant information is at the front of the document. · A statement regarding appropriate dosing and/or a dosing table should be added to enhance safe use of medicine. · A table should be added showing the very common, common and rare side effects of certolizumab, similar to that shown in the	*adapted to the local requirements.*	proposed for Australia. The ASA states that no additional risk minimisation activities will be applied in Australia, however the Sponsor implies in this response that an additional risk minimisation activity (in the form of a brochure) will be applied. The "how to prescribe brochure" was not attached to the S31 responses. Furthermore, there is no mention of this document within the ASA. Due to the potential for serious adverse events with certolizumab treatment, in addition to the ongoing safety concerns associated with the product, additional risk minimisation activities, as applied in the EU, are required in Australia.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
SmPC. • A statement should be added regarding the potential of certolizumab to influence the ability to drive and use machines. This statement should be to the effect of "Cimzia may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of Cimzia"		
PsA and axSpA Patient Medication Guide It is recommended that the sponsor amend the following: This document should be updated for the Australian population, for example changing references to the SmPC. A statement should be added regarding hepatitis B infection under the heading "*information you should know about Cimzia*". A statement should be added regarding the potential of	*UCB Australia currently produces a guide for patients, which will be extended to patients with PsA and axSpA. This guide includes an overview of adverse events and incorporates risks, such as hepatitis infection and infections, but can be updated to include ability to drive and use machines. A copy of the patient guide is attached.*	This response appears inconsistent with those provided below and the content of the ASA. The Sponsor remains unclear regarding their risk minimisation plan proposed for Australia. The "*guide for patients*" was not attached to the S31 responses. Furthermore, there is no mention of this document within the ASA. Due to the potential for serious adverse events with certolizumab treatment, in addition to the

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
certolizumab to influence the ability to drive and use machines. This statement should be to the effect of "Cimzia may have a minor influence on the ability to drive and use machines. Dizziness (including vertigo, vision disorder and fatigue) may occur following administration of Cimzia)". A section should be added regarding when to seek medical advice, such as signs of infection or an injection site reaction. A statement should be added regarding the use of the patient alert card, its purpose and the importance of carrying it with the patient at all times.		ongoing safety concerns associated with the product, additional risk minimisation activities, as applied in the EU, are required in Australia.
General Comments on the Education program It is recommended that the sponsor provide the updated versions of following RA materials to the TGA for review prior to approval [information redacted]	*[information redacted]*	This response appears inconsistent with those provided below and the content of the ASA. The Sponsor remains unclear regarding the risk minimisation plan proposed for Australia. [Information redacted]
The evaluation of	*[information redacted]*	This response

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
the educational materials is discussed in the RA EU-RMP Section 4.2.4 and Annex 8. It is recommended that the Sponsor consider evaluating the effectiveness of these educational materials for Australian physicians and patients. The sponsor should give details of the "third party provider" in Australia as mentioned in the PsA and AS EU-RMP's.		appears inconsistent with those provided above. The Sponsor remains unclear regarding the risk minimisation plan proposed for Australia. [information redacted] The Sponsor should confirm the exact risk minimisation plan proposed for Australia. Due to the potential for serious adverse events with certolizumab treatment, in addition to the ongoing safety concerns associated with the product, additional risk minimisation activities, as applied in the EU, are required in Australia.
The sponsor states that "*Training on the updated materials and the associated need for redistribution was provided to the affiliates in Mar 2012 with instruction to ensure this information is disseminated to all persons responsible for the distribution and tracking of the educational materials.*" The	*UCB confirms that this training as it occurred in the European Union will also take place Australia prior to the distribution of the new educational material if UCB decide to roll-out educational material in Australia.*	The Sponsor remains unclear regarding their risk minimisation plan proposed for Australia.

Recommendation in RMP evaluation report	Sponsor's response	Evaluator's comment
sponsor should clarify if this training has occurred within Australia.		
In regard to the proposed routine risk minimisation activities, the Delegate may wish to revise the draft product information document as suggested in the RMP Round 1 report (see attached).	*UCB confirm that upon receipt of the Delegate's comments on the PI, UCB will work with the TGA to update the PI appropriately.*	This is acceptable.
See Section 12 of the RMP Round 1 Report – "Issues to be amended in RMP documentation".	The Sponsor makes the following statement against one of these comments only – regarding the missing pages from the RMP report: *UCB confirm that as the RMPs have been combined appropriately, this discrepancy is no longer present.*	The updated EU-RMP Version 9.3 with ASA has been provided by the Sponsor. However the Sponsor continues to submit documents with multiple page numbering systems printed on each page. This should be amended on the next update of the RMP.

These concerns may be addressed and resolved after the ACPM meeting. Final outcomes are discussed within the above table and within Section VI below.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended approval (Clinical Evaluation Report (CER),) to extend the indication for certolizumab to include the treatment of active PsA and axial SpA. However the evaluator does not recommend acceptance of the proposed claim of radiographic benefit in patients with active PsA.

The clinical evaluator has reviewed the submitted data, which included:

- 2 pivotal Phase III, randomised, double-blind, parallel-group, placebo-controlled trials; one in adult patients with psoriatic arthritis (Study PsA001); and one in adults subjects with active axial SpA (Study AS001).
- 2 supportive studies in patients with moderate to severe plaque psoriasis; Study C87040 was a Phase II randomised, double-blind, parallel-group, placebo-controlled trial, and Study C87044 was a follow up study to C87040 in patients who had responded to treatment.

The benefits noted by the evaluator included:

- PsA indication – improvement in the signs and symptoms of peripheral arthritis (as per the ACR clinical response criteria), and improvement in physical functioning (as evidenced by treatment related improvements in the HAQ-DI scale).
- Axial SpA indication (for both subjects with confirmed AS and nr-axSpA) – improvement in the symptoms and signs of axial disease (as per improvements in back pain and stiffness), improvement in physical functioning (as per changes in BASDAI and BASFI), and slowing of structural damage (as evidenced by treatment related improvements in MRI parameters).

The concerns noted by the evaluator for both indications included:

- Increased risk of infection, including tuberculosis and other serious opportunistic infections.
- Local injection site reactions, which are generally mild and transient, and do not result in permanent discontinuation from CZP
- Increased incidence of abnormal liver function tests, in particular, raised serum transaminases.
- Potential increased risk of malignancy and adverse cardiovascular events requiring long-term surveillance.
- Formation of anti-CZP antibodies which results in increased plasma clearance of CZP and possible loss, or lack of efficacy.

Pharmacology

No clinical pharmacology studies were submitted, but limited pharmacokinetic (PK) data were collected from all 4 clinical studies. Trough serum samples for CZP concentration were collected at baseline; and Weeks 2, 4, 12, 16 and 24 in Studies PsA001 and AS001. Trough concentrations of CZP were highest following the loading doses at Weeks 1, 2 and 4 for both dose regimens of CZP, and lower at Weeks 12, 16 and 24. Trough CZP concentrations were lower in the CZP 400mg Q4W group compared to the CZP 200mg Q2W group, which is consistent with the difference in dosing interval. Subjects who developed anti-CZP antibodies had significantly lower trough CZP concentrations (by

approximately 70 - 80%) indicating increased plasma clearance of CZP. Trough levels from the supportive studies were consistent with those seen in the pivotal studies with the same dose and dose intervals.

Efficacy – Psoriatic arthritis

Study PsA001

This was a randomised, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of CZP in adults with adult-onset active and progressive PsA. It was conducted at 92 centres in North America, Latin America, Western Europe, and Central/Eastern Europe. The study had 5 treatment periods: screening (up to 5 Weeks), double-blind treatment period (Weeks 0-24), dose-blind treatment phase (Weeks 24-48), open-label treatment period (Weeks 48-158), and the safety follow-up phase 10 weeks after the last dose of study medication (Week 166). Only the screening and double-blind treatment period data were submitted, with the latter phases ongoing. Patients were randomly allocated in a 1:1:1 ratio to: CZP 400mg Q2W at Weeks 0, 2, and 4 followed by CZP 200mg Q2W (starting at Week 6), CZP 400mg Q2W at Weeks 0, 2, and 4 followed by CZP 400mg Q4W (starting at Week 8), or placebo injections. Subjects receiving placebo injections who did not achieve at least a minimal response (defined as a decrease of at least 10% in the number of tender and swollen joints) at both the Week 14 and 16 visits were allocated to blinded CZP escape therapy from Week 16 onwards. All of the placebo escape patients received CZP 400mg on 3 occasions (Weeks 16, 18 and 20) followed by their ongoing CZP regimen (randomised 1:1 to receive CZP 200mg Q2W [starting at Week 22] or CZP 400mg Q4W [starting at Week 24]).

Patients were greater than or equal to 18 years, had adult-onset PsA of greater than or equal to 6 month's duration as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR), and had failed at least 1 DMARD. A stable dose of non-biological DMARD treatment (SSZ < 3g daily, MTX < 25 mg weekly, and/or LEF < 20 mg daily) for greater than or equal to 28 days prior to baseline was allowed. Subjects were also required to have either active psoriatic skin lesions or a documented history of psoriasis. To be included in the study, patients must have had active arthritis at baseline defined as > 3 tender and swollen joints at the screening and baseline visits; and to have fulfilled at least 1 of the following 2 serological criteria during the screening phase (ESR > 28 mm/hour by the Westergren method, or CRP > ULN). Exclusion criteria were extensive, including other inflammatory arthritis, recent use of biologic DMARDs, oral prednisone > 10 mg/day, and > 2 previous biological response modifiers.

In total, 409 subjects were randomised and received at least 1 dose of study medication (placebo n = 136, CZP 200mg Q2W n = 138, CZP 400mg Q4W n = 135). At Week 16, 43.4% of placebo subjects did not achieve the minimal response criteria, and were re-randomised to CZP (200mg Q2W n = 30, 400mg Q4W n = 29). The majority of patients (88-92%) in each of the 3 treatment groups completed the 24-week double-blind treatment period.

Treatment groups were similar at baseline based on demographics, PsA features, disease activity, and prior and concomitant medications: mean age 48 years (range: 19-75 years), 55.3% female, 98% Caucasian, mean disease duration 8.55 years, 82% HLA-B27 positive, 85% with possible axial involvement (BASDAI score greater than or equal to 4), 34% dactylitis, mean tender joint count 20.3, mean swollen joint count 10.7, mean CRP 15.9 mg/L, and mean ESR 40.6 mm/hr. Almost 20% had received previous anti-TNF drugs, 51% greater than or equal to 1 DMARD (MTX 68%, SSZ 25%).

There were 2 primary efficacy outcomes: ACR 20 response rate at Week 12, and the mean change from baseline to Week 24 in the modified Total Sharp Score (mTSS, quantifies bone erosions and joint space narrowing on x-ray). Radiographs were read centrally and

independently by 2 experienced readers who were blind to treatment assignment and time course of the films.

A total of 56 subjects (13.7%) had missing x-rays from 1 or more visits: 35 subjects were missing 1, 17 subjects were missing 2, and 4 subjects were missing all 3 x-rays (total of 81 missing x-rays: 10 from baseline, 27 from Week 12, and 44 from Week 24). There was also an unequal distribution of subjects with no or only 1 radiograph across treatment groups, with > 50% of the placebo group missing x-ray values). The mTSS protocol-defined imputation rules for patients with missing x-ray data were as follows:

- For subjects with less than or equal to1 available radiograph, missing mTSS Baseline data were set to the lowest Baseline value observed in the entire population randomised into the study; in this case 0.
- For subjects with less than or equal to1 available radiograph, missing mTSS Week 24 data were set to the highest Week 24 value observed in the entire population randomised into the study; in this case 356.5.
- There was no definition of a minimum time interval between 2 radiographic measurements in order to perform linear interpolation or extrapolation since the planned radiographs were scheduled 12 weeks apart.

These rules led to physiologically implausible (high) results that were not statistically significant, so post-hoc analyses were performed using the following imputation rules:

- Missing mTSS values were imputed by using median change from Baseline in the entire study population (in this case 0).
- A minimum time interval of 8 weeks between radiographs was defined to perform a meaningful linear interpolation or extrapolation. If the radiographs were less than 8 weeks apart, the second radiograph was considered missing, and the above imputation rule was utilised for subjects with 1 remaining radiograph.

Based on the ACR 20 responder rates at Week 12, both CZP dose regimens were superior to placebo (58.0% for CZP 200mg Q2W, 51.9% for CZP 400mg Q4W versus 24.3% for placebo, $p < 0.001$ for each placebo comparison). Only two of the subgroup analyses showed a difference in ACR 20 response rate at Week 12: patients from Latin America had a smaller treatment difference between CZP and placebo, largely due to a much larger placebo response rate (63.2% compared with 13 – 27% elsewhere), and males had a higher response than females (65.1% versus 46.3%).

Table 3. ACR20 responders at Week 12 (Randomised Set, with imputation)

Week 12	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+CZP 400 mg Q4W N=273
Responders (%) 95% CI[a]	24.3 (17.1, 31.5)	58.0 (49.7, 66.2)	51.9 (43.4, 60.3)	54.9 (49.0, 60.8)
Difference to PBO[b] (%) 95% CI	–	33.7 (22.8, 44.6)	27.6 (16.5, 38.7)	30.7 (21.4, 40.0)
p-value	–	<0.001	<0.001	<0.001

Based on the mTSS at Week 24 (using post-hoc imputation rules), the CZP 200mg Q2W and combined CZP dose groups showed less progression of x-ray changes compared with placebo (0.01 for CZP 200mg Q2W, 0.06 for combined CZP group, and 0.28 for placebo). While the mean change in mTSS was also lower for the CZP 400mg Q4W group (0.11), the difference between CZP 400mg Q4W and placebo was not statistically significant. These

results were supported by multiple post-hoc sensitivity analyses, and were consistent with published studies in PsA with other anti-TNF treatments. In subgroup analyses, subjects who were older (greater than or equal to 45 years), male, or used fewer synthetic DMARDs previously (0 or 1) had greater mean differences to placebo (that is, less progression of radiographic changes).

Table 4. Change from Baseline in mTSS at Week 24 with the post-hoc imputation of median change from Baseline in the entire PsA001 study population and a specified minimum of 8 weeks between radiographs (RS, with imputation)

	Placebo[a] N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mgQ2W+ CZP 400mg Q4W N=273
Post-hoc primary analysis with ANCOVA				
Change from Baseline[b]				
LS mean (SE)	0.28 (0.07)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)
95% CI	(0.13, 0.42)	(-0.14, 0.15)	(-0.04, 0.26)	(-0.06, 0.17)
Difference to placebo[b]				
LS mean (SE)	–	-0.27 (0.09)	-0.17 (0.09)	-0.22 (0.08)
95% CI	–	(-0.45, -0.08)	(-0.35, 0.02)	(-0.38, -0.06)
p-value	–	0.004	0.072	0.007

In response to a question, the sponsor provided radiographic data up to Week 48 in Study PsA001. For each CZP dose group compared with placebo, the mean change in mTSS did not reach statistical significance. It should be noted, however, that all subjects received active treatment (either CZP 200mg Q2W or 400mg Q4W) after the Week 24 time point and therefore, data in placebo subjects at Week 48 are extrapolated.

Table 5. Change from Baseline in mTSS at Week 48 with the post-hoc imputation of median change from Baseline in the entire PsA001 study population and a specified minimum of 8 weeks between radiographs (RS, with imputation)

	PBO[a] N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273
Change from Baseline[b]				
LS mean (SE)	0.32 (0.11)	0.15 (0.11)	0.11 (0.12)	0.13 (0.09)
95% CI	0.10, 0.55	-0.07, 0.37	-0.12, 0.34	-0.05, 0.31
Difference to placebo[b]				
LS mean (SE)	–	-0.17 (0.14)	-0.21 (0.14)	-0.19 (0.12)
95% CI	–	-0.45, 0.11	-0.49, 0.07	-0.43, 0.05
p-value	–	0.240	0.142	0.127

The key secondary efficacy variables (ACR20 response rate, mean change from baseline in HAQ-DI, and PASI 75 response rate at Week 24) were all supportive of the efficacy of both dose regimens of certolizumab compared with placebo. Other efficacy variables (including LEI, PsARC, DAS28[CRP], BASDAI, erosion score, PsAQoL, SF-36 PCS, PtAAP, FASCA, EQ-5D, PASI) provided further supportive evidence of efficacy with certolizumab.

Study C87040 and C87044

Study C87040 was a Phase II randomised, double-blind, parallel-group, placebo-controlled trial which evaluated the efficacy and safety of 10 weeks of CZP in adults patients with

moderate to severe chronic plaque psoriasis who were candidates for systemic treatment and/or phototherapy. Study C87044 was a follow-up trial to Study C87040, whereby patients who had responded to treatment in Study C87040 (achieved at least a PASI 75 response), and who subsequently relapsed (a > 50% reduction in maximum improvement in PASI from baseline) within 24 weeks could receive the same therapy for an additional 12 weeks. Patients received either placebo, CZP 200mg Q2W, or CZP 400mg Q2W (all CZP subjects received an initial 400mg dose of CZP).

The 2 main efficacy outcomes in Study C87040 were the proportion of patients achieving at least a 75% decrease from baseline in PASI score at Week 12, and the proportion of patients with a PGA rating of 'clear' or 'almost clear' (that is 0 or 1) at Week 12. The primary efficacy outcome in Study C87044 was the median difference in PASI scores between Week 12 of Study C87040 (first treatment period) and Week 12 of Study C87044 (re-treatment phase).

Both doses of CZP were superior to placebo ($p < 0.001$) with respect to PASI 75 response rate (74.6%, 82.8%, and 6.8% for CZP 200mg, CZP 400mg, and placebo, respectively), and PGA response rate (52.5%, 72.4%, and 1.7% for CZP 200mg, CZP 400mg, and placebo, respectively). The median difference in PASI response between the 2 treatment periods was not clinically significant for either dose of CZP.

Efficacy –Active axial spondyloarthritis

Study AS001

This was a randomised, double-blind, parallel-group, placebo-controlled trial to evaluate the efficacy and safety of CZP in adults with active axial SpA. It was conducted at 128 centres in North America, Latin America, Western Europe, and Central/Eastern Europe. The study had 5 treatment periods: screening (up to 5 weeks), double-blind treatment period (Weeks 0-24), dose-blind treatment phase (Weeks 24-48), open-label treatment period (Weeks 48-158), and the safety follow-up phase 10 weeks after the last dose of study medication (Week 166). Only the screening and double-blind treatment period data were submitted, with the latter phases ongoing. Patients were randomly allocated in a 1:1:1 ratio to: CZP 400mg Q2W at Weeks 0, 2, and 4 followed by CZP 200mg Q2W (starting at Week 6), CZP 400mg Q2W at Weeks 0, 2, and 4 followed by CZP 400mg Q4W (starting at Week 8), or placebo injections. Subjects receiving placebo injections who did not achieve at least a minimal response (defined as the Axial Spondyloarthritis International Society 20% response criteria, or ASAS 20) at both the Week 14 and 16 visits were allocated to blinded CZP escape therapy from Week 16 onwards (randomised 1:1 to receive CZP 200mg Q2W or CZP 400mg Q4W).

Patients were greater than or equal to 18 years, with a documented diagnosis of adult-onset axial SpA of greater than or equal to 3 month's duration as defined by the ASAS criteria. The protocol specified that 50% of the study population had to fulfil both the modified NY criteria for a definite diagnosis of AS, as well as the ASAS criteria. The other 50% of subjects should not have met the modified NY criteria for definite AS, but greater than or equal to 50% of those patients (that is greater than or equal to 25% of the overall study population) had to meet the new ASAS imaging criteria, and the remainder (up to 25% of the overall population) could be enrolled based on meeting the ASAS clinical criteria only. The design allowed for the recruitment of a mix of patients with AS and nr-axSpA. Patients had to have been intolerant to, or have had an inadequate response to at least 1 NSAID, and were allowed to be receiving stable corticosteroids (less than or equal to 10 mg/day) and/or non-biological DMARD treatment for at least 28 days prior to baseline (SSZ < 3g daily, MTX < 25 mg weekly, or Hydroxychloroquine (HCQ) < 400 mg daily). Subjects were also required to have active disease at baseline with the BASDAI score being > 4, spinal pain > 4 on a 0 to 10 Numerical Rating Scale (NRS), CRP > ULN

and/or current evidence (that is, within the last 3 months from Screening) for sacroiliitis on MRI as defined by the ASAS criteria. Exclusion criteria were extensive, including other inflammatory arthritis, recent use of biologic DMARDs, oral prednisone > 10 mg/day, and > 2 previous biological response modifiers.

In total, 325 subjects were randomised and received at least 1 dose of study medication (placebo n = 107, CZP 200mg Q2W n = 111, CZP 400mg Q4W n = 107). At Week 16, 52.3% of placebo subjects did not achieve the minimal response criteria, and were re-randomised to CZP (200mg Q2W n = 27, 400mg Q4W n = 29). The majority of patients (89-95%) in each of the 3 treatment groups completed the 24-week double-blind treatment period.

Treatment groups were similar at baseline based on demographics, clinical ASAS features, and disease activity: mean age 38 years (range: 19-78 years), 61.5% male, 90% Caucasian, mean disease duration 6.73 years, 78.5% HLA-B27 positive, current inflammatory back pain 98%, elevated CRP levels 80%, evidence of peripheral joint synovitis 41.5%. Differences were noted between the patients with AS and those with nr-axSpA. AS patients tended to be older (41 versus 35 years), male (61.5% versus 48.3%), HLA-B27 positive (81.5% versus 74.8%), and have a longer mean time since diagnosis (8.24 years vs 4.91 years). Consistent with the protocol, sacroiliitis (grade greater than or equal to 2 bilaterally or grade 3-4 unilaterally) was confirmed by x-ray in 100% of subjects classified in the AS subgroup, and in 0% of the nr-axSpA subgroup. Other ASAS criteria and baseline disease activity were generally similar between the AS and nr-axSpA subpopulations once disease duration is taken into account. CRP was higher in the placebo group than in the combined CZP group for the overall axial SpA population (22.4 mg/L versus17.3 mg/L), the AS subgroup (25.2 mg/L versus 19.5 mg/L), and the nr-axSpA subgroup (19.1 mg/L versus 14.5 mg/L). Prior use of anti-TNF drugs and DMARDs was higher in the placebo group than the combined CZP group for the overall axial SpA population (24.3% versus 11.9% and 57.0% versus 45.4%, respectively). Prior use of anti-TNF drugs was also higher in the placebo group than the combined CZP group for the AS subgroup (20.2% versus 16.5%, respectively), and the nr-axSpA subgroup (10.9% versus 6.2%, respectively). The majority of patients reported past (85%) and concomitant (88%) NSAID use, with the percentage similar in each treatment group, and in those with AS and nr-axSpA. Concurrent DMARD (33.3%) and corticosteroid (16.9%) use was similar across the treatment groups.

The primary efficacy outcome was the ASAS 20 response rate at Week 12. In the overall axial SpA population, both CZP dose regimens were superior to placebo (57.7% for CZP 200mg Q2W, 63.6% for CZP 400mg Q4W versus 38.3% for placebo, $p < 0.004$ and $p < 0.001$ versus placebo, respectively). Similar results were seen in both the AS and nr-axSpA subpopulations. Only two of the subgroup analyses showed a difference in ASAS 20 response rate at Week 12: patients from Latin America had a smaller treatment difference between CZP and placebo, largely due to a larger placebo response rate (58.3% compared with 23 – 43% elsewhere), and males had a higher response than females (68.1% versus 48.2%). This pattern was also seen in the AS and nr-axSpA subpopulations.

Table 6. ASAS20 response at Week 12 – primary analysis with Wald test (RS, with imputation).

Week 12	PBO	CZP 200mg Q2W	CZP 400mg Q4W	CZP 200mg Q2W+ CZP 400mg Q4W
Overall axSpA population	**N=107**	**N=111**	**N=107**	**N=218**
Responders (%)	38.3	57.7	63.6	60.6
95% CI [a]	(29.1, 47.5)	(48.5, 66.8)	(54.4, 72.7)	(54.1, 67.0)
Difference to PBO [b] (%)	–	19.3	25.2	22.2
95% CI [a]	–	(6.3, 32.4)	(12.3, 38.2)	(11.0, 33.5)
p-value	–	0.004	<0.001	<0.001
AS subpopulation	**N=57**	**N=65**	**N=56**	**N=121**
Responders (%)	36.8	56.9	64.3	60.3
95% CI [a]	(24.3, 49.4)	(44.9, 69.0)	(51.7, 76.8)	(51.6, 69.0)
Difference to PBO [b] (%)	–	20.1	27.4	23.5
95% CI [a]	–	(2.7, 37.5)	(9.7, 45.2)	(8.2, 38.7)
p-value	–	0.026	0.003	0.003
nr-axSpA subpopulation	**N=50**	**N=46**	**N=51**	**N=97**
Responders (%)	40.0	58.7	62.7	60.8
95% CI [a]	(26.4, 53.6)	(44.5, 72.9)	(49.5, 76.0)	(51.1, 70.5)
Difference to PBO [b] (%)	–	18.7	22.7	20.8
95% CI [a]	–	(-1.0, 38.4)	(3.8, 41.7)	(4.1, 37.5)
p-value	–	0.067	0.021	0.017

The key secondary efficacy variables included: ASAS 20 response rate at Week 24, mean change from baseline in the BASFI, BASDAI and BASMI scores at Weeks 12 and 24, and two MRI parameters - SPARCC (sacroiliac joint) and ASspiMRI-a (spinal) scores at Week 12. CZP treatment was superior to placebo for each outcome in the overall axial SpA population, with similar results seen in the AS and nr-axSpA subpopulations. Baseline imbalance in the SPARCC (higher in the placebo group) and ASspiMRI-a scores (CZP 400mg < PBO < CZP 200mg; lower in the nr-axSpA subpopulation) complicates the interpretation of the MRI parameter results. Quality of life also improved on CZP compared with placebo.

Safety

In study PsA001, 332 subjects (including 59 PBO subjects escaping to CZP due to lack of response at Week 16) were exposed to CZP for a mean of 20.1 weeks (range 4 to 24 weeks). In study AS001, 274 subjects (including 56 PBO subjects escaping to CZP due to lack of response at Week 16) were exposed to CZP for a mean of 20.2 weeks (range 4 to 25 weeks).

In study PsA001, the incidence of treatment emergent adverse events was similar on CZP 200mg (68.1%), CZP 400mg (71.1%), and placebo (67.6%), with most being mild or moderate in severity. The most common TEAEs (combined CZP versus PBO) were nasopharyngitis (8.7% versus 7.4%), upper respiratory tract infection (7.8% versus 5.1%), headache (3.6% versus 1.5%), increased ALT (3.6% versus 1.5%), increased creatine phosphokinase (3.6% versus 2.9%), urinary tract infection (2.1% versus 6.6%), and bronchitis (2.4% versus 4.4%). The incidence of individual TEAEs were generally

similar between the two CZP dose groups. Adverse drug reactions occurred at a similar rate in the CZP and PBO groups with the exception of local injection site reactions. Liver function tests showed increases in AST or ALT (greater than or equal to 3xULN) more frequently in the combined CZP group (3.6%) than in the placebo group (2.2%). Three subjects on CZP 400mg had a bilirubin greater than or equal to 1xULN and an ALT or AST greater than or equal to 3xULN, but there was no discussion whether they were potential Hy's law cases. TEAEs of special interest included:

- ISRs - 6.6% versus 2.2%, none considered serious
- Systemic hypersensitivity reactions - 1.5% versus 1.5%, none considered severe or serious
- Cardiovascular events - cardiac disorders 1.5% versus 0.7%, vascular disorders 3.9% versus 4.4%. With the exception of hypertension, no event was recorded more than once. There were 4 SAEs (acute MI, unstable angina, cardiac arrest [fatal], and CVA) all of which occurred on CZP but were considered unrelated to study drug
- Autoimmune or demyelinating disease – none reported, however a single case of subacute cutaneous lupus was reported in a 64-year-old female treated with CZP 200mg. It was considered moderate in severity, and possibly related to CZP.

In study AS001, the incidence of TEAEs was higher on CZP 200mg (76.6%) and CZP 400mg (74.8%), than on placebo (62.6%). Most AEs were mild to moderate in severity. The most common TEAEs (combined CZP versus PBO) were nasopharyngitis (8.8% versus 6.5%), headache (6.2% versus 6.5%), increased creatine phosphokinase (5.1% versus 1.9%), upper respiratory tract infection (4.0% versus 2.8%), hypertension (2.9% versus 3.7%), and urinary tract infection (2.6% versus 3.7%). The incidence of individual TEAEs were generally similar between the 2 subpopulations (AS and nr-axSpA). ADRs occurred at a higher rate in the combined CZP group (33.2%) than in the placebo group (20.6%), mainly due to a higher incidence of ISRs (6.6% versus 0.9%), and infections and infestations (14.6% versus 4.7%). Liver function tests showed increases in AST or ALT (greater than or equal to 3xULN) more frequently in the combined CZP group (1.8%) than in the placebo group (0.9%) with no Hy's law cases. TEAEs of special interest included:

- ISRs - 6.6% versus 0.9%, none considered serious. ISRs were higher in the CZP 200mg group than the CZP 400mg group (9.0% versus 4.7%).
- Systemic hypersensitivity reactions – 1.8% versus 2.8%.
- Cardiovascular events - cardiac disorders 1.8% versus 0.9%, vascular disorders 5.1% versus 5.6%. With the exception of hypertension, no event was recorded more than twice. There was 1 SAE (SVT) which occurred on CZP 400mg but was considered unlikely to be related to study drug
- Autoimmune or demyelinating disease – a single case of pustular psoriasis was reported in a 32-year-old female treated with CZP 200mg. It was not serious, and considered possibly related to CZP.

The supportive studies had similar AE profiles to those in the pivotal studies. One patient treated with CZP in Study C87040 developed disseminated tuberculosis, and another subject was a screen failure for study C87044 because of latent tuberculosis.

Deaths occurred in 2 patients on CZP in study PsA001 but neither was considered related to study medication. There were no deaths in study AS001, C87040 or C87044. SAEs were more frequent in the combined CZP group than in the placebo group in PsA001 (6.6% versus 4.4%), but occurred at the same frequency in AS001 (4.7% each). No individual SAEs occurred in more than 1 subject, with the exception of cholelithiasis (2 cases in AS001, both on CZP 400mg). The incidence of serious infections was low in PsA001 (combined CZP 1.2%, PBO 0.7%) and occurred with the same incidence in the CZP and

PBO groups in AS001 (4.7% each), with no rare or opportunistic infections reported, and no reported cases of TB. Discontinuations due to AEs were more frequent in the combined CZP group than in the placebo group in PsA001 (3.0% versus 1.5%), but occurred at a similar frequency in AS001 (2.2% versus 1.9%). The only individual AE leading to study withdrawal reported for more than 1 subject was raised serum transaminases (2 cases on CZP 200mg in PsA001).

Anti-CZP antibodies developed in 11-12% of subjects on CZP in study PsA001 (3.7% on PBO) and in 1 – 4% of subjects on CZP in study AS001 (1.2% on PBO). In study PsA001, AEs and ADRs were higher in Ab +ve subjects than in Ab –ve subjects, but SAEs and discontinuations due to AEs were similar. There were only 4 TEAEs reported in AS001 after the development of Ab +ve status. Ab +ve status in study C87040 was not associated with increased incidence or type of AE, but in C87044 there was an apparent association with lack or loss of re-treatment efficacy.

Risk management plan

The TGA has reviewed the certolizumab EU RMP (Version 9.3, dated 1 October 2013), plus the Australian Specific Annex (Version: 1.0, dated 31 October 2013).

The following were outstanding matters and should be followed up with OPR and in the Pre-ACPM Response:

- The sponsor should add the following ongoing safety concerns or provide compelling justification for their exclusion (all the recommended additional safety concerns were supported by ACSOM):
  - Under “infections including TB and serious opportunistic infections”, add Legionella, Listeria, and Invasive fungal infections
  - Under “demyelinating disorders”, add Guillain-Barré syndrome, demyelinating polyneuropathy and multifocal motor neuropathy
  - Injection site reactions
  - HIV or hepatitis C (important missing information)
- ACSOM also advised that the safety concerns identified within the FDA warnings and precautions section, including bacterial sepsis, histoplasmosis, hepatotoxicity and adverse outcomes in patients with heart failure, should be added.
  - Pharmacovigilance
    - The sponsor should advise whether questionnaires for serious infection and hepatitis B reactivation are being developed, and address how data from post-market questionnaires will be collected and reported.
    - It is recommended that the Sponsor report on both the ongoing ARAD and DANBIO registry studies within the PSUR.
  - The sponsor should clarify the proposed risk minimisation plan for Australia, and the inclusion of additional risk minimisation activities (as applied in the EU), which was inconsistently addressed in the S31 responses.
  - Additional advice from ACSOM:
    - ACSOM was concerned about the use and interpretation of the term ‘non-radiographic’ in the axial spondyloarthritis indication. ACSOM advised that it would be more appropriate to include a phrase such as ‘when lack of response to DMARDs and NSAIDs’ to ensure clear communication of the intended use of certolizumab.

- § ACSOM was also concerned that the term 'axial spondyloarthritis', particularly in association with the term 'non-radiographic' would include a large proportion of the population. ACSOM underlined the importance of having a clearly defined disease when disease modifying agents, such as TNFα antagonists are used.
- § In addition, ACSOM advised that the use of the marketing terms in the indication 'Cimzia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function' was not appropriate and that such words should be removed from the indication. Such a statement is beyond the scope of defining the intended population.

Other RMP issues were satisfactorily resolved.

Risk-benefit analysis

Delegate's considerations

Efficacy

The efficacy of certolizumab for the treatment of adult patients with PsA and axial SpA is based on one pivotal study in each indication. For PsA, certolizumab was superior to placebo for both primary efficacy outcomes. The ACR 20 responder rate at Week 12 was significantly higher for CZP 200mg Q2W (58%) and CZP 400mg Q4W (51.9%) compared with placebo (24.3%). There was less progression of x-ray changes at Week 24 (change from baseline in mTSS; using post-hoc imputation rules) for CZP 200mg Q2W (0.01) and CZP 400mg Q4W (0.11) compared with placebo (0.28), but only the CZP 200mg result was statistically significant. While the mTSS results were comparable with those seen for other anti-TNF treatments for PsA, the concern is that they are based on post-hoc analyses as the pre-defined analyses led to physiologically implausible results. In addition, longer-term data are needed (see endpoint claims, below). For axial SpA, the ASAS 20 response rate at Week 12 for CZP was higher for both the 200mg Q2W (57.7%) and 400mg Q4W (63.6%) doses compared with placebo (38.3%). Similar results were seen in both the AS and nr-axSpA subpopulations. In subgroup analyses for both indications males had a better response than females. Key secondary endpoints were supportive for PsA (ACR20 response rate, mean change from baseline in HAQ-DI, and PASI 75 response rate at Week 24) and axSpA (ASAS 20 at Week 24, BASFI, BASDAI, and BASMI scores at Weeks 12 and 24, and two MRI parameters at Week 12). Quality of life also improved on CZP compared with placebo in both the PsA and axial SpA patient populations.

Endpoint claims

For the PsA indication, the sponsor proposed inclusion of x-ray and physical function endpoints (Cimzia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function). The clinical evaluator does not support inclusion of the x-ray endpoint for two reasons: (i) the 24 Week time frame is insufficient to justify the claim; and (ii) radiological efficacy was only positive when post-hoc imputation rules were applied. Although not specifically addressed in the EMA guideline for PsA, these arguments are supported by the RA guideline which recommends not less than one year (ideally two years) of follow-up for x-ray endpoints, and states that the "method for obtaining the final score should be described in detail (for example consensus) and be predefined". In Australia, 2 years of data are normally submitted for RA indications claiming radiographic benefits. Further, the Week 48 data provided by the sponsor in the S31 response did not demonstrate a statistically significant benefit with CZP treatment. The Delegate agrees with these concerns about the

radiographic data, and therefore recommends that the x-ray claim is removed from the indication. While the physical function endpoint did show improvement with CZP treatment, the results of both endpoints may be more appropriately included in the Clinical Trials section of the PI. ACSOM also support this view, particularly since endpoint claims do not define the population to be treated (that is the indication). ACPM's advice is requested on this matter.

Axial SpA subpopulations

The sponsor has included nr-axSpA in the proposed indication. The results for this subgroup were comparable to those seen in the overall axial SpA population and in those with definite AS; therefore inclusion of this subgroup appears reasonable. However, is nr-axSpA sufficiently well-defined and recognised to support its inclusion in the axSpA indication? ACPM's advice is requested on this matter.

Safety and RMP

The safety of certolizumab has been demonstrated in 606 adult patients with active PsA (n = 332) or axial SpA (n = 274) over a period of up to 24 weeks. The most common TEAEs that were more frequent on CZP in either PsA and/or axial SpA included: nasopharyngitis, upper respiratory tract infection, injection site reactions, headache, increased ALT, increased creatine phosphokinase, urinary tract infection. TEAEs were mostly mild or moderate in severity, and the incidence of individual TEAEs were generally similar between the two CZP dose groups. In both studies, cardiac disorders were more common in the CZP treatment groups although no individual event (with the exception of hypertension) occurred in more than 2 patients. There were 2 deaths reported (both on CZP), but neither was considered related to study medication. Serious adverse events and discontinuations due to adverse events were more frequent on CZP in PsA, but similar to placebo in axial SpA. Malignancies (n = 2) and cardiovascular SAEs (n = 5) were reported infrequently, but the study durations were too short to adequately address these issues. Anti-CZP antibodies developed in a small percentage of subjects on CZP, but were not consistently associated with AEs or SAEs, and the only apparent association with lack or loss of re-treatment efficacy was in the supportive C87044 study. The outstanding safety concerns discussed in the RMP section are generally already included in the currently approved PI and therefore their inclusion in the RMP seems appropriate.

Data deficiencies

The major deficiency for the PsA indication was the reliance on post-hoc analyses to support the claim that CZP reduces the rate of radiographic progression, and the lack of longer-term radiographic data.

Conditions of registration

The following are proposed as conditions of registration:

- The implementation in Australia of the EU Risk Management Plan (RMP) for Cimzia (Version 9.3, dated 1 October 2013) with the Australian Specific Annex (Version: 1.0, dated 31 October 2013) and RMP agreements from the Pre-ACPM Response, included with submission PM-2013-00286-2-3, and any subsequent revisions, as agreed with the TGA.
- The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission:
  - the final clinical study reports for Studies PsA001 and AS001.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. It is noted that in July 2013 an FDA Advisory Committee recommended approval of certolizumab for the treatment of axial spondyloarthritis. However the approved indication is for the "treatment of adult patients with active ankylosing spondylitis". Please provide an explanation for the change in the wording of the indication, and whether or not nr-axSpA has been approved by the FDA for Cimzia.
2. Are any further studies planned or underway for PsA with pre-defined radiographic endpoints and including stratification by baseline mTSS?
3. Please address all the outstanding RMP matters as discussed above under Risk Management Plan.
4. Please provide further details on the 3 subjects on CZP 400mg in study PsA001 who had a bilirubin greater than or equal to 1xULN and an ALT or AST greater than or equal to 3xULN, particularly discussing whether they were potential Hy's law cases.
5. Given that cardiac events are a known concern for anti-TNFα agents and that more cardiac disorders were seen with CZP than placebo in both pivotal trials, please comment on what studies and pharmacovigilance activities are planned or underway to further investigate this issue.
6. Please provide a breakdown on the number of patients with nr-axSpA who had lower grades of sacroiliitis on x-ray at baseline (that is < 2 bilaterally or grade 1-2 unilaterally) and whether / how this correlates with sacroiliitis detected on MRI.

Proposed action

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

The Delegate's suggested indication for psoriatic arthritis is as follows:

Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis.

Request for ACPM advice

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

- Psoriatic Arthritis
  - The modified Total Sharp Score (mTSS) was one of the two primary efficacy outcomes. The mTSS protocol-defined imputation rules for patients with missing x-ray data led to physiologically implausible (high) results, so post-hoc analyses were performed. On this basis, is it reasonable to include the radiographic endpoint in the proposed indication?
  - Inclusion of a second (physical function) endpoint was also proposed for the PsA indication. Although improvement in physical function was demonstrated with CZP treatment, would this be more appropriately addressed in the Clinical Trials section of the PI?
- Axial Spondyloarthritis
  - axSpA includes patients with ankylosing spondylitis (AS) and nr-axSpA. Is nr-axSpA sufficiently well-defined and recognised to support its inclusion in the axSpA 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.

Response from sponsor

1. The assessors correctly note that the Arthritis Advisory Committee on 23 July 2013 supported both the demonstration of safety and efficacy as well as supported an approval for the indication of active axial spondyloarthritis (axSpA), including patients with ankylosing spondylitis (AS). Despite the positive outcome and support from the Advisory Committee, the FDA did not grant an indication for treatment of axSpA. In contrast, the Committee for Human Medicinal Products (CHMP) recommended the approval of both Humira and Cimzia for treatment of adult patients with severe active axSpA.

The concept of axSpA as one disease spectrum, which includes both AS patients and patients without clear signs of structural changes in the sacroiliac joints (SIJ) on plain x-ray (nr-axSpA), is now well accepted by rheumatologists in the US, EU and Australia (see Other Delegate's Comments). This is reflected in the update to the 2010 ASAS (The Assessment of Spondyloarthritis International Society) recommendations for the use of anti-TNF agents in axial spondyloarthritis (van der Heijde et al 20111). These recommendations, which represent the collective views of the ASAS organisation which has members from all over the world including the US, EU and Australia, are an update of the 2006 recommendations which were focused solely on AS. The recommendations were updated and broadened to axSpA to enable earlier treatment as a consequence of the growing recognition that the burden of the disease is similar between AS and nr-axSpA patients. Furthermore, in clinical practice, it is the burden of disease that determines therapeutic intervention in axSpA, not whether or not patients have sufficient structural damage to fulfil the mNY classification criteria for AS, especially in light of well-known difficulties in interpreting SIJ x-rays. This approach is very similar to other rheumatic diseases, such as RA, where treatment is not restricted to patients with erosive disease. In AS001 disease burden at baseline as indicated by BASDAI, a measure of disease activity, was very similar in the AS and nr-axSpA subpopulations (Table 7). While spinal mobility (BASMI) and function (BASFI) were markedly impaired in the nr-axSpA subpopulation, BASMI and BASFI scores were lower relative to the AS subjects which may be a consequence of permanent structural changes in the AS subpopulation.

Table 7. Demographic and Baseline Characteristics of Subpopulations (RS)

Characteristic	AS			nr-axSpA		
	Placebo (N=57)	CZP Q2W (N=65)	CZP Q4W (N=56)	Placebo (N=50)	CZP Q2W (N=46)	CZP Q4W (N=51)
Median age, years	41.0	39.0	41.5	37.0	33.0	37.0
Gender, n (%)						
Male	41 (71.9)	47 (72.3)	41 (73.2)	24 (48.0)	20 (43.5)	27 (52.9)
Female	16 (28.1)	18 (27.7)	15 (26.8)	26 (52.0)	26 (56.5)	24 (47.1)
Caucasian, n (%)	51 (89.5)	59 (90.8)	49 (87.5)	44 (88.0)	43 (93.5)	47 (92.2)
Mean (SD) BMI, kg/m^2	28.4 (6.3)	27.0 (4.4)	27.5 (5.8)	27.9 (5.97)	26.4 (6.55)	28.5 (5.80)
Regions (combined sites), n (%)						
North America[a]	15 (26.3)	19 (29.2)	14 (25.0)	15 (30.0)	11 (23.9)	14 (27.5)
Latin America[b]	6 (10.5)	6 (9.2)	8 (14.3)	6 (12.0)	3 (6.5)	4 (7.8)
Western Europe[c]	6 (10.5)	5 (7.7)	1 (1.8)	15 (30.0)	18 (39.1)	18 (35.3)
Eastern Europe[d]	30 (52.6)	35 (53.8)	33 (58.9)	14 (28.0)	14 (30.4)	15 (29.4)
Median time since diagnosis, yrs	6.86	4.65	3.97	3.09	1.79	3.41
Median symptom duration, yrs	10.21	8.82	8.84	4.54	4.83	7.31
Symptom duration, n (%)						
<5 yrs	16 (28.1)	26 (40.0)	15 (26.8)	26 (52.0)	24 (52.2)	19 (37.3)
≥5 yrs	41 (71.9)	39 (60.0)	41 (73.2)	24 (48.0)	22 (47.8)	32 (62.7)
Median CRP, mg/L	16.6	14.0	12.9	13.5	9.95	12.10
Positive for HLA-B27, n (%)	48 (84.2)	53 (81.5)	44 (78.6)	39 (78.0)	34 (73.9)	37 (72.5)
Prior anti-TNFα use, n (%)	16 (28.1)	11 (16.9)	9 (16.1)	10 (20.0)	4 (8.7)	2 (3.9)
Disease burden at baseline, FAS	(N=57)	(N=65)	(N=56)	(N=49)	(N=46)	(N=51)
Mean (SD) BASDAI score	6.44 (1.85)	6.52 (1.67)	6.18 (1.29)	6.40 (1.45)	6.45 (6.63)	6.63 (1.60)
Mean (SD) BASMI score	4.74 (1.62)	1.48 (1.55)	4.31 (1.77)	3.12 (1.55)	3.05 (3.26)	3.26 (1.54)
Mean (SD) BASFI score	5.98 (2.01)	5.61 (2.28)	5.65 (2.25)	4.92 (2.15)	4.76 (2.21)	5.13 (2.42)

Abbreviations: ASAS, Assessment in Axial Spondyloarthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; CZP, certolizumab pegol (Cimzia); FAS, Full Analysis Set; HLA-B27, human leukocyte antigen B27; Q2W, 200 mg every 2 weeks; Q4W, 400 mg every 4 weeks; RS, Randomized Set; TNFα, tumor necrosis factor alpha; ULN, upper limit of normal.

[a] North America included investigational sites in the US and Canada.

[b] Latin America included investigational sites in Mexico, Brazil, and Argentina.

[c] Western Europe included investigational sites in the United Kingdom, Belgium, Germany, Italy, Spain, The Netherlands, and France.

[d] Eastern Europe included investigational sites in Czech Republic, Poland, and Hungary.

[1] van der Heijde et al., 2010 Update of the international ASAS recommendations for the use of anti-TNF agents in patients with axial spondyloarthritis, Ann rheum Dis 2011;70:905–908

During the review of the EU Humira axSpA application (the first product to undergo review for an AxSpA indication), an European expert panel advised the CHMP. There was consensus amongst the experts that axSpA is a clinical entity sufficiently well established for the purpose of issuing a marketing authorisation (Humira EPAR). Recognising the fact that not all axSpA patients require treatment with anti-TNF therapy, the EMA restricted the nr-axSpA indication statement for Humira to patients with "severe axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated C-reactive protein and /or magnetic resonance imaging, who have had an inadequate response to, or are intolerant to non-steroidal anti-inflammatory drugs". By restricting the label to those patients with the most refractory and severe disease, with clear objective signs of inflammation, the potential concerns about inappropriate treatment of axSpA patients that may not have a positive risk benefit with anti-TNF therapy were addressed. These considerations were also taken into account during the CHMP review and positive CHMP recommendation of Cimzia for the treatment of severe active axial spondyloarthritis by requiring the same conditions in the approved SmPC. In order to ensure that treatment with Cimzia is given only to eligible patients, UCB would accept to update the Australian PI to reflect these conditions for nr-axSpA.

1. No further studies are planned or underway for PsA with pre-defined radiographic endpoints.

2. OPR's comments on the RMP are addressed in the "Response to RMP Advice-Round 2 Assessment" document included with this response.

3. During the Week 24 Double-Blind Treatment Period of PsA001, a total of 3 subjects in the certolizumab pegol (CZP) 400mg every 4 weeks (Q4W) group had simultaneous post-Baseline liver function test elevations of bilirubin greater than or equal to 1x upper limit of normal (ULN) and alanine aminotransferase or aspartate aminotransferase greater than or equal to 3xULN (PsA001 Week 24). (Subject 454-00248, Subject 458-00452, and Subject 705-00568). As of 16 Nov 2012, an additional subject (Subject 454-00143) in the CZP 400mg Q4W group met the above criteria for elevated lab values (PsA001 [data cutoff 16 Nov 2012]. These subjects presented with different combinations of risk factors at Baseline including current and former alcohol and tobacco use (3 subjects); in addition, Subject 454-00143 had a history of liver steatosis. Transient high levels of transaminase values were observed in each subject. Taken together, these data suggest that factors other than CZP treatment contributed to the elevated values. None of the subjects had concomitant bilirubin and AST/ALT elevations meeting Hy's law criteria.

4. Cardiac events are indeed a known concern for anti-TNF agents including CZP. With reference to the submitted the safety data collected up to 31 May 2012 in the 2 new indications (PsA and axSpA) along with a safety pooling refresh of clinical trials conducted in RA up to 30 November 2011. The incidence and incidence rates per 100 pat/years for the MedDRA SOC "Cardiac Disorders" in the placebo controlled studies/study periods for PBO and CZP (any dose) as well as in all studies are summarized in this response. When corrected for exposure, there was an increase of cardiac events compared to PBO in RA and PsA but not in axSpA. However, incidence rates were higher in the All CZP group in Placebo-controlled studies compared with the All CZP group in All Studies, suggesting that there is no increase for Cardiac Events with long-term exposure.

Table 8. Cardiac events in Clinical Trials.

	Placebo-controlled studies				All Studies	
Indication	**Placebo**		**CZP all doses**		**CZP all doses**	
RA	**N**	**% (IR)**	**N**	**% (IR)**	**N**	**% (IR)**
	1137	1.8% (5.7)	2965	2.8% (6.6)	4049	7.9% (3.7)
PsA	**N**	**% (IR)**	**N**	**% (IR)**	**N**	**% (IR)**
	136	0.7% (1.9)	332	1.5% (3.8)	393	2.5% (2.2)
axSpA	**N**	**% (IR)**	**N**	**% (IR)**	**N,**	**% (IR)**
	107	1.9% (5.2)	274	1.5% (3.7)	315	3.2% (2.8)

IR=incidence rate; N= number of patients per treatment group; %= percentage of patients with Cardiac Events.
Sources: 2.7.4 PsA and axSpA tables 8.17:1 and 8.11:1; RA Summary of Safety tables 8.1:10 and 8.2:5

No specific clinical studies are planned to investigate this further. This risk is appropriately addressed in the PI (contraindications, precautions and adverse effects sections) as well as in the RMP.

5. There were 147 subjects in the AS001 study that had a Baseline x-ray of < 2 bilaterally or grade 1-2 unilaterally. Among these subjects, 80 (54.4%) had sacroiliitis on MRI, while 67 (45.6%) had no sacroiliitis due to either a missing or a negative MRI.

6. Other Delegate's Comments:

    a. *'Certolizumab was approved in the USA in September 2013 (PsA) and October 2013 (AS), and in Canada in January 2014 (indications below). The certolizumab submission is under evaluation in the EU. It has not been submitted in Switzerland, or New Zealand.'*

        i. Response: Approval in the EU was received on 18 Oct 2013 (axSpA, both AS and nr-axSpA) and on 25 November 2013 (PsA), and in Canada on (PsA on 2

January 2014 and AS on 15 January 2014). The full approved indications for these countries are provided in the current international regulatory status and PI documents provided with this response. CZP is under evaluation in Switzerland for PsA (submitted March 2013) and axSpA (submitted April 2013).T

b. *'The clinical evaluator has recommended approval (Clinical Evaluation Report(CER)) to extend the indication for certolizumab to include the treatment of active PsA and axial SpA. However the evaluator does not recommend acceptance of the proposed claim of radiographic benefit in patients with active PsA, and data deficiencies: The major deficiency for the PsA indication was the reliance on post-hoc analyses to support the claim that CZP reduces the rate of radiographic progression, and the lack of longer-term radiographic data'.*

   i. Response: The statistical model used to support the claim of reduced radiographic progression is as originally specified in the statistical analysis plan, but it is acknowledged that rules used to impute x-rays, the mTSS change from Baseline at Week 24 was imputed as the median change instead of being based on the maximum among all observed mTSS values. The two principal reasons for this change were

      1. the pre-defined approach resulted in physiologically implausible changes in mTSS for these subjects and to align with the approach used in a recent PsA approval for analysis of mTSS data (See "Missing data imputation rules" of Simponi EPAR Assessment Report).

      While the principle of adhering to pre-defined analysis methods is certainly important, a post-hoc imputation approach should not be discounted when it provides more reasonable imputed values and is based on well-accepted methods. It should also be noted that the statistically significant result observed at Week 24 was supported by 2 additional sensitivity analyses applying other imputation approaches (Source: PsA001 Week 24 CSR). Furthermore, FDA used yet another method for handling these missing data which also resulted in a statistically significant difference compared to placebo. The consistency among the conclusions for these various sensitivity analyses is supportive of the robustness of the claim of inhibition of radiographic progression at Week 24.

      The mTSS data at Week 48 in the overall population indicate that subjects on CZP experienced greater inhibition of structural damage as compared to extrapolated placebo, though this difference did not reach statistical significance. As part of the CHMP review, the agency requested an analysis of changes in structural damage in subjects with and without structural changes at Baseline to further establish the effects of CZP in reducing progression of structural damage. Although no commonly accepted cut-off to define structural damage at Baseline is currently available for PsA, consultation with external experts suggested a mTSS score of "6," which was also the median mTSS score at BL in PsA001, as a reasonable cut-off to define the presence of structural damage at Baseline – this was also accepted by the CHMP.

      When a subgroup analysis was done for subjects with Baseline mTSS > 6, the treatment difference between combined CZP and placebo reached statistical significance (p = 0.005) at Week 24. Additionally, the treatment difference between combined CZP and extrapolated placebo for this group of subjects was statistically significant (p = 0.048) at Week 48.

Conversely, subjects with Baseline mTSS less than or equal to 6 showed little radiographic progression in any treatment group at either time point. Taken together, these results indicate a clear trend towards inhibition of structural damage by CZP treatment. As such, this approach was accepted and agreed by both FDA and CHMP as part of their approval of PsA with the resulting inclusion of the inhibition of structural damage progression in the EU and US prescribing information.

c. '*Endpoint claims: For the PsA indication, the sponsor proposed inclusion of x-ray and physical function endpoints (Cimzia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function). While the physical function endpoint did show improvement with CZP treatment, the results of both endpoints may be more appropriately included in the Clinical Trials section of the PI. ACSOM also support this view, particularly since endpoint claims do not define the population to be treated (that is the indication). ACPM's advice is requested on this matter.'*

i. Response: The HAQ-DI scores obtained from Study PsA001 clearly demonstrate CZP treatment improves physical function for subjects with active PsA. UCB proposes alignment of the PsA indication with other TNF-α inhibitors currently approved on the Australian market where "improve physical function" or similar, is included in the indication (eg infliximab, etanercept, golimumab; (Reference, request for ACPM's Advice).

d. '*The concerns noted by the evaluator for both indications included: Increased risk of infection, including tuberculosis and other serious opportunistic infections. local injection site reactions, which are generally mild and transient, and do not result in permanent discontinuation from CZP.'*

i. Response: UCB acknowledge these comments. However the safety profile of CZP in PsA001 and AS001 was consistent with that expected in subjects with inflammatory joint diseases receiving other anti-TNF agents and with previous studies in CZP. These adverse events are appropriately addressed in the PI, as well as in the RMP.

e. '*Axial SpA subpopulations: The sponsor has included nr-axSpA in the proposed indication. The results for this subgroup were comparable to those seen in the overall axial SpA population and in those with definite AS; therefore inclusion of this subgroup appears reasonable. However, is nr-axSpA sufficiently well-defined and recognised to support its inclusion in the axSpA indication? ACPM's advice is requested on this matter.'*

i. Response: [information redacted]

f. '*Conditions of Registration: The following are proposed as conditions of registration: 1) The implementation in Australia of the EU Risk Management Plan (RMP) for Cimzia (Version 9.3, dated 1 October 2013) with the Australian Specific Annex (Version: 1.0, dated 31 October 2013) and RMP agreements from the Pre-ACPM Response of [date], included with submission PM-2013- 00286-2-3, and any subsequent revisions, as agreed with the TGA. 2) The following studies must be submitted to the TGA, as soon as possible after completion, for evaluation as a Category 1 submission: • the final clinical study reports for Studies PsA001 and AS001.'*

i. Response: UCB acknowledges the proposed conditions of registration.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register an extension of indications for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered Cimzia solution for injection containing 200 mg/mL of certolizumab to have a positive benefit–risk profile for the amended indication;

Psoriatic arthritis:

Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis.

Ankylosing spondylitis:

Cimzia is indicated for the treatment of adult patients with ankylosing spondylitis

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of the non-radiographic ankylosing spondylitis (nr-axSPA) indication.

In making these recommendations the ACPM

- noted that the 24 week results from the trial was insufficient to justify the claim for a radiographic endpoint and the relevant EMA guidelines suggest 12 months (ideally 24 months) of follow up for radiographic data
- advised that, in general, physical function claims should not be included in indications and agreed with the delegate that the physical function claim is better placed in the *Clinical Trials* section of the PI
- noted evidence was sufficient for the approval for ankylosing spondylitis (consistent indication with other TNF inhibitors)

Proposed conditions of registration:

The ACPM agreed with the delegate on the proposed conditions of registration

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

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the Clinical Trials section of the PI regarding modified Total Sharp Score (mTSS) should either be remove or state that due to large amount of missing data, only a post-hoc analysis suggested Cimzia had an effect on x-ray progression
- removal of information about the PASI in the PI. This is not an application for use in psoriasis.

Specific advice:

Psoriatic arthritis

1. The modified Total Sharp Score (mTSS) was one of the two primary efficacy outcomes. The mTSS protocol-defined imputation rules for patients with missing x-ray data led to physiologically implausible (high) results, so post-hoc analyses

were performed. On this basis, is it reasonable to include the radiographic endpoint in the proposed indication?

The ACPM advised removal of this statement due the high rate of missing x-ray data.

7. Inclusion of a second (physical function) endpoint was also proposed for the PsA indication. Although improvement in physical function was demonstrated with CZP treatment, would this be more appropriately addressed in the Clinical Trials section of the PI?

The ACPM agreed with the delegate that the physical function claim would be better placed in the Clinical Trials section.

Axial Spondyloarthritis

8. axSpA includes patients with ankylosing spondylitis (AS) and nr-axSpA. Is nr-axSpA sufficiently well-defined and recognised to support its inclusion in the axSpA indication?

The validity of nr-axSpA as a recognised diagnosis is not questioned and includes ASAS valid criteria. However, the nr-axSPA patients are subgroups of the overall study population and the diagnosis of these subjects for the trial is not conclusive as the primary criterium is radiographic evidence of AS. Radiography is a blunt instrument and the use of objective signs of inflammation by elevated CRP and/or MRI would be more convincing. The ACPM advised that further information is required before approving indication for nr-axSPA. A new study along these lines is being developed.

The ACPM advised that the 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 this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Cimzia certolizumab pegol (rbe) 200 mg/mL solution for injection – prefilled syringe indicated for:

> *Psoriatic arthritis: Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis where response to previous disease-modifying anti-rheumatic drug therapy (DMARDs) has been inadequate. Cimzia has been shown to improve physical function.*
>
> *Ankylosing Spondylitis: Cimzia is indicated for the treatment of adult patients with active, ankylosing spondylitis who have been intolerant to or have had inadequate response to at least one nonsteroidal anti-inflammatory drug (NSAID).*

The same loading and maintenance dosage regimen used for RA is proposed for the additional indications of psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA).

Specific conditions of registration applying to these goods

- The Cimzia (certolizumab pegol (rbe)) EU Risk Management Plan (RMP), version 9.3, dated 1 October 201.3 with the Australian Specific Annex (Version: 1.0, dated 24 January 2014) and pre-ACPM response from 24 January 2014, included with submission PM-2013-00286-2-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Cimzia at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>

Attachment 2. Extract from the Clinical Evaluation Report

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