Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Certolizumab pegol (rbe)

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

November2015

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 <https://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
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
CER	clinical evaluation report
CI	confidence interval
CRP	c-reactive protein
CS	corticosteroids
CXR	chest X-ray
CZP	certolizumab pegol
DAS28	disease activity score for 28 joints
DAS28(ESR)	disease activity score for 28 joints, including erythrocyte sedimentation rate (as one of the measures of disease activity)
DMARD	disease modifying anti-rheumatic drug
ES	erosion score
ESR	erythrocyte sedimentation rate
EU	European Union
Fab	fragment antigen binding
Fc	fragment crystallisable
GCP	Good Clinical Practice
GI	gastro-intestinal
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
ITT	intend to treat
JSN	joint space narrowing
LEF	leflunomide

Abbreviation	Meaning
LOCF	last observation carried forward
MedDRA	Medical dictionary for Drug Regulatory Affairs
mTSS	modified total Sharp score
MTX	Methotrexate
NSAID	non-steroidal anti-inflammatory drug
PEG	polyethylene glycol
PK	pharmacokinetic(s)
q2w	Once every two weeks
RA	rheumatoid arthritis
SAE	serious adverse event
SC	subcutaneous(ly)
SD	standard deviation
SOC	system organ class
SSZ	sulfasalazine
TB	tuberculosis
TNFα	tumour necrosis factor alpha
TNFβ	tumour necrosis factor beta

I. Introduction to product submission

Submission details

Type of submission:	Major variation (extension of indications)
Decision:	Approved
Date of decision:	29 January 2015
Active ingredient:	Certolizumab pegol (rbe)
Product name:	Cimzia
Sponsor's name and address:	UCB Australia Pty Ltd T/A UCB Pharma Division PO Box 158 Malvern Vic 3144
Dose form:	Solution for injection
Strength:	200 mg/mL
Container:	Pre-filled syringe
Pack size:	Two
Approved therapeutic use:	*Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX*
Route of administration:	Subcutaneous (SC)
Dosage:	The recommended dose of Cimzia for adult patients with rheumatoid arthritis is 400 mg (2 x 200 mg subcutaneous injections) at weeks 0, 2 and 4, followed by a maintenance dose of 200 mg every 2 weeks via subcutaneous injection (or 400 mg every 4 weeks). (see approved Product Information for full *Dosage and Administration*)
ARTG number:	154726

Product background

This AusPAR describes the application by UCB Australia Pty Ltd T/A UCB Pharma Division (the sponsor) to register Cimzia for the following indication for rheumatoid arthritis:

> *Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.*

Certolizumab pegol[1] is a member of the tumour necrosis factor alpha (TNFα) inhibitor drug class. TNFα is a key pro inflammatory cytokine in the pathogenesis of inflammatory conditions. It is present in significantly elevated concentrations in serum and synovial fluid in patients with rheumatoid arthritis (RA), psoriatic arthritis, and ankylosing spondylitis. 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, and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.

Certolizumab is a recombinant, humanised antibody fragment antigen binding (Fab') fragment that is produced 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 tumour necrosis factor beta (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.

One year radiographic data presented in the initial Cimzia submission showed that clinical improvement was associated with inhibition of progression of structural damage. The TGA advised that 2 year data be assessed to ensure that prevention of structural damage is sustained long term.

Regulatory status

Certolizumab was initially registered on 20 January 2010 for the indication rheumatoid arthritis;

> *Cimzia is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients:*
>
> – *combined with MTX in case of either an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDS); or*
>
> – *as monotherapy in case of a contraindication or intolerance to MTX.*

Certolizumab was approved on 1 May 2014 for the indications psoriatic arthritis and ankylosing spondylitis.

> *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 new indication for rheumatoid arthritis (this application);

[1] Certolizumab pegol will be referred to as Certolizumab or CZP.

Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

was registered on the ARTG on 27 May 2015.

Overseas regulatory status

The proposed indication for the prevention of structural damage for RA was approved in the European Union (EU) (October 2009) as part of the original application (which included 2 year radiographic data).

Certolizumab is also approved for RA in the USA (May 2009) and in Canada (August 2009). The current RA indications for Cimzia in the USA, Canada and EU (at the time of this evaluation) are shown in Table 1.

At the time the TGA considered this application, a similar application for the RA indication had been approved in Argentina, Brazil, Canada, Chile, Colombia, Dominican Republic, Ecuador, El Salvador, European Union (EU), Hong Kong, Iceland, Israel, Japan, Kuwait, Lebanon, Malaysia, Mexico, New Zealand, Norway, Panama, Peru, Russia, Serbia, Singapore, South Korea, Switzerland, Tunisia, Turkey, UAE and the USA. The approved application dates and indication details for USA, the EU, Canada, Switzerland and Japan and are shown in Table 1.

Table 1. Approval dates and indication details for USA, the EU, Canada, Switzerland and Japan.

Country	Application status Status date	Approved application indication details
United States	Approved 22 April 2008	CIMZIA is a tumour necrosis factor (TNF) blocker indicated for: · Reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy (1.1)
United States	Approved 13 May 2009	· Treatment of adults with moderately to severely active rheumatoid arthritis (1.2)
United States	Approved 27 September 2013	· Treatment of adults with active psoriatic arthritis
United States	Approved 17 October 2013	· Treatment of adults with active ankylosing spondylitis
European Union	Approved 1 October 2009	Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to disease-modifying antirheumatic drugs (DMARDS) including methotrexate, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

Country	Application status Status date	Approved application indication details
		Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.
European Union	Approved 18 October 2013	Axial spondyloarthritis Cimzia is indicated for the treatment of adult patients with severe active axial spondyloarthritis, comprising: Ankylosing spondylitis (AS) Adults with severe active ankylosing spondylitis who have had an inadequate response to, or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDS). Axial spondyloarthritis without radiographic evidence of AS Adults with severe active axial spondyloarthritis without radiographic evidence of AS but with objective signs of inflammation by elevated c-reactive protein (CRP) and/or MRI, who have had and inadequate response to, or are intolerant to NSAIDs.
European Union	Approved 25 November 2013	Psoriatic arthritis Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Cimzia can be given as a monotherapy in the case of intolerance to methotrexate or when the continued treatment with methotrexate is inappropriate.
Canada	Approved 12 August 2009	Rheumatoid Arthritis (RA) CIMZIA (certolizumab pegol) in combination with methotrexate (MTX) is indicated for: · Reducing signs and symptoms, inducing major clinical response, and reducing the progression of joint damage as assessed by X-ray, in adult patients with moderately to severely active rheumatoid arthritis (RA). CIMZIA may be used alone for reducing signs and symptoms in adult patients with moderately to severely active rheumatoid arthritis (RA) who do not tolerate MTX
Canada	Approved 02 January 2014	Psoriatic Arthritis (PsA) CIMZIA alone or in combination with

Country	Application status Status date	Approved application indication details
		methotrexate (MTX) is indicated for: · reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray, in adult patients with moderately to severely active psoriatic arthritis (PsA) who have failed one or more DMARDs.
Canada	Approved 15 January 2014	Ankylosing Spondylitis (AS) CIMZIA is indicated for: · reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) who have had an inadequate response to conventional therapy.
Switzerland	Approved 10 June 2010	Cimzia is indicated for the induction of a clinical response and for the maintenance of a clinical response and a remission in patients with active Crohn's disease who have not responded adequately to conventional treatment. Cimzia, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients when the response to DMARDs including methotrexate, has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate. Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function, when given in combination with methotrexate.
Switzerland	Approved 16 July 2014	Psoriatic arthritis Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults which did not respond sufficiently to previous DMARD therapy. Cimzia improves the physical function capabilities of patients with psoriatic arthritis. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.
Japan	Approved 25 December 2012	Treatment of rheumatoid arthritis not responding to conventional therapy (including inhibition of progression of bone structural damage).

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 <https://www.tga.gov.au/product-information-pi>.

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.

Introduction

Clinical rationale

Cimzia is one of the antibody TNFα inhibitors which have been shown to reduce inflammation, reduce symptoms and improve physical function in adult patients with moderate to severe RA who have not responded adequately to disease modifying anti-rheumatic drugs (DMARDs). Joint damage and deformity contribute to progressive disability and impairment of quality of life. One year radiographic data presented in the initial Cimzia submission showed that clinical improvement was associated with inhibition of progression of structural damage. However, the TGA advised, that two year data be assessed to ensure that prevention of structural damage is sustained long-term.

Guidance

There is one specific TGA adopted European guideline which is relevant to this submission:

CPMP/EWP/556/95 (Rev 1) 'Points to consider on Clinical Investigation of Medicinal Products other than NSAIDs for the Treatment of Rheumatoid Arthritis' (effective 29 January 2007).

At the request of the TGA, the sponsor submitted two year follow up efficacy data from the two pivotal, double blind, placebo controlled studies C87027/28 and C87050/51 to support the proposed additional indication.

Contents of the clinical dossier

The submission contained the following clinical information:

Two pivotal studies and one supporting study have been submitted. Studies C87028 and C87051 (Table 2) are long term safety studies which extend the pivotal efficacy studies C87027 (RAPID 1) and C87050 (RAPID 2) approved in the previous application. Both extension studies provide 2 year radiographic data to support the new indication for

prevention of structural damage. The supporting Study C87015 (Table 3) provides long term safety data but no radiographic endpoints to support the new indication.

Table 2. Summary of studies C87028 and C87051.

Type of study[a]	Study identifier	Location of study report	Objectives of the study	Study design and type of control	Test product(s)/ dosage regimen/ route of administration	No. subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status/ type of report
Safety and efficacy for RA	C87028	5.3.5.1.2	**Primary:** To continue to assess the safety of 400 mg CZP sc every 2 weeks in treating signs & symptoms & preventing structural damage in pts with active RA. **Secondary:** 1. assess tolerability of CZP sc every 2 weeks in combination with MTX in pts with active RA. 2. assess efficacy of CZP sc every 2 weeks in combination with MTX in pts with active RA. 3. assess the effect of CZP sc every 2 weeks in combination with MTX on Physical Function in pts with active RA. 4. assess effect of CZP sc every 2 weeks in combination with MTX on Health Outcome Measures in pts with active RA. 5. monitor plasma concentration &immunogenicity profile.	Multi-centre, openlabel, follow-on study to C87027.	Lyophilized; CZP 400 mg sc every 2 weeks followed by CZP 200mg sc every 2 weeks	846	Rheumatoid arthritis patients on MTX	Continued until approval of the marketing application or until further notice from UCB. The mean duration of exposure was 1278.7 days (3.5 years), and maximum duration of exposure per subject was 2143 days (5.9 years). Including the feeder study, the mean duration of exposure was 1518 days (4.2 years), and the maximum duration of exposure per subject was 2268 days (6.2 years).	Full CSR reported Study complete

Type of study[a]	Study identifier	Location of study report	Objectives of the study	Study design and type of control	Test product(s)/ dosage regimen/ route of administration	No. subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status/ type of report
Efficacy and safety for RA	C87051	5.3.5.1.3	**Primary:** To continue to assess the safety of the liquid formulation of CZP (400 mg sc every two weeks and 200 mg sc every two weeks) in treating signs and symptoms and preventing joint damage in patients with active RA. **Secondary:** To assess tolerability of liquid CZP sc every 2 weeks in pts with active RA. To assess the efficacy of liquid CZP sc every 2 weeks in pts with active RA. To assess the effect of liquid CZP sc every 2 weeks on physical function in pts with active RA. To assess the effect of liquid CZP sc every 2 weeks on Health Outcome Measures in pts with active RA. To monitor the pharmacokinetic and immunogenicity profile of liquid CZP	Multi-centre, openlabel, follow-on study to C87050.	Liquid; CZP 400 mg sc every 2 weeks followed by CZP 200mg sc every 2 weeks	567	Rheumatoid Arthritis patients on MTX	Continued until after marketing approval or until further notice by UCB. The mean duration of exposure was 1301.6 days (3.6 years), and maximum duration of exposure per subject was 1945 days (5.3 years). Including the feeder study, the mean duration of exposure was 1423.3 days (3.9 years), and the maximum duration of exposure per subject was 2085 days (5.7 years).	Full CSR reported Study complete

CSR = clinical study report; CZP=certolizumab pegol; MTX = methotrexate; NA=not applicable; pts = patients; RA=rheumatoid arthritis; sc=subcutaneous;

Table 3. Summary of supportive Study C87015.

Type of study[a]	Study identifier	Location of study report	Objectives of the study	Study design and type of control	Test product(s)/ dosage regimen/ route of administration	No. subjects	Healthy subjects or diagnosis of patients	Duration of treatment	Study status/ type of report
STUDY REPORTS OF UNCONTROLLED STUDIES									
Safety and efficacy for RA	C87015	5.3.5.1.1	**Primary:** To assess the long-term safety and tolerability of CZP 400 mg sc every 4 weeks in patients with RA from C87011 & C87014 studies. **Secondary:** - To assess the longterm efficacy of CZP 400 mg sc every 4 weeks in the treatment of the signs and symptoms of RA. - To characterize the dose and type of additional arthritis medication(s) utilized by patients. - To assess the longterm impact of CZP on physical function.	Multi-center, openlabel long-term follow-on study to C87011 and C87014	Lyophilized; CZP 400 mg sc every 4 weeks	402	Rheumatoid arthritis patients (some on MTX)	Continued until after marketing approval or at Investigator's discretion (mean duration of exposure of 1554.1 days and maximum duration of exposure of 2737 days).	Full CSR reported Study complete

Paediatric data

The submission did not include paediatric data.

Good clinical practice

All studies were conducted according to the principles of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP).

Pharmacokinetics

No new pharmacokinetic (PK) data were submitted.

Pharmacodynamics

No new pharmacodynamic (PD) data were submitted.

Dosage selection for the pivotal studies

Not applicable.

Efficacy

Studies providing efficacy data

There were two pivotal efficacy studies (studies C87028 and C87051 were open label extensions to studies C87027 and C87050, respectively, which were provided to support the inclusion of prevention of structural damage for certolizumab pegol (CZP) in the approved RA indication. There was also one supportive efficacy study (Study C87015) submitted to meet a post-approval commitment of submitting long-term open-label extension studies upon completion.

Evaluator's conclusions on efficacy

Designs, methodologies and reporting methods of the feeder studies (C87027 and C87050) were in line with the Outcome Measures in Rheumatology Clinical Trials consensus (www.omeract.org). The scoring system used for assessing radiological change was the modified total Sharp score (mTSS)[2]. This validated X-ray method is a composite of erosion and joint narrowing scores in 32 joints of the hands and 12 joints of the feet. The Sharp score was first proposed in 1971 and the modified Sharp score has been the most widely used scoring system for assessing structural damage in clinical trials for many years.

The score ranges from 0 to 448 points and the smallest detectable and minimum clinically important difference is considered to be 5.0 points. In line with consensus guidelines, the changes from baseline in mTSS were reported as mean, median and inter quartiles, as radiographic damage at baseline in RA patients is not normally distributed. However, bias may have been introduced because different radiological reporters were used in the feeder and follow on studies (the two year assessment of structural damage was not a pre-determined endpoint). There are various methods for handling missing or incomplete data but there is no single agreed method. The sponsor reported the study results using last observation carried forward (LOCF) imputation, linear extrapolation with non imputed baseline for missing data, and non extrapolated data to reduce the risk of bias. The lack of placebo control data beyond 52 weeks in Study C87027 and 24 weeks in Study C87050 was a significant weakness in the analyses. Moreover, there was a high rate of early withdrawals in the placebo groups so the numbers completing each study were small.

Certolizumab pegol 200 mg every other week + methotrexate (MTX) was superior to MTX + placebo in C87027 after 52 weeks with no radiological progression in 69% and 52% of patients, respectively. This difference was statistically significant ($p < 0.001$) and clinically meaningful. The results in C87050 after 24 weeks are quoted as being similar to those of C87027 but the data are not shown in the sponsor's clinical overview of the submission[3],. Control data are not available in C87028 and C87051 so the evidence for continued inhibition of radiological damage over 2 years is necessarily indirect. However, the overall data support the claim for radiological inhibition of structural damage. In the 2 pivotal studies (C87027/8 and C87050/1), the overall progression over 2 years in mean (change from baseline in) mTSS scores was < 1.0 points in both studies for CZP treated subjects, with a median change of 0.0. These radiological findings are similar to published data from studies of other anti TNFα biologics such as etanercept and infliximab. In contrast, in the placebo + MTX group of C87027, radiaographic progression at Week 52 was 2.5 (standard deviation (SD) 4.2, n = 38) mTSS points (for Completers in the C87027/028 extension population), and 1.6 (SD 3.9, n = 15) points in C87050 at Week 24. These data are in line with radiological progression 0.9 to 7.0 in control groups identified in other studies and in a literature review by Strand and Sharp.[4] [5]. Sensitivity analyses using linear extrapolation were broadly comparable, with less radiological progression than placebo (extrapolated from Year 1 to Year 2) noted in patients who received CZP treatment. In addition, more

[2] mTSS is the sum of the erosion score (ES) and the joint space narrowing (JSN) score and has a range of 0 to 398. The ES is the sum of joint scores collected for 46 joints and has a range of 0 to 230. The JSN is the sum of joint scores collected for 42 joints and has a range of 0 to 168. A score of 0 would indicate no change. An erosion score of 0 to 5 is given to each joint analysed, according to the number of erosions; "5" represented total destruction. Joint space narrowing was scored from 0 to 4 with "4" representing alkylosis.

[3] Clarification Data were included in the original submission for RA indication and in the sponsor's response to questions raised by the TGA.

[4] Sharp JT, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomized controlled trials of leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 2000, 43:495-505.

[5] Strand V and Sharp JT. Radiographic data from recent randomized controlled trials in rheumatoid arthritis. *Arthritis Rheum* 2003, 48:21-34

than 60% of Completers, Withdrawers and Switchers (in the CZP treated groups) had no progression (mTSS ≤ 0) over the 2 year treatment period.

The percentage of patients with American College of Rheumatology (ACR20)[6] responses and other clinical indices of disease were sustained for up to six years.[7] There is an imperfect correlation between clinical disease activity and progression of structural damage. However, these findings supported the continued effectiveness of CZP therapy, even though the development of anti-CZP antibodies appears to reduce the overall therapeutic response rate. The combination of CZP + MTX forms the basis of the proposed indication and no data for CZP monotherapy were submitted.

Safety

Studies providing safety data

Safety data were obtained from studies C87027/C87028, C87050/C87051 and C87015.

Patient exposure

In C87028, the mean duration of exposure to CZP was 1518 days (4.2 years) and the maximum duration of exposure was 2268 days (6.2 years). In C87051, the mean duration of exposure to CZP was 1423 days (3.9 years) and the maximum duration of exposure per patient was 2085 days (5.7 years). In C87015, mean duration of exposure to CZP was a minimum of 1554 days (4.3 years) and a maximum of 2737 days (7.5 years).

Safety issues with the potential for major regulatory impact

Injection site reactions

In Study C87028, a total of 9.9% of patients reported at least one adverse event (AE) related to injection site reactions, most commonly pain, erythema and skin discolouration. None of the reactions was considered serious. In Study C87051, 3% of patients reported reactions, most commonly erythema. In Study C87015, injection site reactions were reported in 7.7% of patients, most commonly pain and bruising.

Systemic hypersensitivity reactions

In C87028, the most frequently reported AEs suggestive of systemic hypersensitivity were headache (11.0% of patients), rash (7.4%) and pyrexia (7.2%). Two subjects reported anaphylactic reactions, but neither of the events was serious or considered related to study medication by the investigator. In Study C87051, the most commonly reported AEs suggestive of systemic hypersensitivity were headache (7.8% of patients), pyrexia (3.9%) and rash (3.4%). Asthma was reported in four (0.7%) patients.

In Study C87015, AEs related to systemic hypersensitivity reactions were reported in 20.6% of patients, most commonly cough (20.6%), rash (16.4%) and peripheral oedema (9.7%). There were 12 serious adverse events (SAEs), related to systemic hypersensitivity reactions, most commonly syncope (3) and pyrexia (3).

[6] ACR responses are presented as the numerical improvement in multiple disease assessment criteria. For example, an ACR 20 response is defined as a ≥ 20% improvement in (1) swollen joint count (66 joints) and tender joint count (68 joints) and (2) ≥ 20% improvement in 3 of the following 5 assessments - patient's assessment of pain (VAS), patient's global assessment of disease activity (VAS), physician's global assessment of disease activity (VAS), patient's assessment of physical function as measured by the HAQ and CRP. ACR 50 and ACR 70 are similarly defined.
[7] Clarification; in studies C87015, C87028 and C87051.

All infections

In Study C87028, 665 patients (78.6%) had at least one event in the Infection and infestation system organ class (SOC). SAEs were reported by 16.4% of patients; there were three deaths (0.4%); and 49 patients (5.8%) had AEs leading to withdrawal. The majority of AEs were mild to moderate in severity and 7.2% were severe. SAEs in the infections and infestations SOC reported in at least 0.5% of patients. Tuberculous infections were each reported in 19 (2.2%) patients.

In Study C87051, 395 patients (69.7%) had at least one event in the infection and infestation SOC. SAEs were reported by 13.8% of patients; there were two deaths (0.4%) and 36 patients (6.3%) had AEs leading to withdrawal. The majority of AEs were mild to moderate in severity and 7.9% were severe. SAEs in the Infections and infestations SOC reported in at least 0.5% of patients. Tuberculous infections reported in 17 (3.0%) patients.

In Study C87015, 81.8% of patients reported at least one AE related to infections and infestations, and 40.8% were considered drug-related. Most were mild to moderate, and 14.2% were severe. SAEs were reported in 13.7% of patients, most commonly pneumonia (2.2%). Tuberculous infections were reported in two patients (0.2%).

Malignancies

In Study C87028, 44 patients (5.2%) reported at least one malignancy. The most frequently reported malignancies were basal cell carcinoma (1.2% of patients) and thyroid cancer (0.8%). The most commonly reported malignancy SAEs were basal cell carcinoma (0.4%) and breast cancer (0.4%). In Study C87051, 24 patients (4.2%) reported at least one malignancy. The most frequently reported malignancy was lung cancer (1% of patients), which was also the most commonly reported malignancy SAE.

In Study C87015, the most common malignancies were thyroid (0.7%) and breast (0.7%) cancers.

Cardiac and vascular adverse event s

In Study C87028, 109 (12.9%) patients reported cardiac AEs. SAEs were reported in 3.8% of patients, most commonly atrial fibrillation (0.7%), myocardial infarction (0.6%), angina (0.5%) and cardiac failure (0.5%). Vascular AEs were reported in 256 patients (30.3%), most commonly hypertension (18.9%), hypotension (2.1%) and varicose veins (2.1%).

In Study C87051, 51 (9.0%) patients reported cardiac AEs. SAEs were reported in 1.8% of patients, most commonly, myocardial infarction (0.4%) and myocardial ischemia (0.4%). A total of 107 patients (18.9%) reported at least one vascular AE. The most common AE was hypertension (13.6%) while all other AEs were reported in ≤ 1.2% of patients.

In Study C87015, cardiac AEs were reported in 14.4% of patients, most commonly coronary artery disease (4.0%). Vascular AES were reported in 31.1% of patients, most commonly hypertension (19.7%).

Autoimmune adverse events

In Study C87028, the most frequently reported autoimmune AE was sarcoidosis in four patients (0.5%); this was serious in three cases (0.4%). In Study C87051, the most frequently reported autoimmune AE was thyroiditis in three patients (0.5%). There were no autoimmune SAEs.

In Study C87015, Only two patients reported autoimmune AEs and there were no cases suggestive of demyelinating disorders.

Neurological adverse events

In Study C87028, seven neurological events of interest were identified: amnesia was reported in five patients (0.6%) and there were single cases each of confusional state, grand mal convulsion and ischaemic stroke. SAEs were reported in two patients, both reported a headache. In Study C87051, eleven neurological AEs of interest were identified: transient ischaemic attack was reported in seven patients (1.2%), cerebrovascular accident in two patients (0.4%), and cerebral haemorrhage and cerebral ischemia in one patient each (0.2%). All the events were reported as SAEs with the exception of the single case of cerebral ischemia.

Serious bleeding events

In Study C87028, 16 patients (1.9%) reported SAEs suggestive of bleeding. Events reported in more than one patient were metrorrhagia (0.5% of patients) and contusion (0.2%). In Study C87051, nine patients (1.6%) reported SAEs suggestive of bleeding. Events reported in more than one patient were metrorrhagia (0.5%) and haematuria (0.4%).

In Study C87015, there were five SAEs relating to bleeding.

Bone marrow aplasia

In Study C87028, AEs suggestive of bone marrow aplasia were reported in 22 patients (2.6%). Events reported in more than one patient were thrombocytopenia (0.8%) and lymphopenia (0.4%). A single event of pancytopenia was reported as an SAE. In Study C87051, events suggestive of bone marrow aplasia were reported in 11 patients (1.9%). Events occurring in more than one patient were: thrombocytopenia (0.9%), lymphopenia (0.7%) and neutropenia (0.4%). One event of thrombocytopenia was reported as an SAE.

In Study C87015, there was one SAE of thrombocytopenia.

Serious skin reactions

In Study C87028, there were six SAEs related to skin reactions: single cases each of allergic dermatitis, pityriasis rosea, generalised pruritus, purpura, rash and urticaria. In Study C87051, there was one SAE related to skin reactions (leucocytoclastic vasculitis).

In Study C87015, there were SAEs relating to skin reactions in four patients: subcutaneous abscesses, skin ulceration and erythema (2 cases).

Safety related to anti CZP antibody status

In Study C87028, 98/846 patients (11.6%) had detectable anti CZP antibodies (Ab+). A summary of AEs by anti CZP antibody status is shown in Table 16 Attachment 2. Overall, the incidence of AEs was similar in the Ab + and Ab - patient groups. However, there was a higher incidence in Ab + patients compared with Ab - patients in AEs related to rheumatoid arthritis (28.6% versus 16.4%), pyrexia (13.3% versus 6.4%), rhinitis (13.3% versus 5.7%), conjunctivitis (12.2% versus 5.7%), diarrhoea (11.2% versus 7.4%), dyspepsia (11.2%), cough (10.2% versus 6.4%), alanine aminotransferase (ALT) increased (10.2% versus 5.6%) and rash (10.2% versus 7.1%).

Adverse events occurring within two hours of CZP injection (possibly indicative of hypersensitivity reactions) were recorded in 16.3% and 9.9% of Ab + and Ab - patients, respectively. The incidence of SAEs was higher in Ab + than Ab - patients (51.0% versus 40.4%). There was a higher incidence in Ab + patients compared with Ab - patients of SAEs related to infections (26.5% versus 15.1%), pneumonia (7.1% versus 2.9%) and cardiac disorders (6.1% versus 3.5%).

In Study C87051, 86/567 patients (15.2%) had detectable anti-CZP antibodies. A summary of AEs by anti CZP antibody status is shown in Table 17 Attachment 2. Overall, the incidence of AEs was similar in the Ab + and Ab - patient groups. However, there was a

higher incidence in Ab + patients compared with Ab - patients in AEs related to rheumatoid arthritis (26.7% versus 13.1%), musculoskeletal and connective tissue disorders (53.5% versus 30.8%), pyrexia (9.3% versus 2.9%), and renal and urinary disorders (16.3% versus 8.7%). AEs occurring within two hours of CZP injection were recorded in 2.3% and 1.9% of Ab + and Ab - patients, respectively. The incidence of SAEs was higher in Ab + than Ab - patients (43.0% versus 33.9%). There was a higher incidence in Ab + patients compared with Ab - patients of SAEs related to infections (19.9% versus 12.7%).

In Study C87015, 113/402 patients (28.1%) had detectable anti CZP antibodies. A summary of AEs by anti CZP antibody status was provided. Overall, the incidence of AEs, severe AEs, drug related AEs, AEs leading to death and AEs leading to discontinuation were similar in the Ab + and Ab - patient groups. However, SAEs were reported more commonly in Ab + patients compared with Ab - patients (56.6% versus 41.5%).

Evaluator's conclusions on safety

The safety profile of CZP in the three, long term, extension safety studies in patients with RA was compatible with its safety profile in previous studies of up to one year documented in the approved PI. As expected during exposure of up to 7.5 years, AEs were recorded in over 90% of patients although event rates were unremarkable. The majority of AEs were mild or moderate, although approximately 20% were considered severe and withdrawals due to AEs occurred in 15 to 25% of patients. SAEs were recorded in 35 to 45% of patients, most commonly related to RA, infection, cardiac and vascular events. AEs leading to death ranged from 1.9% to 3.0%, with incidence rates of 0.44 to 0.74 per 100 patient-years in the three studies. The incidence of patients with anti CZP antibodies ranged from 11.6% to 28.1% in the three studies. Overall, AEs were more frequent in Ab + patients than in Ab - patients, although the low number of Ab + patients makes meaningful comparisons of specific AEs difficult. The higher incidence of AEs related to RA in Ab + patients, was presumably due to lower CZP levels in these patients.

AEs of interest (injection and hypersensitivity reactions, infections, malignancies, cardiac, vascular, autoimmune and neurological) were identified based on earlier studies and the known effects of biologic anti TNFα inhibitors. Most AEs of interest were mild or moderate in intensity. There was a high incidence of hypertension, possibly exacerbated by concomitant medications, but most cases were mild and the incidence was also high in patients during the placebo phase of the studies. Most SAEs and SAEs leading to death were consistent with the middle aged study population with active RA disease, including cardiac and vascular events, and malignancies. The incidence of malignancies was 4 to 5%, most commonly lung cancers, with no other tumour types over represented. There was a significant incidence of possible hypersensitivity reactions (mostly headache, pyrexia and rash) but no deaths were recorded. There was a high incidence of infections but the majority were mild or moderate, mostly upper respiratory (> 15% of patients) and urinary tract infections. The incidence of fungal and bacterial opportunistic infections was low. Tuberculosis infections were recorded in 1 to 3% of patients, although fewer infections are likely in a non-endemic region such as Australia. There were no new safety signals related to haematology or biochemistry variables, or to vital signs. Overall, no new safety concerns were identified.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Cimzia in the proposed usage are:

- Increased ACR20, ACR50 and ACR70 response rates
- Reduced markers of inflammation including c-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
- Improved symptom scores
- Improved health related quality of life
- Inhibition of radiological progression of structural damage.

First round assessment of risks

The risks of Cimzia in the proposed usage are:

- Injection site reactions
- Hypersensitivity reactions
- Increased risk of opportunistic infections and tuberculosis.

First round assessment of benefit-risk balance

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

First round recommendation regarding authorisation

The clinical evaluator recommends authorisation for the proposed additional indication:

> *'Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX'.*

Approval is subject to incorporation of suggested changes to the proposed Product Information (PI) and adequate response to the evaluator's questions.

Clinical questions

Efficacy

1. The sponsor's Clinical Overview reports several post hoc sensitivity analyses to support to the proposed indication. These included linear extrapolation of placebo data and an analysis of progression of structural damage in the subset of patients who completed at least two years of treatment with CZP and who had evaluable radiographs at completion. These analyses have been reported for Study C87027/28 but not for Study C87050/51. The sponsor is requested to provide these analyses and to identify any significant differences between the outcomes of the two trials.
2. Different central radiographic readers were used to evaluate Year 1 and Year 2 data as the second year analyses were not pre-determined for studies C87027/28 and C87050/51. The sponsor is requested to provide an estimate of what degree of bias might have been introduced due to observer error.

Product information (PI)

Changes to the PI were also requested but discussion of this is beyond the scope of the AusPAR.

Second round evaluation of clinical data submitted in response to questions

The sponsor's response addresses questions that were raised in the first round clinical assessment.

Question 1

Sponsor's response

The requested analysis was not performed but the sponsor has provided a justification for its omission. The sponsor argues that Study C87027/28 had 982 patients in the intent-to-treat (ITT) population compared with 'only' 619 patients in the Study C87050/51 population. The sponsor also argues that efficacy outcomes in Study C87027/81 are extrapolated from placebo controlled data at Week 52, whereas only 24 week comparator data are available for Study C87050/51.

Evaluator's response: The sponsor's arguments are valid although the second is more cogent than the first. Extrapolation from Week 24 to the end of two years is more subject to error than extrapolation from Week 52. Nonetheless, it would be desirable for this analysis to be performed. While acknowledging the caveats, significant differences between the two analyses would require explanation.

Question 2

Sponsor's response

No statistical assessment of inter reader variability has been provided. However, the sponsor has provided an extensive summary of the methodology and measures taken to minimise reader error, all representing best practice.

Evaluator's response: The sponsor's response is satisfactory.

Second round benefit-risk assessment

Second round assessment of benefits

There is no change to the assessment of benefits summarised in the first round evaluation.

Second round assessment of risks

There is no change to the assessment of risks summarised in the first round evaluation.

Second round assessment of benefit-risk balance

There is no change to the assessment of benefit-risk balance.

Second round recommendation regarding authorisation

Authorisation is recommended for the proposed indication:

> *Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.*

However, approval is subject to incorporation of suggested changes to the proposed PI.

V. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan for this application.

The safety of certolizumab in patients with RA has previously been demonstrated, and no new safety concerns have been identified.

VI. Overall conclusion and risk/benefit assessment

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

Current approved treatment options in Australia for moderate to severe active RA include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS), and non-biological DMARDs (mainly MTX, sulfasalazine (SSZ), and leflunomide (LEF)). Specific pharmaceutical treatments (TNFα inhibitors) registered for the treatment of RA includes adalimumab (Humira), infliximab (Remicade), etanercept (Enbrel) and golimumab (Simponi). Other alternative agents include the anti-interleukin (IL)-6 receptor antibody, tocilizumab (Actemra); the CD80 + CD86 and CD28 interaction co-stimulation modulator, abatacept (Orencia); and the IL-1 receptor antagonist, anakinra (Kineret).

The currently approved RA indications (for other specific pharmaceutical treatments are as follows:

- Adalimumab

  Humira is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

  Humira can be used alone or in combination with methotrexate.

- Infliximab

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

  patients with active disease despite treatment with methotrexate

  patients with active disease who have not previously received methotrexate.

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

- Etanercept

  Rheumatoid Arthritis

  Active, adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more disease-modifying antirheumatic drugs (DMARDs). Enbrel can be used in combination with methotrexate.

  Severe, active rheumatoid arthritis in adults to slow progression of disease-associated structural damage in patients at high risk of erosive disease.

- Golimumab

  Simponi, in combination with methotrexate, is indicated for:

The treatment of moderate to severely active rheumatoid arthritis in adult patients when the response to disease-modifying anti-rheumatic drug therapy, including methotrexate, has been inadequate. SIMPONI has also been shown to inhibit the progression of joint damage as measured by X-ray.

- Tocilizumab

  Rheumatoid Arthritis

  Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs) in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs.

  Actemra is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients with poor prognostic factors (see 'Clinical trials') in combination with MTX in those not previously treated with MTX.

  In the two groups of patients above, Actemra can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

  Actemra has been shown to inhibit the progression of joint damage in adults, as measured by X-ray, when given in combination with methotrexate.

- Abatacept

  Orencia in combination with methotrexate is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an insufficient response or intolerance to other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or tumour necrosis factor (TNF) blocking agents. A reduction in the progression of joint damage and improvement in physical function have been demonstrated during combination treatment with Orencia and methotrexate.

  Orencia in combination with methotrexate is also indicated in the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

- Anakinra

  Kineret (anakinra) is indicated for the treatment of active adult rheumatoid arthritis (RA) in patients who have had inadequate response to one or more other Disease Modifying Anti Rheumatic Drugs (DMARDs). Kineret should be given in combination with methotrexate.

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 reviewed the submitted data, which included:

- Two long-term safety studies (C87028 and C87051), which provide two year radiographic data and extend the pivotal Phase III efficacy studies C87027 and C87050, respectively.
- One supportive long term safety study (C87015), which extends Studies C87011 and C87014.

The benefits noted by the clinical evaluator included:

- In the original pivotal Study C87027, CZP 200 mg once every two weeks (q2w) + MTX was superior to placebo + MTX after 52 weeks with no radiological progression (defined as mTSS ≤ 0.0) in 69% and 52% of patients, respectively. This difference was statistically significant ($p < 0.001$) and clinically meaningful.
- In the original pivotal Study C87050, CZP 200 mg q2w + MTX was superior to placebo + MTX after 24 weeks with no radiological progression in 70.7% and 58.3% of patients, respectively (obtained by the Delegate from the clinical evaluation report (CER) from the previous submission, no p-value included in CER).
- In the two pivotal extension studies (C87028 and C87051) overall progression over two years in mean mTSS[2] scores was < 1.0 points in both studies, with a median score of 0.0. Because control data are not available in Studies C87028 and C87051, this evidence for continued inhibition of radiological damage over 2 years is indirect and based on observed and imputed data in the control group. However the overall data support the claim for radiological inhibition of structural damage.
- The percentage of patients with ACR20 responses[6] and other clinical indices of disease were sustained for up to 6 years. There is an imperfect correlation between clinical disease activity and progression of structural damage. However, these findings support the continued effectiveness of CZP therapy even though the development of anti CZP antibodies appears to reduce the overall therapeutic response rate.

The concerns noted by the evaluator included:

- Increased risk of opportunistic infections and tuberculosis.
- Local injection site reactions, which are generally mild and transient, and do not result in permanent discontinuation from CZP.
- Increased risk of possible hypersensitivity reactions (mostly headache, pyrexia and rash).
- Formation of anti CZP antibodies which causes increased plasma clearance of CZP and possible loss, or lack of efficacy.

Pharmacology

No clinical pharmacology studies were submitted.

Efficacy

Two pivotal studies were included in the submission: Study C87028 (an open label extension to Study C87027) and Study C87051 (an open label extension to Study C87050). Brief descriptions of the two feeder studies are provided.

Study C87027 (RAPID-1)

This was a prospective, multicentre, randomised, double blind, active comparator controlled, parallel group study of 52 weeks duration in subjects with active, adult onset RA of at least six months duration with incomplete response to MTX. Subjects were randomised to one of three treatment groups in 2:2:1 ratio: CZP 200 mg q2w (preceded by

three loading doses of 400 mg given q2w), CZP 400 mg q2w or placebo. This study used the lyophilised formulation of CZP. All patients were also on weekly oral MTX of at least 10 mg/week (up to 25 mg/week). Demographic and other baseline characteristics were comparable between the three treatment groups; mean duration of RA since diagnosis six years, approximately 80% of subjects had had RA for at least two years, mean age 52 years, predominantly female (83.2%, 817 out of 982) and Caucasian (90.7%, 891 out of 82), rheumatoid factor positive 82% (802 out of 982). The co primary efficacy endpoints in this study were: ACR20 response at Week 24, and change from baseline in mTSS at Week 52. A total of 982 subjects (199 for placebo + MTX, 393 for CZP 200 mg + MTX, and 390 for CZP 400 mg + MTX) were included in the ITT population for analysis of efficacy, and 572 (58.3%) subjects completed the 52 weeks of evaluation.

Study C87028

This was a Phase III, open label follow up to Study C87027, to assess the efficacy and safety of CZP + MTX in the treatment of patients with active RA. It was conducted at 121 centres in North America, South America, Europe, Australia, and New Zealand. Two populations were eligible to enrol: 'Withdrawers' were patients who failed to achieve ACR20 at Week 12 of Study C87027 (confirmed at Week 14); and 'Completers' who were patients who completed Week 52 of Study C87027. The study Baseline was the baseline of Study C87027. The study entry visit was Week 16 of Study C87027 for Withdrawers and Week 52 of Study C87027 for Completers.

The main inclusion criteria for Study C87028 were: patients who failed to achieve an ACR20 response at Weeks 12 and 14 in Study C87027, or patients who completed the Week 52 assessment of Study C87027; and patients with a normal chest X-ray at entry. The main exclusion criteria were: a diagnosis of any other inflammatory disease; a secondary non inflammatory arthritis such as osteoarthritis; a history of infected joint prosthesis at any time with the prosthesis still in situ; concomitant biological therapy or other experimental therapy; serious or life threatening infection including tuberculosis; patients at high risk of infection; hepatitis B or C; human immunodeficiency virus (HIV) infection; lymphoproliferative disorders; a history of blood dyscrasias; active malignancy of any type; severe, progressive and/or other diseases; and demyelinating disease.

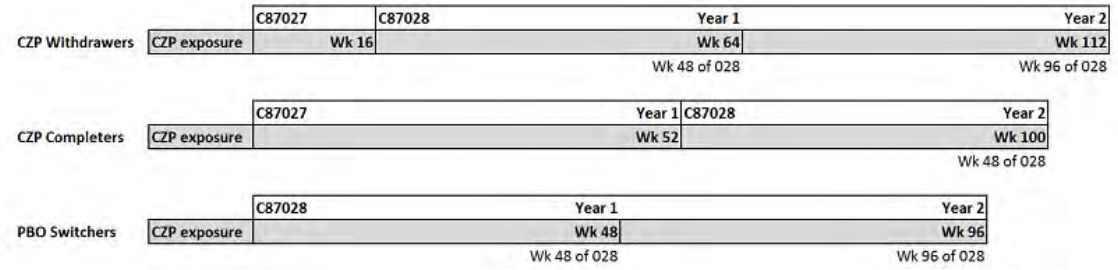
Patients initially received CZP 400 mg SC q2w. This was changed by protocol amendment to CZP 200 mg SC q2w after a minimum of six months of treatment, based on the safety and efficacy results of studies C87027 and C87050, which demonstrated no significant dose effect of CZP.

A total of 845 patients were enrolled in Study C87028 and received at least one dose of CZP. A total of 349 (41.3%) patients withdrew from the study (Withdrawers 51.0%, Completers 35.9%), most commonly due to withdrawal of consent (16.8%) or AEs (16.2%). Both withdrawal of consent and lack of efficacy were higher in Withdrawers (21.5% and 5.7%, respectively) compared with Completers (14.2% and 1.6%, respectively).

The primary endpoint was safety. There were a number of secondary efficacy endpoints including mTSS, ACR20, ACR50 and ACR70, physical function scores, patient and physician global assessment scores, CRP, ESR and anti CZP antibodies. Radiographic assessments were performed at Weeks 24, 48, 72, 96 or Early Withdrawal Visit if it occurred prior to Week 96. The degree of joint damage was assessed using the mTSS, which combines scores for joint erosion and joint space narrowing (JSN). The joint erosion score (ES) is a summary of erosion severity using a six point scale (0 to 5) in 32 joints of the hands and 12 joints in the feet for a maximal score of 280. The JSN score summarises the severity of JSN in 30 joints of the hands and 12 joints of the feet using a seven point scale (0 to 6) for a maximal score of 168. The total mTSS score range is 0 to 448.

To support the proposed new indication, an 'interim' analysis was performed at the Week 96 cut-off point to assess the effects of CZP + MTX in preventing structural damage in patients with active RA after two years. This interim analysis was performed using linear imputation (a combination of extrapolation and interpolation) for missing data. The data were also analysed using both a LOCF imputation method and observed data. Radiographic assessments (digitised with centralised reading) of the hands and feet were obtained at entry. Radiographic assessments were made by a central reader although the readers were different for studies C87027 and C87028. The Year 1 and Year 2 endpoints for radiographic data were assigned based on duration of CZP exposure. For Withdrawers, Weeks 64 and 112 of CZP exposure were used for the Year 1 and Year 2 endpoints; for Completers, Weeks 52 and 100 of CZP exposure were used; and for Switchers (patients who switched from placebo + MTX to CZP + MTX), Weeks 48 and 96 of CZP exposure were used (see Figure 1 below). Final analyses (descriptive statistics of actual values and change from Baseline values) did not contradict the interim analyses.

Figure 1. Selection of Year 1 and Year 2 radiographic endpoints for interim analysis (based on duration of CZP exposure in C87027/C87028).



In the interim analysis, the mean change in mTSS at Year 1 was lower in the patients who had received CZP irrespective of whether they were Completers (0.3), Withdrawers (0.6) or Switchers (patients who switched from PBO + MTX to CZP + MTX) (0.2) compared with the estimated course of progression in the control groups over one year (1.5 to 2.4) (see Table 4 below). It should be noted that only 41 patients were exposed to placebo for 52 weeks, however the results are consistent in the analysis using LOCF (which underestimates progression in all groups with missing data). This effect was maintained at Year 2 (mean change in mTSS between 0.2 and 0.9 in patients on CZP versus an estimated 2.7 to 4.7 in patients on placebo). The percentage of patients with no progression in mTSS (≤ 0) at Year 2 in Completers, Withdrawers, and Switchers was 61.9%, 64.5% and 66%, respectively. From the end of Year 1 to the end of Year 2, no progression was shown in 67.3%, 74.6% and 75.0% of patients, respectively. The LOCF and observed data analyses were supportive of the linear imputation analysis, and the results for the mTSS components (ES and JSN) were consistent with the overall mTSS.

Table 4: Change from Baseline in mTSS (linear extrapolation): Extension Population of Studies C87027/C87028 (interim analysis).

	PBO+MTX		All CZP+MTX		
	Withdrawers (N=136)	Completers (N=41)	PBO+MTX/ CZP+MTX Switchers (N=176)	Withdrawers (N=162)	Completers (N=508)
Year 1					
n	134	40	148	137	446
Baseline mean (SD)	53.4 (57.1)	51.5 (60.5)	54.7 (56.6)	54.4 (69.1)	50.7 (56.8)
Mean change (SD)	1.5 (7.0)	2.4 (4.1)	0.2 (2.3)	0.6 (2.4)	0.3 (2.6)
Median change (Q1/Q3)	0.0 (0.0/3.9)	0.5 (0.0/3.5)	0.0 (-0.5/0.5)	0.0 (0.0/1.0)	0.0 (-0.5/0.5)
Year 2					
n	134	41	146	137	447
Baseline mean (SD)	53.4 (57.1)	51.6 (59.7)	54.5 (56.5)	54.4 (69.1)	50.7 (56.8)
Mean change (SD)	2.7 (12.1)	4.7 (8.1)	0.2 (3.3)	0.9 (3.6)	0.6 (3.4)
Median change (Q1/Q3)	0.0 (0.0/6.9)	0.9 (0.0/7.8)	0.0 (-1.0/0.5)	0.0 (0.0/1.0)	0.0 (-0.5/0.6)

In the final analysis, the mean change in mTSS from Baseline of Study C87027 was 0.53 at Entry into Study C87028 (1.48 versus 0.27 in those patients who had received placebo versus CZP, respectively, during Study C87027) (see Table 5, below). At Week 96, the mean change from Baseline in mTSS for the 661 patients with evaluable data was 0.95. The mTSS scores were lower for subjects originally randomised to CZP compared to placebo, but were higher (more progression) for Completers (both placebo and CZP) compared with Withdrawers. The median change from baseline of Study C87027 in mTSS was 0.00 at all time-points, indicating that at least 50% of patients had no radiographic progression. Similar trends were seen in the component JSN scores and erosion scores, with a median change in JSN and erosion scores from Baseline of 0.00 at all time-points. (Note: the Week 48 and Week 96 results are not comparable across the interim and final analyses. In the interim analysis, the Year 1 and Year 2 radiographic endpoints were selected based on the duration of CZP exposure in Study C87027/28. In the final analysis the Week numbers represent actual weeks in Study C87027/28 including time spent on placebo if applicable. Week 96 in Study C87028 represents up to two years of CZP exposure for Withdrawers and up to three years of CZP exposure for Completers.).

Table 5: Change in mTSS from Baseline of Study C87027 (final analysis, safety set).

	Mean change (SD) in mTSS								
	Withdrawers			Completers			All subjects		
	Placebo N*=136	CZP N=162	Total N=298	Placebo N=41	CZP N=507	Total N=548	Placebo N=177	CZP N=669	Total N=846
Entry into C87028	0.82 (2.58)	0.12 (1.84)	0.44 (2.23)	3.65 (6.11)	0.32 3.27)	0.57 (3.66)	1.48 (3.88)	0.27 (2.98)	0.53 (3.23)
Week 24 (Total N=781)	0.97 (3.40)	0.36 (1.91)	0.64 (2.72)	4.60 (7.72)	0.60 (3.75)	0.90 (4.29)	1.86 (5.05)	0.55 (3.42)	0.81 (3.84)
Week 48 (Total N=725)	1.10 (3.76)	0.39 (2.55)	0.74 (3.22)	4.34 (8.12)	0.48 (4.11)	0.77 (4.64)	1.89 (5.33)	0.46 (3.84)	0.76 (4.23)
Week 72 (Total N=682)	0.58 (5.47)	0.01 (5.28)	0.29 (5.37)	5.18 (9.27)	0.59 (4.45)	0.91 (5.08)	1.67 (6.83)	0.47 (4.64)	0.71 (5.18)
Week 96 (Total N=661)	1.16 (4.63)	0.51 (3.71)	0.83 (4.19)	5.63 (9.16)	0.65 (4.42)	1.01 (5.05)	2.21 (6.27)	0.63 (4.28)	0.95 (4.79)
Completion / Withdrawal‡	1.13 (4.24)	0.48 (3.26)	0.78 (3.75)	5.05 (8.79)	0.59 (4.59)	0.92 (5.14)	2.07 (5.89)	0.57 (4.32)	0.87 (4.72)

Source: Table 2.10:2, pp 1662-1667 Module 5, vol 24. *N is number of patients at Baseline. Numbers decreased in each group with each visit. ‡ Completion/Withdrawal includes last non-missing value for subjects without a labelled Completion/Withdrawal visit

The results for the ACR efficacy variables (ACR20, ACR50 and ACR70) were supportive of the longer term efficacy of CZP, with response rates generally increasing up to Week 48 (ACR20 87.0%, ACR50 63.0%, ACR70 37.7%), then maintained through Week 300 (ACR20 90.9%, ACR50 81.8%, ACR70 36.4%) although the number of patients at this time point was very limited (n = 11). Initial response rates were higher in Completers compared with Withdrawers, but Withdrawer response rates increased with time, and were generally similar to the rates in Completers by Week 96. CRP and disease activity score for 28 joints (DAS28)[8] outcomes were also sustained over the longer term. Response rates in patients who were anti CZP antibody positive were lower than in those patients who were antibody negative.

Study C87050 (Rapid 2)

This was a multicentre, randomised, double blind, active comparator controlled, parallel group study of 24 weeks duration in subjects with active, adult onset RA of at least six months duration with incomplete response to MTX. Subjects were randomised to one of three treatment groups in a 2:2:1 ratio: CZP 200 mg q2w (preceded by three loading doses of 400 mg q2w), CZP 400 mg q2w or placebo injections. This study used the optimised liquid formulation of CZP. All patients received oral MTX weekly at a dose of at least 10 mg. Demographic characteristics and prior treatment were comparable between the three treatment groups; mean duration of RA since diagnosis 6.1 years, approximately 70% of subjects had had RA for at least three years, mean age 51.9 years, predominantly female (81.6%, 505 out of 619), almost exclusively Caucasian (98.1%, 607 out of 619), rheumatoid factor positive 77% (462 out of 601). The primary efficacy endpoint was ACR20 response at Week 24. Change from baseline in mTSS at Week 52 was nominated as a key secondary endpoint. In total, 619 subjects (127 for placebo + MTX, 246 for CZP 200 mg + MTX, and 246 for CZP 400 mg + MTX) were included in the ITT population for analysis of efficacy and 372 (60.1%) subjects completed the 24 weeks of evaluation.

[8] DAS28 is a measure of disease activity in rheumatoid arthritis. DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined for the assessment. The score takes into account the number of swollen joints, the number of tender joints, a measurement of either the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, and a global assessment of health.

Study C87051

This was a Phase III, open label, follow up to Study C87050. It was conducted at 68 centres in 13 countries in Europe and the USA. Two populations were eligible to enrol: 'Withdrawers' were patients who failed to achieve ACR20 at Week 12 of Study C87050 (confirmed at Week 14); and 'Completers' were patients who completed Week 24 of Study C87050. The study baseline was baseline of Study C87050. The study entry visit was Week 16 of Study C87050 for Withdrawers and Week 24 of Study C87050 for Completers. Radiographic assessments (digitised with central reading) of the hands and feet were obtained at entry, and at Weeks 24, 76 and 104 or at early withdrawal if it occurred before Week 104.

The key inclusion criteria were: patients who failed to achieve an ACR20 response at Week 12 in Study C87050, or completed the entire Study C87050; patients who complied with the Study C87050 protocol; a clear chest X-ray at study entry; and MTX therapy continued throughout the study. The key exclusion criteria were: patients with a diagnosis of any other inflammatory disease; a secondary non inflammatory arthritis such as osteoarthritis; a history of infected joint prosthesis at any time with the prosthesis still in situ; concomitant biological therapy or other experimental therapy; patients with congestive cardiac failure; serious or life threatening infection including tuberculosis; patients at high risk of infection; hepatitis B or C; HIV infection; lymphoproliferative disorders; a history of blood dyscrasias; active malignancy of any type; severe, progressive and/or other diseases; and demyelinating disease.

Patients initially received CZP 400 mg SC q2w. This was changed by protocol amendment to CZP 200 mg SC q2w after a minimum of six months of treatment, based on the safety and efficacy results of Studies C87027 and C87050, which demonstrated no significant dose effect of CZP.

A total of 567 patients were enrolled in the study and received at least one dose of CZP. A total of 221 (39.0%) patients withdrew from the study, most commonly due to withdrawal of consent in 87 patients (15.3%) and AEs in 102 patients (18.0%). A similar percentage of Withdrawers (39.9%) and Completers (38.3%) withdrew from Study C87051. A lower percentage of Withdrawers (15.9%) withdrew due to AEs compared with Completers (19.2%), and a higher percentage of Withdrawers withdrew due to withdrawal of consent and lack of efficacy (17.8% and 4.3%, respectively), compared with Completers (13.9% and 0.8%, respectively).

The primary study objective was safety. There was no primary efficacy objective but the main secondary efficacy objective was to assess the effects of CZP in preventing structural damage in patients with active RA. Other objectives included the effects of CZP in treating the signs and symptoms of RA, the effects on physical function and health outcomes, and safety and tolerability.

The mean change in mTSS from baseline of the feeder study was 0.42 at entry into Study C87051, which increased to 0.99 at Week 104. The mTSS scores were generally lower for subjects originally randomised to CZP compared with placebo, and for Completers compared with Withdrawers. The median change from Baseline of the feeder Study C87050 in mTSS was 0.00 at all time-points, indicating that at least 50% of patients had no radiographic progression. Similar trends were seen in JSN scores and erosion scores, with a median change in JSN and erosion scores from Baseline of 0.00 at all time-points.

Table 6: Change in mTSS from Baseline of feeder Study C87050 (final analysis, safety set).

	Mean change (SD) in mTSS								
	Withdrawers			Completers			All subjects		
	Placebo N*=103	CZP N=105	Total N=208	Placebo N=17	CZP N=342	Total N=359	Placebo N=120	CZP N=447	Total N=567
Entry into C87051	0.52 (5.09)	0.15 (3.24)	0.33 (4.25)	0.56 (0.95)	0.46 (5.31)	0.47 (5.19)	0.53 (4.73)	0.39 (4.90)	0.42 (4.86)
Week 24 (Total N=527)	1.15 (4.81)	0.45 (3.61)	0.80 (4.26)	0.71 (1.66)	0.58 (5.66)	0.58 (5.53)	1.08 (4.48)	0.55 (5.26)	0.66 (5.11)
Week 76 (Total N=469)	2.11 (7.87)	0.92 (3.05)	1.52 (6.01)	1.00 (2.11)	0.19 (2.86)	0.23 (2.83)	1.95 (7.30)	0.35 (2.92)	0.69 (4.29)
Week 104 (Total N=423)	2.89 (9.69)	0.83 (3.23)	1.89 (7.35)	1.04 (2.53)	0.45 (2.78)	0.48 (2.77)	2.63 (9.04)	0.54 (2.89)	0.99 (4.99)
Completion / Withdrawal‡	2.42 (8.90)	0.91 (3.14)	1.68 (6.74)	2.09 (4.16)	0.37 (2.80)	0.46 (2.89)	2.38 (8.37)	0.49 (2.88)	0.90 (4.70)

Source: Table 2.10:2, pp 1306-1310 Module 5, vol 38. *N is number of patients at Baseline. Numbers decreased in each group with each visit. ‡ Completion/Withdrawal includes last non-missing value for subjects without a labelled Completion/Withdrawal visit

The results for the ACR efficacy variables (ACR20, ACR50 and ACR70) were supportive of longer term efficacy, with response rates increasing up to Week 52 (ACR20 81.7%, ACR50 48.9%, ACR70 26.2%) and then essentially maintained through Week 244 (ACR20 88.9%, ACR50 62.5%, ACR70 31.9%), although the number of patients at this time point was limited (n = 72). Response rates were higher in Completers compared with Withdrawers, but Withdrawer response rates became similar to the rates in Completers by Week 244. CRP and DAS28 outcomes were also sustained over the longer term. Patients who developed anti CZP antibodies had lower response rates than those patients who were antibody negative.

Efficacy – Supporting study

Study C87015 was a multicentre, open-label, long-term extension, safety and efficacy Study CZP 400 mg every four weeks, with or without concomitant MTX or other DMARDs, in patients with active RA. Eligible patients had participated in Study C87011 or C87014 (Phase III studies that were previously evaluated) during which they had received double blind treatment placebo or CZP for at least 12 weeks. It was conducted at 71 centres in 7 countries. A total of 402 patients (186 patients from Study C87011 and 216 patients from Study C87014) were enrolled into the study; 192 patients had previously received placebo and 210 patients had previously received CZP 400 mg. 'Withdrawers' were patients who withdrew from the feeder study (with the exception of withdrawals due to AEs or non-compliance) and 'Completers' were patients who completed Week 24 of the feeder study. Treatment was continued until marketing approval or at the investigator's decision.

The primary objective was safety. There was no primary efficacy endpoint but efficacy criteria included ACR20/50/70 response rates, and other measures of physical function and disease activity (mTSS was not measured). Of the 402 patients who enrolled in the study, 56.7% previously treated with CZP withdrew compared with 60.4% previously treated with placebo. The most common reasons for withdrawal were AEs (24.1%) and withdrawal of consent (13.4%). However, withdrawals due to lack of efficacy or AEs or worsening of RA occurred in only 8.0% of the overall population. There was an improvement in ACR20 responder rates from 36.6% at entry to 62.5% at Week 12. At Year 3, 64% of Withdrawers and 70% of Completers achieved an ACR20 response. The improvement was maintained for up to 6.5 years of treatment in patients who remained in the study. The response rate at 6.5 years in the 62 of the 402 patients who remained in the study was 67.7% (95% confidence interval (CI): 56.1, 79.4). The response rate in the

overall 402 enrolled patient population was 57.2% (95% CI: 52.4, 62.1%) assessed at study completion or the time of withdrawal. Similar results were observed for ACR50 and ACR70 response rates although patient numbers achieving ACR70 were small. The disease activity score for 28 joints using the ESR (DAS28), CRP values improved from baseline and the improvement was maintained for up to 6.5 years in patients who continued in the study (-2.812 for Withdrawers and -3.180 for Completers).

Safety

In Study C87027/C80728, 846 subjects were exposed to CZP for a mean of 216.9 weeks (4.2 years) with a range of four weeks to 324 weeks (6.2 years). In Study C87050/C87051, 567 patients were exposed to CZP for a mean of 203.3 weeks (3.9 years) with a range of two weeks to 298 weeks (5.7 years). In Study C87015, 402 subjects were exposed to CZP for a mean of 222 weeks (4.3 years) with a range of one day to 391 weeks (7.5 years).

Treatment related AEs were reported by 528 patients (62.4%) in Study C87028 and by 267 patients (47.1%) in Study C87051. The most commonly reported treatment related AEs in both studies were infections (42.2% and 28.7%, respectively) and abnormal investigations (16.8% and 15.9%, respectively). The majority of AEs were mild or moderate in severity. Serious adverse events were reported by 352 patients (41.6%) in Study C87028 and by 200 patients (35.3%) in Study C87051. The most commonly reported SAEs in both studies were infections and infestations (16.4% and 13.8%, respectively) and musculoskeletal and connective tissue disorders (8.7% and 8.1%respectively). Common individual SAEs occurring in both studies were: rheumatoid arthritis (4.0% and 3.4% in Study C87028 and Study C87501 respectively) pneumonia (3.4% and 1.6%) and pulmonary tuberculosis (1.1% and 1.6%). Sixteen patients in Study C87028 had AEs leading to death, five of which were considered related to study medication by the investigator (pneumonia, malignant neoplasm, gastric cancer, disseminated tuberculosis (TB), and colon cancer). In Study C87051, 17 patients had AEs leading to death, six of which were considered related to study medication by the investigator (colon cancer, gastric cancer, metastatic gastro intestinal (GI) cancer, hepatic cirrhosis, streptococcal toxic shock syndrome, and CNS TB). AEs of interest with TNFα inhibitor use (injection site reactions, systemic hypersensitivity reactions, infections, malignancies, cardiac, vascular, autoimmune and neurological events) were observed in both pivotal trials at incidences consistent with other RA trials and duration of treatment.

Anti CZP antibodies were detected in 98 patients (11.6%) in Study C87028 and 86 patients (15.2%) in Study C87051. While the overall incidence of AEs was similar in the Ab + and Ab - patient groups, there was a higher incidence of some AEs in Ab + patients compared with Ab - patients (for example, AEs related to rheumatoid arthritis, pyrexia).

Clinical evaluator's recommendation

The clinical evaluator has recommended approval to extend the indication for certolizumab pegol to include '*Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.*'

Risk management plan

No RMP was required to be submitted.

Summary

Efficacy

In the pivotal extension Study C87027/C87028, CZP has demonstrated that it reduces the rate of progression of joint damage as assessed by X-ray when used in combination with MTX. The mean change from baseline in mTSS at Year 2 was lower in the patients who had received CZP irrespective of whether they were Completers (0.6), Withdrawers (0.9) or Switchers (0.2) compared with the estimated course of progression in the control groups over two years (4.7 for Completers and 2.7 for Withdrawers). This result was performed as an interim analysis on Study C87028, but was supported by the final results for change from baseline mTSS reported from both Study C87028 (0.95 at Week 96) and Study C87051 (0.99 at Week 104) which demonstrated little change/worsening over time. A change of 5.0 points in mTSS is considered the smallest detectable and minimum clinically important difference, however the submitted data, based on placebo extrapolation, showed a difference for completers of 4.1 (4.7 to 0.6) that is, slightly less than the minimum clinically important difference. The results are based on placebo extrapolation out to two years since there was no placebo arm in the second year of the study, but are considered reasonable given the projected improvement from Year 1 where the difference for completers was 2.1 (2.4 to 0.3). The early benefits for other efficacy outcomes were also largely maintained for the extended duration of the studies (up to approximately six years).

Safety and RMP

The safety of CZP in patients with RA has previously been demonstrated and no new safety concerns have been identified.

Data deficiencies

mTSS data from patients in Study C87050/C80751 were not subject to the same interim analysis as Study C87027/C87028 in support of the proposed new indication. Although in the response to the questions raised by the TGA the sponsor argued that *'analyses performed on C87050/51 would provide less robust data than obtained for C87027/028'*, because the patient numbers were smaller in Study C87050/C80751 (619 versus 982 (for Study C87027/C87028) and the placebo data were only available for a maximum of 24 weeks in Study C87050/C80751 compared with 52 weeks in Study C87027/C80728. It is still considered that the analysis would be valuable to verify the Study C87027/C80728 results. Although the overall results for change from baseline in mTSS reported from both Study C87028 (0.95 at Week 96) and Study C87051 (0.99 at Week 104) are comparable, the results in Withdrawers (0.83 and 1.89, respectively) and Completers (1.01 and 0.48) are sufficiently different to warrant the interim analysis to be conducted on the C87050/51 and/or for this difference to be explained by the sponsor.

Conditions of registration

There are no specific conditions of registration proposed.

Questions for the sponsor

The sponsor is requested to address the following issues:

1. A change in mTSS of 5.0 is considered the smallest detectable and minimum clinically important difference. Please provide the percentage of subjects who had a change in mTSS of ≥ 5.0.
2. Please provide an interim analysis of Study C87050/51 as was conducted for Study C87027/28.
3. Completers on CZP had greater changes in mTSS than Withdrawers on CZP at each of Weeks 24, 48, 72 and 96 in Study C87028, despite receiving CZP for a longer duration

of time. This was not seen in the later stages of Study C87051. Although Completers had been observed for an additional 36 weeks compared with Withdrawers in Study C87027 prior to entering the extension study (compared with an additional 8 weeks in Study C87051), the sponsor is requested to comment on these findings.

Summary of Delegate's issues

The primary issues with this submission are as follows:

1. Large percentage of subjects withdrew from the pivotal extension studies (approximately 41% in C87028, approximately 3% due to lack of efficacy; 39% in C87051, 2.1% due to lack of efficacy; 60% in C87015, 8% due to lack of efficacy). At Week 96 (C87028) and Week 104 (C87051) the withdrawal rates were approximately 25%.
2. There was no placebo controlled data beyond 52 weeks in C87027/28 and 24 weeks in C87050/51. Moreover, due to the high rate of early withdrawals in the placebo groups in the feeder studies the numbers of 'Completers' enrolled in each extension study were small (n = 41 in C87028; n = 17 in C87051).
3. The interim analysis performed in support of the proposed change in indication was only performed on Study C87027/28, not Study C87050/51.

Proposed action

The Delegate had no reason to say, that the application for certolizumab pegol should not be approved for registration.

Request for ACPM advice

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

1. The sufficiency of the data to support the claim of a reduction in the rate of progression of joint damage, given that:
    a. Placebo data were extrapolated from a small number of patients who had completed 52 weeks of placebo treatment in C87027.
    b. There was a large percentage of withdrawals from both pivotal extension studies.
    c. Data from patients in C87050/51 were not subject to the same interim analyses as C87027/28 in support of the proposed new indication.
2. Are the results considered clinically meaningful even though a change of 5.0 points in the mTSS is considered the smallest detectable and minimum clinically important difference?

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

Specific questions to the sponsor by the Delegate

Question 1

A change in mTSS of 5.0 is considered the smallest detectable and minimum clinically important difference. Please provide the percentage of subjects who had a change in mTSS of ≥ 5.0.

Sponsor's response

A summary of subjects with a change in mTSS ≥ 5.0 in the active treatment groups in Studies C87027/028 is presented in Table 7. A high majority of subjects had a change from Baseline in mTSS < 5.0 at Year 1 (≥ 93.5%) and Year 2 (≥ 87.0%), demonstrating that CZP and MTX effectively inhibited the progression of joint damage over the 2 year period.

Table 7: Percentage of subjects with a change in mTSS ≥ 5.0 (linear extrapolation): Extension population of Studies C87027/028.

Time	All CZP+MTX		
	PBO+MTX/ CZP+MTX Switchers (N=176)	Withdrawers (N=162)	Completers (N=508)
Year 1 Change from Baseline			
Subjects with change of mTSS ≥5.0	5/149 (3.4%)	9/138 (6.5%)	24/448 (5.4%)
Year 2 Change from Baseline			
Subjects with change of mTSS ≥5.0	7/147 (4.8%)	18/138 (13.0%)	35/449 (7.8%)
Year 2 versus. Year 1			
Subjects with change of mTSS ≥5.0	3/148 (2.0%)	4/138 (2.9%)	15/446 (3.4%)

CZP=certolizumab pegol; mTSS=modified total Sharp score; MTX=methotrexate; PBO=placebo

Question 2

Please provide an interim analysis of Study C87050/51 as was conducted for Study C87027/28.

Sponsor's response

As discussed in the response to the clinical evaluator's question, the analyses performed on C87027/028 presented in this submission have not been performed on C87050/051. However the sponsor reiterates the rationale for not performing equivalent analyses on C87050/051.

- A comparison of the mean and median change from Baseline in mTSS scores and the mTSS components (erosion and joint space narrowing score) obtained in CZP treated subjects and placebo treated subjects in Studies C87027 and C87050 at Week 24 was performed and showed similar results. The results of the aforementioned comparison suggest that similar results would be obtained if these analyses were performed on C87050/051.
- Moreover, an equivalent analyses performed on C87050/051 would provide less robust data, subject to error. The number of subjects participating in Studies C87050/051 was much less than in Studies C87027/028, and the '*real-time data*' available in the C87050 placebo treatment group (up to Week 24 with 2 time points at Week 0 and 24) was also much less than the C87027 placebo treatment group (up to Week 52 with 3 time points at Week 0, 24 and 52).

Question 3

Completers on CZP had greater changes in mTSS than Withdrawers on CZP at each of Weeks 24, 48, 72 and 96 in Study C87028, despite receiving CZP for a longer duration of time. This was not seen in the later stages of Study C87051. Although Completers had been observed for an additional 36 weeks compared with Withdrawers in Study C87027 prior to entering the extension study (compared with an additional 8 weeks in Study C87051), the sponsor is requested to comment on these findings.

Sponsor's response

For Completers, Week 24 of Study C87028 represents 52 + 24 = 76 weeks post Baseline, whereas for Withdrawers it represents 16 + 24 = 40 weeks post Baseline. Thus comparing changes at Week 24 for Completers and Withdrawers is not suitable. Indeed while Completers have had a longer duration of CZP, they have also had a longer time for progression to occur. As noted by the Delegate, in Study C87051 the time differential between Completers and Withdrawers is shorter: for Completers, Week 24 represents 24 + 24 = 48 weeks post Baseline, whereas for Withdrawers it represents 16 + 24 = 40 weeks post Baseline. Thus in C87051 the, difference in mTSS change from Baseline between CZP Completers and Withdrawers is also expected to be smaller.

The more applicable comparisons are placebo versus CZP Completers, and placebo versus CZP Withdrawers. A comparison of change from Baseline in mTSS and the mTSS components for the placebo controlled feeder studies (C87027 and C87050) was provided in Table 8 below. These results show that the change in both mTSS components from Baseline at Week 24 in the CZP 200mg q2w and CZP 400mg q4w treatment groups were significantly smaller than observed in placebo group in both studies ($p \leq 0.01$) and the results were similar for the 2 CZP dose groups within both studies and between studies.

Table 8. Baseline Values and Change from Baseline in mTSS, Erosion Score and Joint Space Narrowing Score Observed in Studies C87027 and C87050 at Week 24 – ITT Population.

	Study C87027			Study C87050		
	PBO Q2W +MTX (N=199)	CZP 200mg Q2W[a] + MTX (N=393)	CZP 400mg Q2W+ MTX (N=390)	PBO Q2W +MTX (N=127)	CZP 200mg Q2W[a]+ MTX (N=246)	CZP 400mg Q2W + MTX (N=246)
mTSS						
Baseline mTSS						
N	180	353	355	112	214	222
Median (SD)	39.9 (45.3)	37.9 (47.6)	38.9 (48.4)	47.2 (60.6)	40.2 (50.6)	48.2 (56.9)
Median (Q1/Q3)	21.3 (7.5/54.0)	20.0 (5.5/49.0)	19.0 (6.5/52.0)	20.5 (6.5/66.3)	20.5 (5.0/58.5)	28.5 (6.0/71.0)
Estimated Yearly Progression[b]	6.42	6.31	6.35	8.69	6.58	7.38
Change from Baseline at Week 24						
Mean (SD)	1.3 (3.8)	0.2 (3.2)	0.2 (4.2)	1.2 (4.1)	0.2 (2.7)	-0.4 (2.1)
Median (Q1/Q3)	0.0 (0.0/2.0)	0.0 (-0.5/0.5)	0.0 (-0.5/0.5)	0.0 (0.0/0.5)	0.0 (-0.5/0.5)	0.0 (-1.0/0.0)
Difference vs. PBO+MTX (97.5% CI)[c]		-0.5 (-0.8, 0.0)	-0.5 (-0.7, 0.0)		-0.3 (-0.8, 0.0)	-0.7 (-1.0, 0.0)
P-value[d]		<0.001	<0.001		≤0.01	<0.001
% inhibition vs. PBO+MTX[e]		86.7%	82.7%		81.0%	133.7%
Erosion Score						
Baseline Erosion Score						
Median (SD) [n]	14.3 (20.7) [199]	14.9 (24.3) [391]	14.4 (22.8) [389]	23.1 (32.1) [125]	19.0 (26.8) [241]	21.6 (29.7) [240]
N	180	353	355	112	214	222
Median (Q1/Q3)	6.8 (1.0/19.3)	5.5 (0.5/18.0)	5.0 (1.0/17.0)	8.3 (2.5/32.3)	8.0 (1.5/26.5)	9.8 (2.0/32.5)
Change from Baseline at Week 24						
Mean (SD)	0.7 (2.1)	0.0 (1.5)	0.1 (2.4)	0.7 (2.6)	0.1 (2.0)	-0.3 (1.8)
Median (Q1/Q3)	0.0 (0.0/1.0)	0.0 (0.0/0.0)	0.0 (0.0/0.0)	0.0 (0.0/1.0)	0.0 (-0.5/-0.5)	0.0 (-0.5/0.0)
Difference vs. PBO+MTX (97.5% CI)[c]		0.0 (-0.5/0.0)	0.0 (-0.5/0.0)		0.0 (-0.5/0.0)	0.0 (-0.7/0.0)
P-value[d]		<0.001	<0.001		≤0.01	<0.001
Joint Space Narrowing Score						
Baseline Joint Space Narrowing Score						
Median (SD) [n]	24.6 (26.8) [199]	24.0 (27.7) [391]	24.0 (26.5) [389]	23.4 (27.7) [125]	20.6 (24.4) [241]	25.1 (28.1) [240]
N	180	355	355	112	214	222
Median (Q1/Q3)	15.5 (5.5/36.5)	13.0 (4.5/35.0)	12.5 (4.0/36.0)	11.5 (2.0/35.0)	10.5 (2.5/33.5)	16.0 (3.5/40.0)
Change from Baseline at Week 24						
Mean (SD)	0.7 (2.4)	0.2 (2.5)	0.2 (2.4)	0.5 (2.3)	0.1 (1.4)	-0.1 (1.0)
Median (Q1/Q3)	0.0 (0.0/0.8)	0.0 (0.0/0.0)	0.0 (0.0/0.0)	0.0 (0.0/0.6)	0.0 (0.0/0.0)	0.0 (0.0/0.0)
Difference vs. PBO+MTX (97.5% CI)[c]		0.0 (0.0/0.0)	0.0 (0.0/0.0)		0.0 (0.0/0.0)	0.0 (0.0/0.0)
P-value[d]		≤0.01	≤0.01		≤0.01	≤0.01

Note: Linear extrapolation was used to estimate values at Week 24 when early withdrawal data were available.
[a] Following 3 loading doses of 400 mg each.
[b] Calculated by dividing the mean mTSS by the mean disease duration at Baseline.
[c] Hodges-Lehmann point estimate of difference versus PBO + MTX and corresponding non-parametric 95% CIs.
[d] P-values for the comparison of treatment groups were calculated using ANCOVA of rank change in score with factors for treatment and geographic region and a covariate of the Baseline rank score.
[e] % inhibition was calculated as (1 – [change from Baseline in mTSS in active treatment/change from Baseline in mTSS in control treatment])*100

In addition, mean changes in mTSS data tends to be skewed, where large mTSS changes in a small number of patients can have a substantial impact on the mean. Thus comparing the median changes instead of the mean changes is a more appropriate approach. With this approach, looking at all time-points in both Studies C87028 and C87051, the median change from Baseline for CZP subjects is 0.

Advisory committee considerations

This submission seeks to register an extension of indications for certolizumab pegol (rbe).

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 pegol to have an overall positive benefit–risk profile for the indication:

Rheumatoid arthritis:

Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

In making this recommendation, the ACPM took into account the current clinical approach which is expected to contribute to the low numbers of patients with a 5 point difference; it is considered likely that the current studies have demonstrated that there is a reduction in radiographic progression and therefore is clinically meaningful.

Proposed conditions of registration

The ACPM advised on the inclusion of the following proposed conditions of registration:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA.
- Negotiation of Product Information and Consumer Medicine Information to the satisfaction of the TGA.

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 Dosage and Administration section of the PI and relevant sections of the CMI with regard to Renal Impairment should contain clearer guidance for use in patients with renal impairment.
- A statement in the Clinical Trials section of the PI on the levels of withdrawals from the trials and the reasons for these.
- Table 4 of the PI 'Radiographic Changes at 6 and 12 months in study RA-1' should be amended to include both studies RA1 and RA2, as this would be helpful to the clinician.

Specific advice

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

1. *The sufficiency of the data to support the claim of a reduction in the rate of progression of joint damage, given that:*

    a. *Placebo data were extrapolated from a small number of patients who had completed 52 weeks of placebo treatment in C87027.*

The ACPM advised that while placebo data were extrapolated from a small number of patients who had completed 52 weeks of placebo treatment, placebo controlled studies beyond 52 weeks are difficult to perform in the modern rheumatoid trial setting. There are ethical considerations to not treating patients when known treatments are available. In addition, research suggests that the earlier the intervention the better the outcome, irrespective of continued treatment.

The design of the study was such that patients on placebo would only remain on the study for 6 to 12 months if it was perceived they were deriving benefit. This would have progressively skewed the placebo group to those with less aggressive disease. This artefact would tend to favour the placebo intervention. The small numbers would make the results less robust. In summary the committee agreed that use of the extrapolated data was acceptable given the limitations in the current clinical trial setting.

    b. *There was a large percentage of withdrawals from both pivotal extension studies.*

The ACPM advised that while a high rate of withdrawals was reported this would not be unexpected. There were also protocol deviations related to lack of chest X-ray (CXR) (17%).

Withdrawals might skew the results to being more favourable, but it appears that patients mainly withdrew not because of lack of efficacy but rather for other reasons. The information regarding this should be included in the PI where its totality should be available to prescribers rather than in the indication.

c. Data from patients in C87050/51 were not subject to the same interim analyses as C87027/28 in support of the proposed new indication.

The ACPM advised that to perform the same analysis on Study C87050/51 would probably not have influenced the results and is not an issue of concern. This difference was due to differences in the duration of the studies and the results at 12 months would be more meaningful than the interim 6 month data (if it had been performed).

2. Are the results considered clinically meaningful even though a change of 5.0 points in the mTSS is considered the smallest detectable and minimum clinically important difference?

The ACPM noted the (sponsor's) pre-ACPM response acknowledged there are only a few patients who demonstrated an increase of 5+ points. However, it is likely that the current studies have demonstrated that there is a reduction in radiographic progression in those treated with Cimzia. The current standard treatment strategy ('treat to target') means the majority of patients should have little radiographic progression. The ACPM noted that in this treatment climate X-ray data do not have sufficient refinement and that MRI data are being explored as a possible alternative with more discrimination.

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

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The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of 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 pre-filled syringe, indicated for:

Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

Specific conditions of registration applying to these goods

This approval does not impose any requirement for the submission of Periodic Safety Update Reports (PSURs). Note that it is a requirement that all existing requirements for the submission of PSURs as a consequence of the initial registration or subsequent changes must be completed.

Attachment 1. Product Information

The Product Information approved for Cimzia at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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