Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Certolizumab pegol

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

June 2017

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

Contents

Common abbreviations

Abbreviation	Meaning
ACPA	Anticyclic citrullinated peptide antibody
ACPM	Advisory Committee on Prescription Medicines
ACR	American College of Rheumatology
AE	Adverse event
ALT	Alanine transaminase
ANA	Anti-nuclear antibody
ARTG	Australian Register of Therapeutic Goods
AST	Aspartate transaminase
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CRP	C-reactive protein
CSR	Clinical Study Report
CZP	Certolizumab (pegol)
DAS28 (ESR)	Disease Activity Score 28 erythrocyte sedimentation rate
DMARD	Disease modifying anti-rheumatic drug
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
Fab’	Fragment antigen binding
FAS	Full analysis set (Study C-OPERA)
FAS1	Full analysis set (Study C-EARLY)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IR	Incidence rate
IXRS	Interactive Voice/Web Response System

Abbreviation	Meaning
LDA	Low disease activity
MHC	Major histocompatibility complex
mTSS	Modified total Sharp score
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PBO	Placebo
PEG	Polyethylene glycol
PI	Product Information
PI	Product Information
PSUR	Periodic Safety Update Report
Q1	First quartile
Q3	Third quartile
RA	Rheumatoid arthritis
RAD1	Radiographic set Period 1 (Study C-EARLY)
RF	Rheumatoid factor
RMP	Risk Management Plan
SAE	Serious adverse event
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SJC	Swollen joint count
SOC	System Organ Class
SPC	Summary of Product Characteristics
SS	Safety set (Study C-OPERA)
SS1	Safety set Period 1 (Study C-EARLY)
TB	Tuberculosis
TEAE	Treatment emergent adverse event

Abbreviation	Meaning
TJC	Tender joint count
TNFα	Tumour necrosis factor alpha
ULN	Upper limit of normal
US	United States

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	7 November 2016
Date of entry onto ARTG	9 February 2017
Active ingredient:	Certolizumab pegol
Product name:	Cimzia
Sponsor's name and address:	UCB Australia Pty Ltd PO Box 158 Malvern VIC 3144
Dose form(s):	Solution for injection
Strength(s):	200 mg/mL
Container(s):	Pre-filled syringe
Pack size(s):	2 x 1 mL pre-filled syringes
Approved therapeutic use:	*Cimzia in combination with MTX is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs.'*
Route of administration:	Subcutaneous (SC)
Dosage:	See product background, below
ARTG number:	154726

Product background

This AusPAR describes the application by the sponsor to extend the rheumatoid arthritis indication of Cimzia certolizumab pegol (rbe) 200 mg/mL solution for injection pre-filled syringe to include the following:

> *'Cimzia in combination with methotrexate is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs.'*

The purpose of the submission is to extend the certolizumab pegol rheumatoid arthritis (RA) indication to include first line use of certolizumab (CZP) with methotrexate in adult patients with severe active and progressive RA.

Cimzia first entered the Australian Register of Therapeutic Goods (ARTG) on 20 January 2010. At the time the TGA considered this submission, Cimzia had been approved for the following indications:

'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 (see Dosage and Administration).*

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

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).'[1]

RA is a progressive autoimmune disease that is characterised by synovial inflammation of multiple joints, manifesting as pain and swelling, and results ultimately in joint destruction, and systemic manifestations.

In the context of RA, CZP belongs to a category of drugs called disease-modifying antirheumatic drugs (DMARD) characterised by preventing or slowing disease progression. DMARDs currently approved for use in Australia can be further categorised as synthetic such as methotrexate (MTX); or biologic, including adalimumab, infliximab, etanercept and golimumab.

Certolizumab pegol itself is a biological product, a recombinant, humanised antibody fragment antigen binding (Fab') fragment that is expressed in an *Escherichia coli* expression system and then subsequently purified and conjugated to polyethylene glycol (PEG).

CZP selectively inhibits and neutralises tumour necrosis factor alpha (TNFα). Biological activities ascribed to TNFα include the upregulation of cellular adhesion molecules and chemokines, upregulation of major histocompatibility complex (MHC) class I and class II molecules, and direct leukocyte activation. TNFα stimulates the production of downstream inflammatory mediators, including interleukin-1, prostaglandins, platelet activating factor, and nitric oxide. Elevated levels of TNFα have been implicated in the pathology of rheumatoid arthritis. Increased TNFα levels are found in the synovial fluid of RA patients and play an important role in the joint destruction that is a hallmark of this disease.

Regulatory status

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

[1] UCB Pharma (a division of UCB Australia Pty Ltd). Australian product information document for Cimzia (certolizumab pegol). Date of most recent amendment: 14 October 2015. TGA, Canberra.

At the time the TGA considered this application, a similar application for Cimzia had been approved in the European Union on the 16 December 2015 for the:

> *'treatment of severe, active and progressive RA in adults not previously treated with MTX or other DMARDs.'*

No submission is planned in the US (United States) or Canada as the RA indication (approved in both countries in 2009) as Cimzia is already indicated for the:

> *'treatment of adults with moderately to severely active rheumatoid arthritis.'*

The sponsor states the US/Canadian indication already encompasses the RA indication extension in MTX or other DMARD-naïve adults.

Product Information

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

II. 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

In the Clinical Overview the sponsor highlights that RA is a progressive autoimmune disease that is characterised by synovial inflammation of multiple joints, manifesting as pain and swelling, and results ultimately in joint destruction, and systemic manifestations. The sponsor indicates that certolizumab neutralises human TNFα, a pro-inflammatory cytokine that mediates joint inflammation and destruction, as well as inhibiting the production of inflammatory cytokines by monocytes.

To support the use of certolizumab in the proposed indication, the sponsor highlights that in the early stages of RA there is a window of opportunity during which some patients may need to commence concomitant MTX and a biologic DMARD to maximise control of the signs and symptoms of RA, to limit joint damage and to improve physical function.

The sponsor indicates that there was a need for additional anti-TNFα drug options for patients who have severe, active and progressive RA and are DMARD-naïve. The sponsor highlights that, in the EU, infliximab is approved for patients with severe, active and progressive RA not previously treated with MTX or other DMARDs and that adalimumab, etanercept and golimumab have been approved for patients who have severe, active and

progressive RA and have not been previously treated with MTX. The achievement of sustained remission was chosen by the sponsor as the primary outcome of the trial as it is known to result in better structural and functional outcomes than the targets that allow more residual activity.

The clinical evaluator accepted the sponsor's clinical rationale.

It appears that CZP has a different mechanism of action compared with the other tumour necrosis factor inhibitors adalimumab, infliximab, etanercept and golimumab. CZP is a humanised Fab fragment combined with polyethylene glycol but etanercept is a TNF receptor p75 Fc fusion protein and adalimumab, infliximab and golimumab are anti-TNFα antibodies.[2,3,4,5,6]

The proposed RA indication for CZP is not identical to the approved RA indications for these other biological DMARDs. In Australia, adalimumab is indicated for reducing the signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active RA, including patients with recently diagnosed moderate to severely active RA who have not received MTX.[4] Infliximab, in combination with MTX, 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 MTX treatment and in patients with active disease who have not previously received MTX.[5] These respective indications remain silent on the use of other DMARDs and previous use of DMARDs, other than MTX, does not appear to be a prerequisite to use. It is assumed that MTX is generally the first line choice of DMARD in the treatment of RA unless it is contraindicated or there is some other reason the patient could not be treated with it. Etanercept is indicated for active adult RA in patients who have had an inadequate response to one or more DMARDs and can be used in combination with MTX.[3] It is also indicated in adults with severe, active RA to slow progression of disease-associated structural damage in patients at high risk of erosive disease.[3] With regard to this latter indication, it is not clear to the clinical evaluator if the patient is required to have had an inadequate response to one or more DMARDs before CZP, with or without MTX, is initiated. Golimumab, in combination with MTX, is indicated for the treatment of moderate to severely active RA in adult patients when the response to DMARD therapy, including MTX, has been inadequate.[6]

Guidance

In addition to a number of general guidelines there are two specific TGA adopted European Union (EU) guidelines which may be relevant to this submission:

1. Points to Consider on Clinical Investigation of Medicinal Products Other than NSAIDs for Treatment of Rheumatoid Arthritis (CPMP/EWP/556/95 rev 1/Final)
2. Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)

[2] UCB Pharma (a division of UCB Australia Pty Ltd). Australian product information document for Cimzia (certolizumab pegol). Date of most recent amendment: 14 October 2015. TGA, Canberra.
[3] Pfizer Australia Pty Limited. Australian product information document for Enbrel (etanercept (rch)). Date of most recent amendment: 7 December 2015.
[4] AbbVie Pty Ltd. Australian product information document for Humira (adalimumab). Date of most recent amendment: 31 August 2015, Version 33. TGA, Canberra.
[5] Janssen Cilag Pty Ltd. Australian product information document for Remicade powder for injection (infliximab). Date of most recent amendment: 10 November 2015. TGA, Canberra.
[6] Janssen Cilag Pty Ltd. Australian product information document for Simponi (golimumab) solution for injection in a pre-filled syringe, solution for injection in a pre-filled pen SmartJect. Date of most recent amendment: 6 July 2015. TGA, Canberra.

Contents of the clinical dossier

The submission contained the following clinical information:

- Clinical Study Report (CSR) for Period 1 of Study RA0055 (Study C-EARLY) dated 3 December 2014
- Interim CSR for Study RA0096 (Study C-OPERA) dated 23 April 2014
- Integrated Summary of Safety:
  - Integrated RA safety pooling (data cut off: 30 November 2011) listings
  - Integrated RA safety pooling (data cut off: 30 November 2011) tables
- Reference to Periodic Safety Update Report (PSUR) for the period covering 7 March 2013 to 6 March 2014

Due to the discovery of errors in the Period 1 CSR for Study C-EARLY, on 10 September 2015, the sponsor submitted additional/replacement data:

- Amendment 1 CSR for Study RA0055 (Study C-EARLY) Period 1 dated 14 August 2015
- Interim CSR for Study RA0096 (Study C-OPERA)
- Integrated Summary of Safety:
  - Integrated RA safety pooling (data cut off: 30 November 2011) listings
  - Integrated RA safety pooling (data cut off: 30 November 2011) tables
- Reference to the PSUR for the period covering 7 March 2013 to 6 March 2014

The evaluator commented that data submitted on the 10 September 2015 were evaluated rather than the data submitted on 3 June 2015.

> In the remainder of the report, Study RA0055 will be referred to as Study C-EARLY and Study RA0096 will be referred to as Study C-OPERA. It is noted that for Study C-EARLY, the duration of treatment in the study was through Week 104 and the study had two periods, Period 1 and Period 2. Only Period 1 (through Week 52) is described in the CSR. The sponsor indicates that Period 1 of Study C-EARLY is the primary basis for the submission. It is indicated in the PPF that the results from Study C-OPERA and the integrated safety analyses are supportive data.

Paediatric data

The submission does not include paediatric data. The application form states that there are no paediatric data/formulations for this product. There is no Paediatric Development Plan for this product included in this submission.

The proposed indication is in adults. No subjects in Study C-EARLY and Study C-OPERA were aged less than 18 years.

Good clinical practice

The sponsor indicates that Period 1 of Study C-EARLY was conducted in accordance with the applicable regulatory and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) requirements that were current at the time that the study was being undertaken and in accordance with the ethical principles originating in the Declaration of Helsinki and local laws. Written informed consent was obtained from each subject.

The sponsor indicates that the 52-week double blind Treatment Period of Study C-OPERA was conducted in compliance with GCP, the ethical principles described in the Declaration of Helsinki, Pharmaceutical Affairs Law and the study protocol. The sponsor indicates that, for Study C-OPERA, it conducted the study in compliance with Standards for the Conduct of Clinical Trials on Drugs GCP (MHW ordinance No.28, 27 March 1997). Institutional Review Boards at each study site reviewed and approved the proposed conduct of the study. Written informed consent was obtained from study subjects.

The sponsor's declarations regarding the conduct of Period 1 of Study C-EARLY and the Treatment Period of Study C-OPERA are accepted.

Pharmacokinetics

Studies providing pharmacokinetic data

There are no pharmacokinetic studies included in the submission. Study C-EARLY and Study C-OPERA both provided data in relation to plasma certolizumab concentrations and immunogenicity data.

The pharmacokinetics of certolizumab are described in the currently approved PI.[2] The sponsor proposes no changes to the Pharmacology section of the PI.

Evaluator's conclusions on pharmacokinetics

Subjects who were positive for anti-CZP antibodies in both Study C-EARLY and Study C-OPERA had lower geometric mean plasma CZP concentrations than subjects who were negative for anti-CZP antibodies after a certain measurement time point in the respective studies.

Pharmacodynamics

There are no pharmacodynamic studies included in the submission.

Dosage selection for the pivotal studies

The sponsor indicates that, for Study C-EARLY, the dosage of CZP selected was chosen as it is the currently approved standard dose of CZP, and the dosage of MTX selected was chosen as the titration schedule, and range of maintenance doses, are consistent with those cited in a systematic review, and with the MTX dose regimens considered by rheumatologists to be likely to lead to rapid and effective control of inflammation while minimising toxicity.

The sponsor's rationale for the doses of CZP and MTX selected for Study C-EARLY are accepted. As no alternative treatment regimens were evaluated, it is possible that DMARD-naïve subjects in Study C-EARLY receiving CZP + MTX may have had a similar efficacy outcomes, compared with subjects in the PBO + MTX group, on a lower dose of CZP.

Period 2 of Study C-EARLY evaluates the efficacy and safety of three different study treatment regimens although only in subjects who had achieved sustained low disease activity (LDA) during initial treatment with CZP. As RA is a chronic disease and long-term treatment is anticipated, it would be useful to review the results of both Periods of the study to assess the benefits and risks of ongoing treatment with different dosages of CZP.

Of note, concomitant CZP and MTX treatment was reported to have had no effect on the pharmacokinetics of CZP and, in RA patients, co-administration of CZP with MTX was

reported to have had no significant effect on the pharmacokinetics of MTX and the pharmacokinetics of CZP were reported to have been similar to the pharmacokinetics of CZP observed in healthy subjects.[2]

Efficacy

Studies providing efficacy data

In this submission, 2 studies were submitted and assessed for evaluation of efficacy; these studies were:

- Study C-EARLY (Study RA0055, Period 1); and
- Study C-OPERA (Study RA0096).

Study C-EARLY was considered as a pivotal efficacy study with Study C-OPERA being supportive in the evaluation of efficacy. Further details the study design and outcomes is available in Attachment 2.

Evaluator's conclusions on efficacy

One pivotal study, Study C-EARLY, was submitted to support the proposed indication 'Cimzia in combination with methotrexate is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs.' In Study C-EARLY, 96.5% of all subjects had severe RA based on their DAS28 (ESR) value at Baseline.[7] All subjects were required to have had active disease as defined in the inclusion criteria. A high proportion of study subjects had erosions at Baseline (77.8%) indicating progressive disease. The study population overall were also considered, by the sponsor, to be at risk for rapid progression of RA at an early stage of disease based on the high mean values for DAS28 (ESR), swollen joint count (SJC), tender joint count (TJC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF) and anticyclic citrullinated peptide antibody (ACPA), respectively. It is unclear whether all subjects had RA that was severe and active and progressive. It is not clear to the clinical evaluator whether Australian medical practitioners assess patients as having severe, active and progressive RA in the same way as the sponsor has done in this submission and if they use the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria to define adult onset RA.

Based on this pivotal study, there was a statistically significant improvement in the CZP + MTX group, compared with the placebo (PBO) + MTX group, in relation to the efficacy outcomes in the hierarchical test procedure. The efficacy outcomes related to disease activity, clinical response, inhibition of structural damage and physical function. The results of other efficacy analyses were generally supportive. The sponsor indicates that a ≥ 10% difference between the treatment groups in sustained DAS28 (ESR) remission at Week 52 is clinically meaningful based on the expert opinion of the members of the study's Steering Committee. It is unclear to the clinical evaluator if this difference would be considered clinically meaningful by Australian medical practitioners. It is noted

[7] DAS28 (ESR) = Disease Activity Score 28-erythrocyte sedimentation rate. The DAS28 is a validated and commonly used scoring system used in both clinical practice and clinical trials calculated from four components: tender joint count, swollen joint count (both performed by the treating doctor, using 28 joints), visual analogue scale (VAS) score of the patient's global health and the laboratory parameter erythrocyte sedimentation rate (ESR). Prevoo M et al. Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum. 1995 Jan;38(1):44-8.

that the power of Study C-EARLY was based on a 20% difference between the treatment groups in the expected percentages of subjects in sustained DAS28 (ESR) remission at Week 52.

The proposed indication does not specify a timeframe since diagnosis in which concomitant CZP + MTX can be initiated. In Study C-EARLY subjects were to have had a time since diagnosis of adult onset RA of less than one year as defined by the 2010 ACR/EULAR classification criteria from the Screening Visit. There are no efficacy data to support use of CZP in the proposed indication in patients with a time since diagnosis of adult-onset RA of more than one year. It is unknown if Australian medical practitioners would only initiate CZP + MTX concomitantly in patients with a diagnosis of RA within the previous year. In addition, the results of Study C-EARLY may not be generalisable to the target population to whom the proposed indication pertains if patients initiated on CZP + MTX concomitantly are only able to tolerate a dose of MTX that is less than 15 mg/week. If CZP and MTX are initiated concomitantly, it is also possible that Australian medical practitioners may not titrate MTX in exactly the same way as was done in this pivotal study.

It is noted that the TGA-adopted guideline 'Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study' recommended that there should be no indications of a potential bias in cases where the confirmatory evidence is to be provided by only one pivotal study.[8] There were potential sources of bias in Study C-EARLY. A proportion of subjects in each treatment group discontinued the study during Period 1. Bias may have been introduced through the imputation of data and it appears that, for certain efficacy outcomes, not all subjects contributed to each efficacy outcome at every measurement time point despite the use of imputation to handle missing data. Other potential sources of bias are the use of unblinded study centre personnel to determine the ESR, the use of unblinded laboratory staff to analyse the CRP concentration and record the ESR values received from study centres, and the use of study protocols with local amendments in some countries. The ESR was a component of the primary efficacy variable, DAS28 (ESR). It is recommended that the sponsor provide justification as to why a single pivotal study is adequate to support the proposed indication given the potential sources of bias identified in relation to Study C-EARLY.

Despite these potential source of bias, the results of the primary efficacy outcome and the secondary efficacy outcomes included in the hierarchical test procedure showed a consistent trend of a greater improvement in the CZP + MTX group compared with the PBO + MTX group regardless of the analysis set or imputation method used and across different efficacy outcomes related to disease activity, clinical response, inhibition of joint damage and physical function. The results of the other efficacy analyses in Study C-EARLY were also generally supportive as were the results of the efficacy analyses for the Treatment Period of Study C-OPERA, a study in Japanese subjects with moderate or severe RA and poor prognostic factors who were MTX-naïve or leflunomide-naïve.

As RA is a chronic disease, it is anticipated that long-term pharmacological management will be required. Period 1 of Study C-EARLY only provides efficacy data through Week 52. The efficacy of ongoing treatment in the proposed dosage regimen in the proposed target population is not known.

The currently approved dosage and administration recommendations in relation to the maintenance dose for RA include an alternative dosage regimen of 400 mg every four weeks.[2] No efficacy data are provided in this submission to support this dosage regimen in the proposed indication. From a biological perspective, it is anticipated that a maintenance

[8] Committee for Proprietary Medicinal Products. Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study. CPMP/EWP/2330/99. Adopted by the TGA with annotation. Effective: 27 March 2002. TGA: Canberra.

dosage of CZP of 400 mg every four weeks plus MTX will be efficacious in the target group to which the proposed indication pertains given the efficacy results in Period 1 of Study C-EARLY. Nonetheless, to recommend this alternate RA maintenance dosage regimen for the proposed indication, supporting efficacy data are required. The sponsor is requested to clarify why such data are not provided to support this dosage regimen in the proposed indication.

Safety

Studies providing safety data

Study C-EARLY and Study C-OPERA provided evaluable safety data.

Patient exposure

Study C-EARLY, Period 1

Based on the Safety set Period 1 (SS1), in Period 1 of Study C-EARLY, the median number of CZP injections administered was 29.0 (range 2, 29). The median dose of CZP received was 5800.0 mg (range 400, 5800). Median exposure to CZP was 364.0 days (range 14, 378) and the median exposure to PBO was comparable (median 364.0 days (range 14, 375)). After Week 8, the median weekly dose of MTX was 25.0 mg (range 14, 25; mean (SD) 22.3 (3.6)) in the PBO + MTX group (n = 200) and the median weekly dose of MTX was 22.7 mg (range 7, 25; mean (SD) 21.1 (4.2)) in the CZP + MTX group (n = 615).

The total patient-years at risk in Period 1 was longer for subjects in the CZP + MTX group (605.3 patient years) compared with the PBO + MTX group (192.6 patient years) as the number of subjects in the CZP + MTX group was approximately three times the number in the PBO + MTX group.

In the SS1, 84.6% (n = 741) of subjects overall were aged > 18 to < 65 years, 114 subjects (13.0%) were aged ≥ 65 to < 75 years, 1.9% (n = 17) were aged ≥ 75 to < 85 years, and one subject, who was in the CZP + MTX group was aged ≥ 85 years.

500 subjects in the CZP + MTX group completed Week 52 compared with 143 subjects in the PBO + MTX group (see Figure 6 in the Efficacy section for this study, Attachment 2).

It would appear that all 500 subjects in the CZP + MTX group who completed Week 52 would have been exposed to CZP + MTX for 365 days as the last administration of CZP was at Week 50 and MTX was administered until Week 51. The sponsor is requested to confirm the number of subjects who were exposed to CZP + MTX for at least 365 days.

The total patient-years at risk was longer in the CZP + MTX group compared with the PBO + MTX group. It is anticipated that the longer exposure in the CZP + MTX group would have assisted, to a certain extent, the identification of any new safety issues with concomitant initiation of CZP + MTX in DMARD-naïve subjects.

As only 14 subjects in the CZP + MTX group were aged ≥ 75 years, it is unlikely that a new safety signal in the proposed indication in this patient subgroup would have been identifiable.

Study C-OPERA

Based on the Safety set (SS), the number of injections of study drug received by subjects in each treatment group during the Treatment Period was similar (PBO + MTX (n = 157): mean (SD) 18.5 (7.0), median 18.0 (range 1, 26), CZP + MTX (n = 159): mean (SD) 21.5 (6.3), median 25.0 (range 4, 26)). Patient-years of exposure to the study medication were also similar (PBO + MTX: 116.01 patient-years; CZP + MTX: 136.16

patient years). Drug exposure in days was shorter in the PBO + MTX group similar (PBO + MTX: mean (SD) 265.1 (99.2), median 258.0 (range 15, 370), CZP + MTX: mean (SD) 308.6 (89.7), median 365.0 (range 57, 370)).

The mean and median doses of MTX in mg/week during the Treatment Period in the SS were comparable in the two treatment groups (PBO + MTX: mean (SD) 11.61 (2.68), median 11.92 (range 4.2, 15.2; first quartile (Q1) 9.68, third quartile (Q3) 14.00); CZP + MTX: mean (SD) 11.62 (2.95), median 11.84 (range 2.0 15.3; Q1 9.48, Q3 14.20)).

In the CZP + MTX group, 111 subjects completed Week 52 and 73 subjects in the PBO + MTX group completed Week 52 (see Figure 8, in the Efficacy section for this study, in Attachment 2).

With regard to exposure to CZP + MTX, it appears that the 111 subjects in the CZP + MTX group who completed Week 52 would have been exposed to CZP + MTX for 365 days given the last administration of CZP was at Week 50 and MTX was administered until Week 51. The sponsor is requested to confirm the number of subjects who were exposed to CZP + MTX for at least 365 days.

Safety issues with the potential for major regulatory impact

Liver toxicity

No subjects met the criteria for Hy's Law during Period 1 of Study C-EARLY. In the CZP + MTX group, hepatotoxicity related to the study medication was reported in one subject, aged 36 years, and another subject, aged 21 years, was reported with hepatocellular injury related to the study medication. The onset of the drug-related adverse events (AE) was reported one day after the most recent CZP injection in each of these subjects and both were receiving 14 mg MTX weekly. Both AEs were reported to have been non-serious and of moderate severity. Neither AE led to study discontinuation. Of subjects in the PBO + MTX group who had a hepatic event, 65.4% had received a maximum dosage of MTX > 20 mg/week at any time up to the time of the onset of the event. In the CZP + MTX group, of subjects who had a hepatic event, 46.5% had received MTX at a maximum dosage of 10 mg to 20 mg/week, and 44.2% at a dosage of > 20 mg/week, up to the onset of the hepatic event.

During the Treatment Period of Study C-OPERA, there were no cases of Hy's Law and no cases in the CZP + MTX group of serious drug-related treatment emergent adverse events (TEAE) in the Hepatobiliary disorders System Organ Class (SOC).

The proportions of subjects in both the PBO + MTX and CZP + MTX groups in Study C-EARLY reported with any hepatic event (PBO + MTX: 12.0% (n = 26); CZP + MTX 13.1% (n = 86)) are notably higher than the corresponding proportions of Cimzia treated and placebo treated subjects reported with hepatic adverse events in placebo-controlled RA studies in the PI (Cimzia treated 1.2%, placebo treated 0.7%).[2] It is possible that initiating treatment with CZP and MTX concomitantly may increase the risk of serious liver toxicity although it is noted that the proportions of subjects in the PBO + MTX group and the CZP + MTX group reported with any hepatic event in Period 1 of Study C-EARLY were similar suggesting that the initiation of CZP with MTX in DMARD-naïve subjects may only increase the risk of any hepatic event to a small extent compared with initiating patients on MTX alone.

Haematological toxicity

During Period 1 of Study C-EARLY, based on the SS1, there were two cases of pancytopenia in the CZP + MTX group considered to be related to the study medication.

During the Treatment Period of Study C-OPERA, there were single reports of drug-related anaemia, granulocytopenia, idiopathic thrombocytopenia and leucopenia in the CZP + MTX group but these were not reported as serious.

It is not clear if these haematological adverse events are considered related to CZP or MTX or both. The 'Adverse effects' section of the PI for Cimzia includes pancytopenia, anaemia, thrombocytopenia and leukopenia as adverse drug reactions reported in RA clinical trials and post-marketing.**Error! Bookmark not defined.** In the 'Adverse effects' section of the Australian I, in relation to the currently approved RA indication, it is indicated that, for placebo-controlled and open-label adverse drug reactions, all AEs that were recorded as at least possibly related to the study medication were considered. Based on the EU SPC for Cimzia, it would appear that the adverse drug reactions reported in clinical trials and post-marketing have been assessed by the sponsor as at least possibly related to CZP.[9] The sponsor is requested to confirm this.

Serious skin reactions

During Period 1 of Study C-EARLY, based on the SS1, there were no cases of serious skin reactions Stevens Johnson Syndrome, toxic epidermal necrosis or erythema multiforme in either treatment group based on the SS1. One subject in the PBO + MTX group was reported with serious treatment-emergent urticaria.

During the Treatment Period of Study C-OPERA, no subject was reported with a serious skin reaction.

Cardiovascular safety

During Period 1 of Study C-EARLY, based on the SS1, two subjects in the CZP + MTX group had major adverse cardiac events (acute myocardial infarction (n = 1), myocardial infarction (n = 1)) that were serious adverse events (SAE) and of severity severe. Neither event was considered to be drug-related.

During the Treatment Period of Study C-OPERA, there were no serious TEAEs reported that fell under the Cardiovascular disorders SOC or Vascular disorders SOC.

Unwanted immunological events

In Period 1 of Study C-EARLY, based on the SS1, cumulatively, through Week 52/Withdrawal Visit, 2.8% of subjects in the CZP + MTX group and 2.9% of subjects in the PBO + MTX group shifted from a normal anti-nuclear antibody (ANA) result at Baseline to antibodies present, and 2.0% of subjects (n = 13) in the CZP + MTX group and 0.5% of subjects (n = 1) in the PBO + MTX group shifted from a negative anti-dsDNA antibody result at Baseline to a positive result.

In the CZP + MTX group, one subject was reported with the SAE of lupus-like syndrome which the investigator considered to be related to the study medication. This SAE was of severe severity and led to discontinuation from the study. A single subject in the PBO + MTX group was reported with systemic lupus erythematosus but this was not considered, by the Investigator, to be related to the study medication.

In Study C-EARLY, by visit, the proportion of subjects who were positive for anti-CZP antibody at that visit was 0.3% (n = 2) at Week 0, Week 2 and Week 4 and increased at Week 8 (0.9% (n = 6)), Week 12 (2.6% (n = 17)) and Week 20 (3.5% (n = 23)). At the subsequent Visits the proportions of subjects who were positive for anti-CZP antibody were similar.

During the Treatment Period of Study C-OPERA, there was one report of drug-related Behcet's syndrome in the CZP + MTX group. There were no reports of systemic lupus

[9] UCB Pharma SA. European Union Summary of Product Characteristics for Cimzia 200 mg solution for injection. 21 May 2015. European Medicines Agency, London.

erythematosus or lupus-like syndrome. At Week 52, all subjects were negative for anti-ds DNA and similar proportions of subjects in each treatment group had a shift from normal at Baseline to ANA positive at Week 52/Withdrawal Visit (PBO + MTX: 1.9% (n = 3), CZP + MTX: 2.5% (n = 4)).

During the Treatment Period of Study C-OPERA, 8.8% of subjects (n = 14) who received CZP + MTX had anti-CZP antibodies at one or more measurement time points. At each measurement time point, between one and three subjects had anti-CZP antibodies with no obvious increasing trend over the Treatment Period. For 8 of the 14 subjects, anti-CZP antibodies were detected at only one measurement time point.

Serious infections

During Period 1 of Study C-EARLY, the IR of any TEAEs in the Infections and infestations SOC was higher in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX: 52.70 per 100 patient years, CZP + MTX: 71.77 per 100 patient-years) but comparable in relation to serious TEAEs in this SOC (PBO + MTX: 3.69 per 100 patient-years, CZP + MTX: 3.34 per 100 patient years). The IR of any TEAEs in this SOC leading to death or hospitalisation was similar in each treatment group (PBO + MTX: 2.63 per 100 patient years, CZP + MTX: 3.17 per 100 patient years) and the proportions of subjects in each treatment group with serious and related TEAEs in the Infections and infestations SOC was the same (1.8%). A subject in the CZP + MTX group had active tuberculosis (TB) and died. Further discussion of this is available in Section: 8.3.4.1. (Deaths and serious adverse events) of Attachment 2.

During the Treatment Period of Study C-OPERA, the IR of serious infections was 3.70 per 100 patient years in the CZP + MTX group and 6.08 per 100 patient-years in the PBO + MTX group. The majority of serious drug-related TEAEs in the Infections and infestations SOC were single reports. Three subjects in the CZP + MTX group were reported with serious drug-related *pneumocystis jiroveci* pneumonia compared with two subjects in the PBO + MTX group and one the subjects in the CZP + MTX group developed fungal meningitis after CZP + MTX was discontinued at the time of the pneumonia. There was one report of viral hepatitis in the CZP + MTX group manifested by a positive hepatitis B DNA assay and nausea. There were no cases of tuberculosis.

Malignancy

During Period 1 of Study C-EARLY, the IRs of treatment-emergent malignant tumours (including unspecified tumours) were similar in the two treatment groups based on the SS1 (PBO + MTX: 1.04 per 100 patient years, CZP + MTX: 1.33 per 100 patient years). Except for basal cell carcinoma, which was reported in two subjects in the CZP + MTX group, all treatment-emergent malignant tumours were reported in single subjects in either treatment group.

During the Treatment Period of Study C-OPERA, benign lung neoplasm and cervix carcinoma were reported in subjects in the CZP + MTX group as serious drug-related TEAEs.

Neurological events

There were no TEAEs suggestive of demyelinating disorders during Period 1 of Study C-EARLY and no other notable neurological events. One subject in the CZP + MTX group had a fatal cerebrovascular accident which was not considered to be related to the study medication.

During the Treatment Period of Study C-OPERA, there were no cases of demyelinating disorders reported.

Injection reactions (including hypersensitivity)

During Period 1 of Study C-EARLY, based on the SS1, a higher proportion of subjects in the CZP + MTX group had local injection site reaction TEAEs and systemic injection site reaction TEAEs compared with the PBO + MTX group (local: PBO + MTX: 2.3% (n = 5), CZP + MTX: 6.4% (n = 42); systemic: PBO + MTX: 0.5% (n = 1), CZP + MTX: 1.2% (n = 8)). The local injection site reactions were reported as non-serious. Delayed systemic injection reaction TEAEs were reported in 7 subjects (1.1%) in the CZP + MTX group and one subject (0.5%) in the PBO + MTX group. In the subjects who had these TEAEs, AE preferred terms were reported in single subjects. The TEAEs were assessed as non-serious and were all mild or moderate in severity. One subject in the CZP + MTX group had an acute systemic hypersensitivity reaction (pre-syncope) which was mild in severity and assessed as non-serious.

During the Treatment Period of Study C-OPERA, five subjects in the CZP + MTX group (3.1%) had injection site reactions (administration site reaction (n = 2), injection site reaction (n = 2), injection site induration (n = 1)), compared with two subjects (1.3%) in the PBO + MTX group (administration site reaction (n = 1), injection site haemorrhage (n = 1)). Systemic hypersensitivity reactions were reported in a higher proportion of subjects in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX: 9.6% (n = 15), CZP + MTX: 12.6% (n = 20)). Rash was reported at a notably higher incidence rate (IR) in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX: 1.74 per 100 patient-years, 95% CI (0.21, 6.28), CZP + MTX: 8.49 per 100 patient-years, 95% CI (4.24, 15.19)).

Serious bleeding events

There were small numbers of treatment-emergent serious bleeding events during Period 1 of Study C-EARLY based on the SS1 and the IR in the CZP + MTX was similar to that in the PBO + MTX group (PBO + MTX: 0.5% (n = 1), IR 0.52 per 100 patient-years, 95% CI (0.01, 2.90); CZP + MTX: 0.6% (n = 4), IR 0.66 per 100 patient-years, 95% CI (0.18, 1.70)). None of the serious bleeding events were considered to be related to the study medication and none led to study discontinuation.

There were no serious bleeding events during the Treatment Period of Study C-OPERA.

Haematopoietic cytopenia

Six subjects in the CZP + MTX group had serious hematopoietic cytopenia TEAEs during Period 1 of Study C-EARLY based on the SS1 (anaemia (n = 3), pancytopenia (n = 2), bone marrow toxicity (n = 1)). No haematopoietic cytopenia TEAEs were reported in subjects in the PBO + MTX group. The cases of pancytopenia were considered to be related to the study medication. Except for one serious case of anaemia, the other five haematopoietic cytopenia TEAEs were of severity severe.

During the Treatment Period of Study C-OPERA, there were no serious drug-related cases of haematopoietic cytopenia TEAEs.

The fact that there were no cases of pancytopenia in the PBO + MTX group but there were in the CZP + MTX seems to suggest that this AE is associated with CZP rather than MTX. Pancytopenia is listed in the PI as an adverse drug reaction reported in RA clinical trials and post-marketing.[2] The frequency category of this adverse reaction is rare. The frequency of pancytopenia in the SS1 during Period 1 of Study C-EARLY is 0.3% (2/659) which would be classified as uncommon based on the frequency categories specified in the PI.

Interstitial lung disease

During Period 1 of Study C-EARLY, based on the SS1, two cases of interstitial lung disease were reported in the CZP + MTX group, both of which were assessed to be related to the

study treatment, were serious, and led to study discontinuation. There were no subjects reported with interstitial lung disease in the PBO + MTX group.

During the Treatment Period of Study C-OPERA, there were five reports of interstitial lung disease in the CZP + MTX group of which four were assessed as drug-related compared with one drug-related case in the PBO + MTX group.

Interstitial lung disease is listed as an adverse reaction in the PI in the frequency category rare.[2] Based on the proportions of subjects in the CZP + MTX groups reported with interstitial lung disease related to study treatment during Period 1 of Study C-EARLY and the Treatment Period of Study C-OPERA (Study C-EARLY 0.3% (2/659), Study C-OPERA 4/159 (2.5%)), it would appear that interstitial lung disease would be classified in a higher frequency category, based on the frequency categories specified in the PI, if these TEAEs are considered related to CZP. The sponsor is requested to clarify if it will be including these results in the PI given that the proportions of subjects reported with drug-related interstitial lung disease in the study populations of Study C-EARLY and Study C-OPERA, respectively, reflect higher frequency categories than the frequency category of interstitial lung disease in the PI based on other RA clinical trials and post-marketing.

Safety related to drug-drug interactions and other interactions, use of CZP concomitantly with MTX

In the interim CSR for Study C-OPERA, the sponsor indicates that it appears that there is an increased risk of certain adverse events, including serious infection, hepatic disorders, and haematological cytopenias, when CZP was combined with doses of MTX in the range > 12 mg/week to 16 mg/week in this study, as compared to the lower dose ranges for MTX (0 to 8 mg/week, > 8 to 12 mg/week). The absolute numbers of subjects who were reported with these AEs by MTX dose at the onset of the AE were, however, small for a number of the AEs as shown in Table 1, below.

Table 1. Study C-OPERA, Treatment Period: Selected AEs of interest during the Treatment period analysed by MTX dose at AE onset (SS)

MedDRA version 14.1 Category	MTX onset dose (mg/week)							
	Treatment group							
	PBO+MTX, N=157				CZP+MTX, N=159			
	0-8	8<-12	12<-16	Any	0-8	8<-12	12<-16	Any
	n	n	n	n (%)	n	n	n	n (%)
Any infection	31	44	40	87 (55.4)	39	32	48	97 (61.0)
Any serious infections	2	2	3	7 (4.5)	2	1	3	5 (3.1)
Any pneumonia (except interstitial pneumonia)	1	4	4	8 (5.1)	1	1	5	7 (4.4)
Any interstitial lung disease	0	0	1	1 (0.6)	0	2	3	5 (3.1)
Any hepatic disorder[a]	11	28	34	69 (43.9)	15	26	34	68 (42.8)
Any hematopoietic cytopenias[b]	4	5	5	13 (8.3)	5	2	5	12 (7.5)
Any nausea, vomiting, decreased appetite	8	12	18	32 (20.4)	15	11	18	39 (24.5)
Stomatitis	8	11	11	26 (16.6)	6	9	7	19 (11.9)

AE=adverse event; CZP=certolizumab pegol; MedDRA=Medical Dictionary for Regulatory Activities; MTX=methotrexate; PBO=placebo; SMQ=standard MedDRA query; SS=Safety Set; TEAE=treatment-emergent adverse event

Note: Only 109 subjects (68.6%) in CZP+MTX group and 115 subjects (73.2%) in the PBO+MTX group reached an MTX dose of at least 12mg/week (Table 2.8.2a).

Note: Percentages are based on the number of subjects in the analysis set.

[a] The SMQs for hepatic disorders were SMQ 20000009-cholestasis and jaundice of hepatic origin; SMQ 20000013-hepatic failure, fibrosis, and cirrhosis and other liver damage-related conditions; SMQ 20000010-hepatitis, noninfectious; SMQ 20000008-liver-related investigations, signs and symptoms; and SMQ 20000015-liver-related coagulation and bleeding disturbances.

[b] The SMQ for hematopoietic cytopenias was SMQ 20000027.haemotopoietic cytopenias (including decrease in platelets).

Based on Table 1 above, there is an apparent dose-response, in relation to MTX dose intervals, in both treatment groups for hepatic disorders and interstitial lung disease, and

in the PBO + MTX group for nausea, vomiting and decreased appetite. As highlighted by the sponsor it is difficult to interpret these data as the absolute numbers for some AEs are small, not all subjects reached the highest dose of MTX (16 mg) and the dose of MTX could have been temporarily decreased or withdrawn.

Post-marketing data

No post-marketing data are included in the submission. The sponsor indicates, in the submission, that the Periodic Safety Update Report (PSUR) covering the period 7 March 2013 to 6 March 2014 has received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in the EU.

The most recent PSUR submitted to the TGA is dated 5 May 2015 and covers the period from 7 March 2014 to 6 March 2015. Of note from the Executive Summary, during the PSUR period:

- the Company Core Data Sheet (CCDS) was updated to add '(pulmonary, extra-pulmonary and disseminated)' in relation to the adverse drug reaction, TB
- the development of TB despite prior or concomitant prophylactic TB treatment was confirmed as a new safety signal
- long-term immunogenicity in RA and Crohn's disease were being evaluated as new safety signals
- hepatitis B virus reactivation has been reclassified as an important identified risk.

Evaluator's conclusions on safety

The adverse effects associated with the initiation of CZP + MTX in DMARD-naïve subjects with moderate to severe, active RA at higher risk for rapid progression in Period 1 of Study C-EARLY were generally consistent with the known safety profile described in the currently approved PI for Cimzia.[2] Adverse effects occurring at lower frequencies may not, however, have been identified in Period 1 of Study C-EARLY.

A number of related TEAEs reported in the CZP + MTX group in Period 1 of Study C-EARLY are not included in the currently approved PI and there were adverse events reported during this study that were reported in ≥ 1% of subjects in the CZP + MTX group, and which were reported in a lower proportion of subjects in the PBO + MTX group, that are not specified in the summary of adverse events table in the currently approved PI or draft PI and are not specifically included elsewhere in the 'Adverse effects' section.

The frequencies of a number of drug-related adverse events in Period 1 of Study C-EARLY, specifically pancytopenia, hepatic events and interstitial lung disease, were higher in subjects in the CZP + MTX group in this study compared with the frequencies described in the currently approved PI for Cimzia based on other RA clinical trials and post-marketing experience.[2] However, it does not appear to be distinguished whether drug-related TEAEs in subjects in the CZP + MTX group in Period 1 of Study C-EARLY were considered to be related to CZP alone, or to both CZP and MTX, or to MTX alone. This point requires clarification by the sponsor.

As RA is a chronic condition it is anticipated that treatment with Cimzia will be long term. It would appear that all 500 subjects in the CZP + MTX group in Period 1 of Study C-EARLY who completed Week 52 would have been exposed to CZP + MTX for 365 days as the last administration of CZP was at Week 50 and MTX was administered until Week 51. This exposure, if confirmed to be correct by the sponsor, would seem adequate. However, it is not clear to the clinical evaluator if the types and frequencies of adverse effects that may occur at low frequencies with use of CZP in the proposed indication are consistent with the known safety profile of CZP used in the currently approved RA indications. From a

biological perspective, it is possible that DMARD-naïve patients with RA for whom treatment with both CZP and MTX is initiated concomitantly could present with different frequencies of adverse effects, and possibly additional adverse effects, compared with patients who have CZP added to MTX later in the course of their condition after having either an inadequate response, or intolerance, to previous therapy with one or more DMARDs.

The safety findings from Treatment Period 1 of Study C-OPERA and from the integrated RA safety data were included in the submission as supporting data. The safety results of the Treatment Period of Study C-OPERA also suggest that the frequency of interstitial lung disease in MTX-naïve Japanese subjects may be higher with CZP + MTX compared with PBO + MTX. The integrated safety set overall RA pool was from 14 RA studies of which 12 had been completed and two were ongoing at the cut-off date, 30 November 2011. Subjects that were included in this pool could have received any dose of CZP. The early RA subpool of the overall RA pool included subjects who had had RA for less than one year. Subjects were not DMARD-naïve. No specific new safety issues were identified from the integrated safety data that are not already identified in the PI. However, the IR of any hepatic event in the CZP + MTX group in Study C-EARLY group (15.54 per 100 subject years) was notably higher than the IR in subjects in the All Data pool who had RA disease for less than one year and were receiving CZP Q2W (5.61 per 100 patient years).

The currently approved dosage and administration recommendations for the maintenance dose for RA include an alternative dosage regimen of 400 mg every four weeks.[2] No clinical studies are provided in this submission to support this dosage regimen in the proposed indication. From the safety results from the early RA subpool, which was comprised of subjects who were not DMARD-naïve, the IRs of some TEAEs were higher in subjects receiving CZP 400 mg every four weeks compared with subjects receiving CZP 200 mg every two weeks. However, there were only small absolute numbers of subjects included in the CZP 400 mg Q4W group in all studies (n = 50) and in the PC data pool (n = 35). It is not clear, from a biological perspective, if a maintenance dosage of CZP of 400 mg every four weeks, compared with 200 mg every 2 weeks, could result in additional safety concerns associated with the use of CZP in the proposed indication. The former maintenance dosage regimen is already approved for use in adult patients with moderate to severe RA in case of either an inadequate response or intolerance to previous therapy with one or more DMARDs. However, in the patient sub-population to which the proposed indication pertains, DMARD-naïve patients, it is possible the safety profile may be different.

In conclusion, if CZP + MTX are started concomitantly as first-line treatment in RA the risk of certain adverse effects may be greater than with either drug alone. In clinical practice, if CZP + MTX are started concomitantly and an adverse event occurs, it may be difficult to determine which of the two medicines the adverse event may be associated with. In such an event, it may be necessary for the patient to discontinue treatment with both CZP and MTX, which will impact of the continuity of treatment of the patient's RA. No clinical studies are included in the submission to support the safety of the currently approved alternative maintenance dosage regimen in the RA indication of 400 mg every four weeks.[2]

First round benefit-risk assessment

First round assessment of benefits

The benefits of the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection are:

- Based on the results of the primary efficacy outcome and secondary efficacy outcomes included in the hierarchical testing procedure in Period 1 of Study C-EARLY, there were statistically significant benefits in relation to disease activity, clinical response, inhibition of joint damage and physical function at Week 52, compared with Baseline, with CZP + MTX, compared with PBO + MTX, in study subjects.

First round assessment of risks

The risks of the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection are:

- The proposed extension of indication is based on one pivotal study only. Potential sources of bias have been identified in relation to this study.
- It is not clear to the clinical evaluator whether Australian medical practitioners assess patients as having severe, active and progressive RA in the same way as the sponsor has done in this submission.
- It is not clear to the clinical evaluator whether Australian medical practitioners treating patients with severe, active and progressive RA would consider the results for the primary efficacy outcome and secondary efficacy outcomes included in the hierarchical testing procedure in Period 1 of Study C-EARLY to be clinically significant.
- It is anticipated that long-term treatment will be required for the management of RA. Period 1 of Study C-EARLY only provides efficacy and safety data through Week 52. The efficacy of ongoing treatment in the proposed dosage regimen in the proposed target population is not known. It is possible that adverse effects occurring at lower frequencies may not have been identified in Period 1 of Study C-EARLY so it is not known if the types and frequencies of such events with use of CZP in the proposed indication are consistent with the known safety profile of CZP used in the currently approved RA indications. From a biological perspective, it is possible that DMARD-naïve patients with RA being initiated with both CZP and MTX concomitantly could have a different frequency of adverse effects, and possibly additional adverse effects, compared with patients who have CZP added to MTX later in the course of their condition after having either an inadequate response, or intolerance, to previous therapy with one or more DMARDs.
- It appears that there may be differences in the safety profile of initiating treatment with CZP + MTX compared with the PBO + MTX. In Period 1 of Study C-EARLY, the IR of TEAEs was higher in the CZP + MTX group compared with the PBO + MTX group. The IRs of events falling under the Infections and infestations SOC, as well as 'headache' and 'ALT increased', were notably higher in the CZP + MTX group compared with the PBO + MTX. Also of note were TEAEs reported only in subjects in the CZP + MTX group, specifically 'neutrophil count decreased' (n = 4), 'white blood cell decreased' (n = 3), pancytopenia, thrombocytopenia, hypersensitivity and interstitial lung disease, each of which were reported in two subjects, and bone marrow toxicity, cardiac arrest, hepatocellular injury, anaphylactic shock and exfoliative rash, each reported in single subjects. The differences in the subjects reported with these TEAEs between the two treatment groups may reflect the shorter patient-years of exposure in the PBO + MTX group compared with the CZP + MTX group. Of these TEAEs in the CZP + MTX group, two cases of pancytopenia and interstitial lung disease, and single cases of thrombocytopenia, hepatocellular injury and exfoliative rash were considered to be related to the study drug. However, it does not appear to be distinguished whether drug-related TEAEs in subjects in the CZP + MTX group in Period 1 of Study C-EARLY were considered to be related to CZP alone, to both CZP and MTX, or to MTX alone. The safety results of the Treatment Period of Study C-OPERA also suggest that the frequency of drug-related abnormal hepatic function and interstitial lung disease

in MTX-naïve Japanese subjects may be higher with CZP + MTX compared with PBO + MTX.

- It appears that there may be differences in the known safety profile of CZP use in the currently approved RA indications described in the PI and the safety results in Period 1 of Study C-EARLY in which DMARD-naïve subjects received first-line treatment with concomitant CZP + MTX for RA. In Period 1 of Study C-EARLY, the frequencies of drug-related pancytopenia and interstitial lung disease were higher in subjects in the CZP + MTX group compared with the frequencies described in the currently approved PI for Cimzia based on other RA clinical trials and post-marketing experience.[2] However, as previously stated above, it does not appear to be distinguished whether drug-related TEAEs in subjects in the CZP + MTX group in Period 1 of Study C-EARLY were considered to be related to CZP alone, to both CZP and MTX, or to MTX alone.

  In Period 1 of Study C-EARLY, the proportions of subjects in both the PBO + MTX and CZP + MTX groups in Study C-EARLY reported with any hepatic event are notably higher than the corresponding proportions of Cimzia-treated and placebo-treated subjects reported with hepatic adverse events in placebo-controlled RA studies in the PI.[2]**Error! Bookmark not defined.** The IR of any hepatic event in the CZP + MTX group in tudy C-EARLY group was notably higher than the IR in subjects in the integrated data (All Data pool) that had RA disease for less than one year and were receiving CZP Q2W. It is possible that these differences are related to a difference in the doses of MTX administered in Period 1 of Study C-EARLY compared with the other RA studies or to the fact that subjects in Study C-EARLY were DMARD-naïve. These results suggest that the frequencies of certain TEAEs in DMARD-naïve patients for whom treatment with CZP + MTX are initiated concomitantly may be higher than the frequencies in patients who are not DMARD-naïve when concomitant treatment with CZP + MTX is initiated.

- Only one dosage regimen of CZP, consisting of a loading dosage and maintenance dosage, in combination with MTX, has been evaluated in Period 1 of Study C-EARLY. It is possible that alternative dosage regimens of CZP, in combination with MTX, may have greater efficacy and a lower risk of adverse effects.

- The currently approved dosage and administration recommendations for the maintenance dose for RA include an alternative dosage regimen of 400 mg every four weeks.[2] No efficacy data are provided in this submission to support this dosage regimen in the proposed indication. From the safety results from the early RA subpool, which was comprised of subjects who were not DMARD-naïve, the IRs of some TEAEs were higher in subjects receiving CZP 400 mg every four weeks than in subjects receiving CZP 200 mg every two weeks. There were, however, only small absolute numbers of subjects included in the CZP 400 mg Q4W analysis groups.

First round assessment of benefit-risk balance

The benefit-risk balance of the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection is favourable, based on the available evidence at this point in time.

The results of the primary efficacy outcome and secondary efficacy outcomes included in the hierarchical testing procedure in Period 1 of Study C-EARLY, the single supporting pivotal study, show statistically significant benefits in relation to disease activity, clinical response, inhibition of joint damage and physical function at Week 52, compared with Baseline, with CZP + MTX, compared with PBO + MTX, in the study subjects. Subjects in this study were adults with a time since diagnosis of adult-onset RA less than one year as defined by the 2010 ACR/EULAR classification criteria from the Screening Visit, and who had not been previously treated with MTX or other, for all but two subjects, DMARDs. Subjects were required to have had active RA disease to be included in the study. Nearly

all subjects (96.5%) had severe RA disease based on the Baseline DAS28 (ESR) value. A high proportion of study subjects had erosions at Baseline (77.8%) indicating progressive disease. The study population overall were also considered, by the sponsor, to be at risk for rapid progression of RA at an early stage of disease based on the high mean values for DAS28 (ESR), SJC, TJC, CRP, ESR, RF and ACPA, respectively. Although this seems reasonable, it is not clear to the clinical evaluator whether Australian medical practitioners assess patients as having severe, active and progressive RA in the same way as the sponsor has done in this submission. The sponsor is also requested to clarify the definition of severe, active, progressive RA in the proposed indication.

The efficacy results in Period 1 of Study C-EARLY were supported by the efficacy results from an ongoing study in MTX-naïve Japanese subjects with early RA.

Of concern, there was only a single pivotal study submitted to support the proposed extension of the RA indication and potential sources of bias were identified. There appear to be increased risks of initiating treatment with CZP + MTX, compared with initiating treatment with PBO + MTX, based on the results of Period 1 of Study C-EARLY, but further clarification is required from the sponsor regarding whether all the drug-related TEAEs in Period 1 of Study C-EARLY were considered to be related to CZP. Of specific concern are infections, abnormal liver function, haematological toxicity and interstitial lung disease. It also appears that initiating concomitant CZP + MTX as first line treatment of RA in patients who are DMARD-naive may have increased risk of hepatic events, pancytopenia and interstitial lung disease compared with initiating concomitant treatment with CZP + MTX in patients who are not DMARD-naïve. As for other studies of limited duration and with limited patient exposure to the study treatment(s), it is possible that adverse effects occurring at lower frequencies may not have been identified in Period 1 of Study C-EARLY so it is not known if the types and frequencies of such events with use of CZP in the proposed RA indication are consistent with the known safety profile of CZP used in the currently approved RA indications. It is anticipated that such risks with the first line use of CZP + MTX in the treatment of RA will be identified through post-marketing experience.

First round recommendation regarding authorisation

It is recommended that the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection is approved subject to the sponsor:

- providing satisfactory answers to the clinical questions raised by the clinical evaluator
- amending the draft PI as recommended or providing justification as to why the recommended changes should not be made.

Clinical questions

For details of the clinical questions raised please see Attachment 2.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefit of the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection is unchanged from those identified above in the first round assessment of benefits.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection are:

- Given the novel primary efficacy outcome in Period 1 of Study C-EARLY, it is not clear whether a 13.9% difference between the treatment groups in sustained remission at Week 52 is clinically meaningful and how Australian medical practitioners treating patients with severe, active and progressive RA would consider this result.
- There is uncertainty in relation to whether subjects in Period 1 of Study C-EARLY met all three criteria relating to RA in the proposed indication, specifically severe and active and progressive RA.
- It appears that there may be differences in the safety profile of initiating treatment with CZP + MTX compared with PBO + MTX as highlighted in the first round assessment of risks. For example, in Period 1 of Study C-EARLY, there were certain TEAEs of note such as pancytopenia and interstitial lung disease, albeit in small absolute numbers, reported only in subjects in the CZP + MTX group. It is biologically plausible that initiating treatment with two medicines concomitantly may increase the risk of adverse effects. The submission does not include evidence to assess whether a lower dosage of CZP, in combination with MTX, may result in similar efficacy as achieved with the proposed dosage but with lower risk of adverse effects.
- As highlighted above in the first round assessment of risks, the safety profile of concomitant treatment with CZP + MTX in DMARD-naïve subjects, based on the results in Period 1 of Study C-EARLY, may be less favourable compared with the safety profile of CZP described in the PI, which is based on the overall RA pool and post-marketing data.[2]

Second round assessment of benefit-risk balance

The benefit-risk balance of the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection is favourable.

As commented in the first round assessment of benefit-risk balance, the results of the primary efficacy outcome and secondary efficacy outcomes included in the hierarchical testing procedure in Period 1 of Study C-EARLY, the single supporting pivotal study, show statistically significant benefits in relation to disease activity, clinical response, inhibition of joint damage and physical function at Week 52, compared with Baseline, with CZP + MTX, compared with PBO + MTX, in the study subjects. The efficacy results in Period 1 of Study C-EARLY were supported by the efficacy results from an ongoing study in MTX-naïve Japanese subjects with early RA.

In relation to the definition of severe, active, and progressive RA in the proposed indication, the sponsor has clarified that the subject population for Study C-EARLY represent a severe, active, and progressive RA population based on a combination of factors, and has specified how it has defined severe RA, active RA and progressive RA. As commented in the first round assessment of benefit-risk balance, subjects in this study

were adults with a time since diagnosis of adult-onset RA less than one year as defined by the 2010 ACR/EULAR classification criteria from the Screening Visit, and who had not been previously treated with MTX or other, for all but two subjects, DMARDs. Subjects were required to have had active RA disease, as defined by the sponsor, to be included in the study. Nearly all subjects (96.5%) were considered by the sponsor to have had severe RA disease based on a Baseline DAS28 (ESR) value > 5.1. A high proportion of study subjects had erosions at Baseline (77.8%) indicating progressive disease. The study population overall were also considered, by the sponsor, to be at risk for rapid progression of RA at an early stage of disease based on the high mean values for DAS28 (ESR), SJC, TJC, CRP, ESR, RF and ACPA, respectively. The sponsor has clarified that it did not attempt to quantify the number of subjects who had severe and active and progressive RA. It appears that most subjects would have met the sponsor's criteria for severe, active and progressive disease or risk of progressive disease given the Baseline characteristics in RA of the study population. As there do not appear to be standard definitions of severe RA, active RA and progressive RA, the study population in Period 1 of Study C-EARLY is considered acceptable to support the target population of the proposed indication, especially given that the sponsor proposes to specify in the PI how it has defined severe, active and progressive RA.

There was only a single pivotal study submitted to support the proposed extension of the RA indication. The sponsor has addressed the prerequisites from the TGA-adopted guideline 'Points to Consider on Application with 1. Meta-Analyses: 2. One Pivotal Study. CPMP/EWP/2330/99' is referenced to support the submission of this single pivotal study.[8] The sponsor's argument to support the submitted single pivotal study seems reasonable. In addition, the proposed indication is the third indication for use of CZP for the treatment of RA, differing from the other RA indications in relation to the nature of the RA (severe, active and progressive) and in relation to the use of concomitantly initiated CZP + MTX in a different RA patient sub-population (DMARD-naïve).

The currently approved dosage and administration recommendations for the maintenance dose for RA include an alternative dosage regimen of 400 mg every four weeks.[2] No efficacy data are provided in this submission to support this dosage regimen in the proposed indication. No reason for a difference in the efficacy and safety of this alternate dosage regimen in DMARD-naïve patients with severe, active and progressive RA compared with patients in the approved RA indications can be identified. Therefore, the inclusion of this alternative dosage regimen for the proposed indication seems reasonable.

The frequencies of TEAEs considered related to CZP in Period 1 of Study C-EARLY are unknown as in Period 1 of Study C-EARLY, the investigator was to consider if the TEAE was related, or not related, to CZP/PBO and MTX without indicating a specific study medication. Therefore, it is difficult to compare the safety data from this study with the safety profile described in the PI, which relates to CZP.[2] As highlighted by the sponsor, it is possible that some of the TEAEs reported in Period 1 of Study C-EARLY are related to MTX, as MTX was initiated and up-titrated to a maximum of 25 mg/week during the study and certain adverse effects reported are consistent with those described for MTX.[10]

On further consideration of the possible safety concerns raised in the first round clinical evaluation in relation to the proposed indication, the apparent increased risks of infections, abnormal liver function, haematological toxicity and interstitial lung disease with the initiation of treatment with CZP + MTX, compared with PBO + MTX, based on Period 1 of Study C-EARLY and/or the Treatment Period of Study C-OPERA, may be due to chance, or may be associated with either CZP or MTX alone or reflect an additive effect of CZP + MTX. The apparent increased risk of hepatic events, pancytopenia and interstitial

[10] Pfizer Australia Pty Ltd. Australian product information document for Methoblastin tablets 2.5 mg and 10 mg. Date of most recent amendment: 15 February 2016. TGA, Canberra.

lung disease in DMARD-naïve subjects commenced on concomitant CZP + MTX in Period 1 of Study C-EARLY, compared with the safety profile of CZP described in the PI, may reflect the different safety data on which the safety profile described in the PI is based.[2] It is anticipated that medical practitioners choosing to prescribe both CZP and MTX concomitantly will have considered the adverse effect profiles of both medications and discussed the possibility of these adverse effects with their patients.

Second round recommendation regarding authorisation

It is recommended that the proposed extension of the RA indication for Cimzia (certolizumab pegol) 200 mg/mL injection is approved subject to the sponsor:

- providing comment on the finding of the higher mortality rate in the all CZP-treated subjects in all studies in the early RA subpool compared with the overall RA pool (early RA subpool: 1.22 deaths per 100 patient-years, 95% CI (0.56, 2.32), overall RA pool: 0.63 deaths per 100 patient-years, 95% CI (0.47, 0.81)) (see the clinical evaluator's comments in section 8.6.2 'Safety: Integrated safety results; Early RA subpool' of Attachment 2)
- providing its analysis of the drug-related TEAEs in Period 1 of Study C-EARLY. Specifically, whether a drug-related TEAE was considered by the sponsor to be related to CZP or MTX or both drugs.

V. Pharmacovigilance findings

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

VI. Overall conclusion and risk/benefit assessment

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

Quality

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

Nonclinical

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

Clinical

The clinical evaluator has recommended approval subject to the sponsor providing comment on the higher mortality rate in the all CZP-treated subjects in all studies in the early RA subpool compared with the overall RA pool and an analysis of TEAE in Period 1 of Study C-EARLY.

The clinical evaluator has reviewed the submitted data which included:

- One pivotal, Phase III, multicentre, randomised, double blind, placebo controlled study, evaluating the efficacy and safety of CZP in combination with MTX as first-line

treatment in DMARD naïve adults with early active rheumatoid arthritis (Study C-EARLY).

- An interim report from a Phase III, multicentre, randomised, double blind, placebo controlled, parallel group study comparing the efficacy of CZP with placebo in MTX naïve patients with early rheumatoid arthritis (Study C-OPERA). All patients received concomitant MTX therapy.

Benefits noted by the evaluator included:

- Statistically significant benefits in relation to disease activity, clinical response, inhibition of joint damage and physical function at Week 52, compared with Baseline, with CZP, compared with placebo, in study subjects in Period 1 of Study C-EARLY. All study subjects received concomitant MTX therapy.

Concerns noted by the evaluator included:

- It is not clear whether a 13.9% difference between the treatment groups in sustained remission at Week 52 in C-EARLY is a clinically significant result.
- There is uncertainty in relation to whether subjects in Period 1 of Study C-EARLY met all three criteria relating to RA in the proposed indication, specifically severe and active and progressive RA.
- It appears that there may be differences in the safety profile of initiating treatment with CZP plus MTX compared with placebo plus MTX. For example, in Period 1 of Study C-EARLY, there were certain TEAEs of note such as pancytopenia and interstitial lung disease, albeit in small absolute numbers, reported only in subjects in the CZP group. It is biologically plausible that initiating treatment with two medicines concomitantly may increase the risk of adverse effects. The submission does not include evidence to assess whether a lower dosage of CZP, in combination with MTX, may result in similar efficacy as achieved with the proposed dosage but with lower risk of adverse effects.
- The safety profile of concomitant treatment with CZP and MTX in DMARD-naïve subjects, based on the results in Period 1 of Study C-EARLY, may be less favourable compared with the safety profile of CZP described in the PI, which is based on the overall RA pool and post-marketing data.

Pharmacology

No clinical pharmacology studies were submitted but Studies C-EARLY and C-OPERA both provided data in relation to plasma CZP concentrations and immunogenicity. The design of these studies is discussed in the efficacy sections below. In Study C-EARLY, the geometric mean plasma CZP concentration was highest at Week 4. CZP plasma concentrations decreased to Week 12 and then were similar at the measurement time points to Week 52. Overall, 9.6% of subjects (n = 63) were positive for anti-CZP antibodies. This resulted in a lower geometric mean plasma CZP concentration in comparison to subjects who were negative for anti-CZP antibodies between Weeks 8 and 52.

In Study C-OPERA geometric mean plasma concentrations were stable from Week 12. In subjects who were positive for anti-CZP antibody, the geometric mean CZP concentrations were lower than the geometric mean CZP concentrations reported in subjects who were anti-CZP antibody negative at each of the measurement time points from Week 6. Over the Treatment Period, 8.8% of subjects who received CZP plus MTX had anti-CZP antibodies at one or more measurement time points.

These results are consistent with the information presented in the Cimzia PI Immunogenicity section for the RA indication. It is unclear whether the plasma

concentration results are comparable to previous RA studies including studies in support of the alternative dosing regimen of 400 mg every 4 weeks.

Efficacy

Pivotal study, Study C-EARLY

Study C-EARLY was a Phase III, multicentre, multinational, randomised, double blind, placebo controlled study. The study had two treatment periods, Period 1 (Week 0 to 52) and Period 2 (Week 52 to 104). The aim of Period 1 was to evaluate the safety and efficacy of CZB in combination with MTX as first-line treatment in inducing and sustaining clinical remission of RA and limiting radiographic progression in DMARD-naïve adults with active early RA. The aim of the Period 2 was to investigate the effects of reducing the frequency of CZP administration compared with stopping CZP administration in subjects who had achieved sustained low disease activity (LDA) during initial treatment with CZP. Period 2 is reported to be ongoing and the sponsor indicates that the results will be reported in a separate CSR.

The main inclusion criteria were males or females aged at least 18 years old and a positive RF or positive ACPA result at the Screening Visit, time since diagnosis of adult-onset RA less than one year as defined by the 2010 ACR/EULAR classification criteria, DMARD-naïve at Screening and Baseline (except anti-malarials) and active RA disease defined as:

- ≥ 4 swollen joints and ≥ 4 tender joints (DAS28) at Screening and Baseline
- DAS28 (ESR) > 3.2 at Screening and Baseline
- CRP) ≥ 10 mg/L at Screening and/or ESR ≥ 28 mm/hour (h) at Screening and Baseline

Subjects were randomised to the following treatment arms in a 3:1 ratio:

1. Certolizumab: CZB 400 mg at Weeks 0, 2 and 4 plus MTX followed by CZB 200 mg every 2 weeks plus MTX.
2. Placebo: PBO 2 syringes at Weeks 0, 2 and 4 plus MTX followed by PBO 1 syringe every 2 weeks plus MTX.

MTX was initiated at randomisation at a dosage of 10 mg/week. The dosage was to be escalated by 5 mg every 2 weeks to a maximum dosage of 25 mg/week, achieved by Weeks 6 to 8. Subjects who did not tolerate at least 15 mg MTX during the first 8 weeks of the study were withdrawn. The maximum tolerated dose of MTX reached at Week 8 was to be maintained throughout the study. If the subject did not tolerate MTX 15 mg/week after Week 8, a temporary reduction in MTX to 10 mg/week for 2 weeks could be applied. The subject was withdrawn from the study if he/she was not tolerating a MTX dosage of 15 mg/week when it was reintroduced.

A sufficient improvement in disease activity was defined as LDA (DAS28 (ESR) ≤ 3.2) and/or improvement in DAS28 (ESR) ≥ 1.2 points compared with Baseline. A subject who did not improve sufficiently at Week 20 was again evaluated at Week 24 and was withdrawn, and the Week 52 assessments performed, if he/she had not improved sufficiently.

The primary efficacy outcome was the proportion of subjects in sustained remission at Week 52, defined as DAS28 (ESR) < 2.6 at both the Week 40 Visit and at the Week 52 Visit. The EU guideline 'Points to consider on clinical investigation of medicinal products other than NSAIDs for treatment of rheumatoid arthritis' state that validated composite endpoints such as DAS are acceptable as additional primary or secondary endpoints. The evaluator notes that DAS28 (ESR) remission (DAS28 (ESR) < 2.6) at both the Week 40 and Week 52 Visits is a novel primary efficacy outcome.

The key secondary efficacy outcome was the proportion of subjects in sustained LDA at Week 52, defined as DAS28 (ESR) ≤ 3.2 at both the Week 40 Visit and at the Week 52 Visit. Other secondary objectives were to compare the efficacy of that CZP plus MTX and placebo plus MTX in relation to radiographic progression, clinical response, patient-reported outcomes and productivity within and outside the home, respectively.

Of the 879 randomised subjects, 660 subjects were randomised to receive CZP and 219 subjects were randomised to receive placebo. In the CZP group 500 randomised subjects (75.8%) completed Week 52 compared to 143 subjects (65.3%) in the placebo group. The proportions of randomised subjects who completed Period 1 (that is, had a Week 52 Visit and were eligible for Period 2 as they were in sustained LDA) were 44.2% versus 30.6% in the CZP and placebo groups respectively. The proportion of randomised subjects who discontinued was 24.2% versus 34.7%. The proportion of subjects who discontinued due primarily to adverse events was similar in the 2 treatment groups (8.5% versus 9.1%). Mandatory withdrawals based were slightly higher in the placebo group than the CZP group at Week 20 and Week 52.

The mean age of all subjects was 50.6 years. The majority of subjects were women (76.7%), white (86.3%) and of non-Hispanic or Latino ethnic origin (79.0%). The median calculated time since first diagnosis of RA was 1.63 months (mean 2.87). The median calculated time since first symptoms of RA was 6 months in both treatment groups.

Demographic attributes were generally similar between treatment arms. However, there was a slightly lower proportion of females in the CZP group compared with placebo (75.6 versus 80.2%) and a slightly higher proportion of subjects in the placebo group had a body mass index of ≥ 30. Baseline disease characteristics were also similar between treatment arms. Overall, 96.8% of subjects were RF positive and 84.0% were ACPA positive. The median RF value (IU/mL) was slightly higher in the placebo group (CZP 95.00; placebo: 108.50). Median ACPA values (IU/mL) were similar in the two groups. The baseline data based on the Full analysis set Period 1 (FAS1) were consistent with those based on the Safety Set Period 1 (SS1).

The majority of subjects (96.5%) had high DAS28 (ESR) disease activity, defined as a DAS28 (ESR) > 5.1. The mean DAS28 (ESR) score was 6.722 and the mean swollen joint count and tender joint count values were 12.53 and 15.76 respectively. The median HAQ-DI at baseline was 1.625 in the CZP group and 1.750 in the placebo group. The median mTSS was 3.0 in the CZP group and 2.8 in the placebo group. Median erosion score and JSN values were comparable in the two groups at Baseline. In all subjects, at Baseline the median erosion score was 1.5 (mean 4.4) and median JSN value was 0.0 (mean 3.1). The majority of subjects had erosions at Baseline (77.8%). Based on the Radiographic set Period 1 (RAD1), the results for the baseline radiographic assessments (mTSS, erosion score, JSN and presence of erosions) were similar to those based on the FAS1.

CRP and ESR values at baseline were comparable in the two treatment groups. The proportions of subjects in each treatment group with previous and ongoing medical histories falling under specific System Organ Classes and common preferred terms (reported by ≥ 3% of all subjects) were generally similar. A higher proportion of subjects in the CZP group were receiving concomitant medication that fell within the Anatomic Therapeutic Chemical Level 3 code 'beta-lactam anti-bacterials, penicillins' (placebo 9.7%; CZP 15.8%) which the sponsor states is to be expected as CZP is associated with an increased risk of infection.

The majority of subjects (83.6%) did not use rescue medication during the study. Of the 142 subjects who did, the proportions of subjects in each group were comparable.

Primary efficacy outcome

The proportion of subjects who were in DAS28 (ESR) remission (DAS28 (ESR) < 2.6) at both the Week 40 and Week 52 Visits was higher in the CZP group compared with the placebo and the difference was statistically significant (28.9% versus 15.0%; odds ratio (OR) 2.283, 95% CI (1.503, 3.468); p < 0.001). The original sample size calculations indicate an expected difference in sustained remission between the two groups of 20%. The actual proportion of subjects in sustained remission was lower than assumed and the difference between the groups was smaller. The sponsor considers a ≥ 10% difference between the groups in sustained remission at Week 52 to be clinically meaningful. The results of the sensitivity analyses were supportive of the results of the primary analysis.

A lower proportion of subjects who were anti-CZP antibody positive on at least one visit during Period 1 were in sustained remission at Week 52 compared with subjects who were anti-CZP antibody negative at all Visits in Period 1 (14.3% versus 30.4% respectively).

Key secondary efficacy outcome

The proportion of subjects who had DAS28 (ESR) ≤ 3.2 at both the Week 40 and Week 52 Visits was higher in the CZP group compared with placebo and the difference was statistically significant (43.8% versus 28.6%; OR 1.957, 95% CI (1.384, 2.767); p < 0.001). The sponsor considers the result to be clinically meaningful. The subjects who met the primary efficacy outcome also met this efficacy outcome. The sensitivity analyses were supportive of the results.

Other secondary efficacy outcomes

The proportion of subjects who had an ACR50 response at Week 52 was higher with CZP compared to placebo and the difference was statistically significant (61.8% versus 52.6%; OR 1.446, 95% CI (1.052, 1.989); p = 0.023).

At Week 52, the change from Baseline in HAQ-DI was greater with CZP compared to placebo and the difference was statistically significant (CZP minus placebo -0.177, 95% CI (-0.273, -0.082); p-value < 0.001). The sponsor indicates that it considers the change from Baseline in the CZP group clinically meaningful. A minimum clinically important difference (MCID) was defined as an improvement of at least 0.22 points from Baseline.

At Week 52, there were small mean increases from Baseline in mTSS based on the RAD1 (0.2 versus 1.8; CZP minus placebo -0.978, 95% CI (-1.005, -0.500); p-value < 0.001) (results included in Table 7 of the draft PI 'mTSS').

Additional efficacy outcomes the sponsor proposes including in the PI

The clinical evaluator has noted that the study was not powered for the comparison of CZP and placebo in relation to these secondary efficacy outcomes described and there was no adjustment for multiple comparisons. The results are considered hypothesis-generating and the 95% CI and p-values descriptive only:

- Change from Baseline in DAS28 (ESR) by week was a secondary efficacy outcome for Week 12, Week 24, Week 52/Withdrawal Visit and an 'other efficacy outcome' for Weeks 2, 4, 6, 8, 20, 36 and 40. There was a greater mean reduction in DAS28 (ESR) from Baseline in the CZP group compared with the placebo at each of the above measurement time points.
- The secondary efficacy outcome 'remission' was based on five criteria including DAS28 (ESR) < 2.6. The proportions of subjects with DAS28 (ESR) < 2.6 at Week 12, Week 24, and Week 52 were higher in the CZP group compared with the placebo group (see table 5 of the draft PI 'Remission').

- The proportion of subjects who achieved LDA (DAS28 (ESR) ≤ 3.2) were higher in the CZP group compared to placebo at Week 12, Week 24, and Week 52 (see Table 5 of the draft PI 'Low disease activity').
- The proportion of subjects who achieved ACR50 at Week 12, Week 24, and Week 52 were higher in the CZP group compared to placebo (see Table 5 of the draft PI 'ACR50').
- The proportions of subjects who achieved ACR70 at Week 12, Week 24, and Week 52 were higher with CZP compared to placebo (see Table 5 of the draft PI 'ACR70').
- Based on the RAD1, the mean increase from baseline in joint erosion score at Week 52 was lower in the CZP group compared with placebo (CZP: mean (SD) 0.1 (2.1), placebo: mean (SD) 1.1 (3.0) (results included in Table 7 of the draft PI 'Erosion score').
- At Week 52, there were small mean increases from Baseline in JSN score in both treatment groups based on the RAD1 with linear extrapolation. The mean increase was smaller in the CZP group compared with placebo but the median change was the same in both groups (placebo: mean (SD) 0.7 (2.3), median (range) 0.0 (-7, 15), CZP: mean (SD) 0.1(1.7), median (range) 0.0 (-16, 13)) (results included in Table 7 of the draft PI 'JSN score').
- At Week 52, the change from baseline Patient assessment of Arthritis Pain (PtAAP) was greater with CZP compared to placebo (CZP: LS mean -48.5; placebo: LS mean -44.0). The sponsor has included this result in the draft PI under Physical Function Response and health-related outcomes.
- At Week 52, the proportion of subjects who reached normative physical function, defined as a HAQ-DI score ≤ 0.5 was higher in the CZP group (CZP: 48.1%, placebo: 35.7%). The sponsor has included this result in the draft PI under Physical Function Response and health-related outcomes.
- At Week 52 a higher proportion of subjects in the CZP group compared with the placebo group had radiographic non-progression (change in mTSS ≤ 0.5 from Baseline) based on the RAD1 with linear extrapolation (CZP: 70.3%, placebo: 49.7%). The sponsor has included this result in the draft PI under Radiographic response.

Supportive study, Study C-OPERA

Study C-OPERA is an ongoing, Phase III, multicentre, randomised, double blind, placebo controlled, parallel group comparison study in Japan. The objective of the study was to compare the efficacy of CZP, in MTX-naïve subjects with early RA and poor prognostic factors, to placebo using inhibition of joint damage progression after one year of treatment as the primary efficacy outcome. All subjects received concomitant MTX.

The study has four periods including a 4-week Screening Period, a 52-week double-blind, placebo-controlled Treatment Period, a 52-week Follow-Up Observation Period and a Rescue Treatment Period. The Screening Period and Treatment Period have been completed and the results are reported in the interim CSR included in the submission. In the Treatment Period, subjects received one of the two following study treatments:

1. Certolizumab: CZP 400 mg SC at Weeks 0, 2 and 4 followed by CZP 200 mg SC every 2 weeks from Week 6 to Week 50 plus MTX weekly orally from Week 0.
2. Placebo: Placebo 2 syringes SC at Weeks 0, 2 and 4 followed by placebo 1 syringe SC every 2 weeks from Week 6 to Week 50 plus MTX weekly orally from Week 0.

Subjects were to be aged between 20 years and 64 years at the time of giving informed consent, have early RA (within one year of the onset of continuous symptoms of RA), have had no past use of MTX, have active disease in moderate or high degree as evidenced by

DAS28 (ESR) ≥ 3.2, and poor prognostic factors as evidenced by ACPA titre ≥ 13.5 U/mL plus RF > 20 IU/mL and/or the presence of bone erosions on X-ray examination of the hands and feet.

The primary efficacy variable was mTSS. During the Treatment Period, the primary efficacy outcome was the inhibition of joint damage progression at Week 52, evaluated as change from Baseline in mTSS at Week 52. During the Treatment Period, the secondary efficacy outcomes were:

- the inhibition of joint damage progression at Week 24 (mTSS at Week 24)
- clinical remission at Week 24 and Week 52:
  - DAS28 (ESR) remission rate at Week 24 and Week 52
  - ACR/EULAR remission rate at Week 24 and Week 52
    - Simplified Disease Activity Index (SDAI)-based
    - Boolean-based.

The majority of subjects were female (81.0% (n = 256) and the mean age was 49.3 years. All subjects were from Japan and of Asian ethnic background. Demographic and other baseline characteristics were generally comparable in the two treatment groups.

Primary efficacy outcome

At Week 52, the mean change from Baseline for the mTSS was smaller in the CZP group compared with the placebo group (CZP: 0.36, placebo: 1.58). The median change from Baseline in each treatment group was 0.00. Overall the sensitivity analyses for the primary efficacy outcome were supportive of the primary analysis.

Secondary efficacy outcomes

The clinical evaluator notes that the p-values described for these secondary efficacy outcome results are nominal only as the study was not designed to compare the treatment groups with regard to these efficacy outcomes. There was no control for multiple comparisons. Therefore, the statistical analyses for the secondary efficacy outcomes were hypothesis-generating. Subgroup analyses were also hypothesis-generating.

The mean change from Baseline for the mTSS at Week 24 was smaller in the CZP group compared with the placebo group (CZP: 0.26, placebo: 0.86,). The proportion of subjects with non-progression of joint damage at Week 24, based on a change from Baseline in mTSS ≤ 0.5 was higher in the CZP group compared with the placebo group (CZP: 87.3% (n=138)), 95% CI (81.1, 92.1); placebo: 74.5% 95% CI (67.0, 81.1)).

A higher proportion of subjects in the CZP group met DAS28 (ESR) remission criteria (DAS28 (ESR) < 2.6) at Week 24 and at Week 52 (Week 24: CZP: 52.8% 95% CI (44.8, 60.8), placebo: 30.6% 95% CI (23.5, 38.4); Week 52: CZP: 57.2% 95% CI (49.2, 65.0), placebo: 36.9% 95% CI (29.4, 45.0)).

A higher proportion of subjects in the CZP group met ACR/EULAR remission criteria, both SDAI-based and Boolean-based, at Week 24 and Week 52 (SDAI-based, Week 24: CZP: 48.4% 95% CI (40.4, 56.5), placebo: 29.3% 95% CI (22.3, 37.1); Week 52: CZP: 57.9% 95% CI (49.8, 65.6), placebo: 33.8% 95% CI (26.4, 41.7); Boolean-based, Week 24: CZP: 36.5% 95% CI (29.0, 44.5), placebo: 22.3% 95% CI (16.0, 29.6); Week 52: CZP: 45.3% 95% CI (37.4, 53.4), placebo: 28.0% 95% CI (21.2, 35.7)). The results of subgroup analyses were generally supportive although in some strata the proportions of subjects who met ACR/EULAR remission criteria were higher in the placebo group compared with the MTX group.

Safety

Study C-EARLY

Five hundred subjects in the CZP group completed Week 52 compared with 143 subjects in the placebo group. Median exposure to CZP was 364.0 days and the median exposure to placebo was comparable (364.0 days). After Week 8, the median weekly dose of MTX was 22.7 mg in the CZP group and 25.0 mg in the placebo group.

In Period 1 of Study C-EARLY, the proportion of subjects with any treatment-emergent adverse event (TEAE) was higher in the CZP group compared with placebo (79.7% versus 72.8%). The incidence rate (IR) was 250.77 per 100 subject-years in the CZP group compared to 195.66 per 100 subject-years in the placebo group.

The TEAEs, and the proportions of subjects with specific TEAEs, reported in Study C-EARLY, are generally consistent with the adverse events described in the PI. However, there were adverse events reported during this study that were reported in ≥ 1% of subjects in the CZP group, and which were reported in a lower proportion of subjects in the placebo group, including diarrhoea, vomiting, fatigue, seasonal allergy, laceration, paraesthesia, that are not specified in the summary of adverse events table in the currently approved PI or draft PI and which are not specifically included elsewhere in the 'Adverse Effects' section.

In Period 1 of Study C-EARLY, the proportion of subjects with drug-related TEAEs was higher in the CZP group (42.2% (n = 278)) compared with the placebo group (31.8% (n = 69)). Of note, in the CZP group, two cases of pancytopenia, one of the cases of thrombocytopenia, single cases of hepatocellular injury and hepatotoxicity, respectively, and the case of exfoliative rash were considered related to the study drug. Two cases of interstitial lung disease in the CZP group were also reported to be related to the study drug.

The proportion of subjects in each group who had serious TEAEs was similar (CZP: 10.6% (n = 70), placebo: 9.2% (n = 20)).

In Period 1 of Study C-EARLY, one subject in the CZP group discontinued due to a fatal AE. The proportion of subjects in each group who discontinued due to TEAEs was similar (CZP: 8.6% (n = 57), placebo: 9.2% (n = 20)) as was the IR per 100 subject years (CZP: 9.60 per 100 subject years, 95% CI (7.27, 12.44), placebo: 10.60 per 100 subject years, 95% CI (6.48, 16.38)).

In Period 1 of Study C-EARLY, one subject (0.5%) in the placebo group and two subjects (0.3%) in the CZP group had TEAEs leading to death. The subject in the placebo group had respiratory failure leading to death. In the CZP group one subject had pulmonary TB, TB gastrointestinal and acute respiratory distress syndrome leading to death and the other subject had a cerebrovascular accident. The investigator considered the pulmonary TB, TB gastrointestinal and acute respiratory distress syndrome leading to death as related to CZP or MTX. The adverse events leading to the other two deaths were not considered to be related to the study medication. The mortality rate was 0.33 deaths per 100 subject-years in the CZP group and 0.52 deaths per 100 subject years in the placebo group. Ischaemic coronary artery disorders and arrhythmias (including atrial fibrillation) are listed in the PI as uncommon adverse drug reactions in RA clinical trials and postmarketing.

The proportion of subjects in each treatment group with shifts in specific haematological parameters from normal at Baseline to low or high at the end of Period 1 were generally similar. The proportions of subjects who shifted from normal leukocyte values and normal neutrophil values at Baseline to low values at the end of Period 1 was higher in the CZP group (leukocytes: CZP: 4.6%, placebo: 1.8%; neutrophils: CZP: 6.7%, placebo: 1.4%,). The proportion of subjects in the CZP group who shifted from normal neutrophils/leukocytes values at Baseline to low at the end of Period 1 was also higher than the placebo group

(CZP: 5.8%, placebo: 1.4%). Neutropenia and leukopenia are listed as common adverse drug reactions in RA clinical trials and post-marketing.

Three subjects in the CZP group had 'abnormal, clinically significant' 12-lead ECG reports at Week 52 (right bundle branch block, incomplete right bundle branch block and atrial fibrillation) compared with one subject at Week 2 (Screening). None of the subjects in the placebo group had 'abnormal, clinically significant' 12-lead ECG reports at either of these measurement time points.

The proportions of subjects in both the CZP and placebo groups that were reported with any hepatic event were 13.1% and 12.0% respectively. These results are noted to be higher than the corresponding proportions of Cimzia treated and placebo treated subjects reported with hepatic adverse events in placebo controlled RA studies in the PI (Cimzia treated 1.2%, placebo treated 0.7%). The proportions of subjects in the CZP group with ALT increased (6.4%), AST increased (3.0%), and hepatic enzyme increased (2.4%), respectively, are higher that the rates in placebo-controlled RA studies reported in the PI (1.8%, 1.2%, 1.1%, respectively). The proportions of subjects with these TEAEs in the placebo group were also higher than the proportions reported in the PI.

Study C-OPERA

One hundred and eleven subjects completed Week 52 in the CZP group and 73 subjects completed Week 52 in the placebo group. The mean number of injections of study drug received by subjects in each treatment group during the Treatment Period was similar (certolizuamb: 21.5, placebo: 18.5). Patient years of exposure to the study medication were also similar (CZP: 136.16 versus placebo: 116.01). Mean drug exposure in days was shorter in the placebo group (CZP: 308.6, placebo 265.1). The median doses of MTX in mg/week were comparable in the two treatment groups (CZP: 11.84; placebo: 11.92).

Nearly all subjects in each treatment group had at least one TEAE (CZP: 96.2% (n = 153) versus placebo: 94.3% (n=148)). The IR was higher with CZP compared to placebo group but the event rate (ER) was similar (CZP: IR 601.93 per 100 patient years, 95% CI (510.33, 705.22), ER 541.26 per 100 patient years; placebo: IR 556.89 per 100 patient years, 95% CI (470.78, 654.18), ER 547.38 per 100 patient years). A higher proportion of subjects in the placebo group had one or more TEAEs of severity severe (placebo: 5.1% (n = 8), CZP: 2.5% (n = 4)).

There were no deaths during the Treatment Period of Study C-OPERA. A similar proportion of subjects in each treatment group had one or more SAEs (CZP: 8.2% (n = 13), placebo: 8.9% (n = 14)). The SAEs were generally single reports in one or other of the treatment groups.

A similar proportion of subjects in each treatment group had one or more TEAEs leading to discontinuation of the study drug (CZP: 5.7% (n = 9), placebo: 4.5% (n = 7)). Five subjects (3.1%) discontinued CZP due to interstitial lung disease compared to one subject (0.6%) in the placebo group.

There were several drug-related TEAEs that were reported in the CZP group only. There were single reports of granulocytopenia and idiopathic thrombocytopenic purpura, eight reports of cell marker increased, and six reports, respectively, of rash and neoplasms. All reports of neoplasm were different and five were classified as benign. Drug-related hepatic function abnormal was noted to have been reported in a higher proportions of subjects in the CZP group (17.0% (n = 27)) compared with the placebo group (12.7% (n = 20)) as was interstitial lung disease (CZP: 2.5% (n = 4), placebo: 0.6% (n = 1)).

Integrated safety results

The data in the overall RA pool was from 14 RA studies of which 12 had been completed and two were ongoing at the cut-off date, 30 November 2011. In the All Data Pool, 4049 subjects had received CZP treatment (All CZP in All Studies) and the estimated

exposure was 9277 patient years. Subjects that were included in this pool could have received any dose of CZP. In the Placebo-controlled (PC) Data Pool, there were 2965 subjects treated with CZP (All CZP in PC) and 1137 subjects who were treated with placebo.

The early RA subpool of the overall RA pool included subjects who had RA that was less than one year in duration based on the date of RA diagnosis and/or medical judgement of the duration of the RA. Subjects could have received any dose of CZP and were not DMARD-naïve. In the All CZP group in the All Studies group of the All Data Pool there were 401 subjects who had received CZP.

The overall mortality rate in all CZP treated subjects in all studies was reported to be 0.63 deaths per 100 patient years and 0.84 deaths per 100 patient-years in the All CZP in PC group. The mortality rate in all CZP treated subjects in all studies in the early RA subpool was higher than in the overall RA pool (early RA subpool: 1.22 deaths per 100 patient years, 95% CI (0.56, 2.32) overall RA pool: 0.63 deaths per 100 patient years, 95% CI (0.47, 0.81)).

SAEs were reported to have occurred most often in the SOC Infections and infestations (All CZP in PC group: 3.1%, placebo group: 0.8%) and for all other SOCs the incidence of SAEs was < 1.5%. In the All CZP in PC group, the proportion of subjects who had TEAEs that led to study withdrawal (discontinuation) was 4.4% and it is indicated that the most common TEAEs that led to study withdrawal fell in the SOC Infections and infestations.

The results in the CZP group in Study C-EARLY were generally consistent with results in the All CZP in PC group in the overall RA pool summarised by the sponsor. Of note, the proportion of subjects who had AEs that led to discontinuation in the CZP group in Study C-EARLY (8.6%) was higher than the proportion of subjects who discontinued for this reason (4.4%) in the All CZP in PC group. The IR of serious bleeding events was higher in the CZP group of Study C-EARLY (0.66 per 100 patient years) compared with the All CZP in PC group (0.31 per 100 patient years). The proportion of subjects in CZP group in the SS1 of Study C-EARLY with any hepatic event (13.1%) was higher than the proportion of subjects in the All CZP in PC group with any hepatic event (5.8%). The sponsor suggests that this difference may relate to the fact that subjects were MTX-naïve in Study C-EARLY and the MTX dose was up-titrated to the maximum dose specified in the protocol, or to the maximum tolerated dose within the protocol specified range, whereas subjects in the overall RA pool were, in general, taking a stable tolerated MTX dose during the study.

Risk management plan

An RMP was not included in the submission.

Risk-benefit analysis

Discussion

Efficacy

Study C-EARLY demonstrated an increase in the proportion of subjects who were in DAS28 (ESR) remission for the CZP group compared with placebo (28.9% versus 15.0%; OR 2.283, 95% CI (1.503, 3.468); p < 0.001). The key secondary endpoint of DAS28 (ESR) ≤-3.2 and the other secondary endpoints of ACR50, HAQ-DI and mTSS at Week 52 were supportive. The actual proportion of subjects in sustained remission was lower than assumed in the original power calculations and the difference between the groups was smaller than expected. The sponsor considers a ≥ 10% difference between the groups in sustained remission at Week 52 to be clinically meaningful. Study C-EARLY used a novel

primary efficacy outcome and it is unclear whether the difference in proportion of subjects in sustained DAS28 (ESR) remission is considered clinically significant. ACR20 is more commonly used as a primary efficacy outcome in RA trials but this parameter has not been commented on in the analysis. Whilst the result for the primary efficacy outcome was statistically significant the clinical significance of this result is unclear and advice is sought from ACPM on this issue.

The proposed extension of indication is based on one pivotal study and one supporting study. The evaluator has identified several sources of bias in relation to the pivotal Study C-EARLY. The TGA-adopted EU guideline 'Points to consider on application with 1. Meta-analyses; 2 One pivotal study' state that '*The minimum requirement is generally one controlled study with statistically compelling and clinically relevant results*'. The results of this pivotal study primary efficacy outcome are statistically significant but as noted above a novel primary efficacy outcome has been used. The sponsor considers the result to also be clinically significant. The sponsor has also argued that the results of Study C-EARLY have internal validity as potential sources of bias have been avoided or minimised, the results have external validity and are of sufficient quality. The results Study C-EARLY are stated to have shown internal consistency in different pre-specified sub-populations and all important efficacy outcomes showed similar findings. The hypothesis tested is considered biologically plausible and a similar indication has been approved for other anti-TNFs. Only one pivotal study has been included in the submission but previous studies have examined the efficacy and safety of CZP in other populations of patients with RA and the supporting Study C-OPERA also evaluated the use of CZP in early RA.

Patients who did not tolerate concomitant MTX were withdrawn from Study C-EARLY study. There is a risk that the proposed indication when read in the context of the currently approved indications for RA may suggest that the first-line use of CZP without concomitant MTX has been shown to be effective. It is noted that both the US and Canadian indications allow first-line use without concomitant MTX therapy. The wording for the new indication appears to mitigate this risk by separating the distinct indications and is considered acceptable but comment is sought from the committee regarding this issue.

In the C-EARLY study, the mandated withdrawal of patients who did not improve sufficiently is not mentioned in the draft PI. This information may be of use to prescribers considering withdrawing CZP therapy in patients who have not responded well.

The currently approved dosage and administration recommendations for RA include an alternative dosage regimen of 400 mg every 4 weeks. No clinical studies are provided in this submission to support the efficacy and safety of this dosage regimen in the proposed indication. However, 2 Phase III studies were provided to support a maintenance dosage of 400 mg every 4 weeks for the RA indication during the initial marketing authorisation application. The efficacy results in both studies showed comparable efficacy and safety results to the alternative maintenance dosage, 200 mg every 2 weeks, and that in both studies there were statistically significant benefits for subjects compared with placebo. Given that no reason for a difference in the efficacy and safety of this treatment regimen in DMARD-naïve patients has been identified it seems reasonable to extrapolate this result to DMARD-naïve patients with RA assuming the plasma concentration results are comparable for Study C-EARLY and these 2 studies.

Safety and RMP

The safety of CZP in patients with RA has previously been demonstrated, and no new safety concerns have been identified. The results in the CZP group in Study C-EARLY were generally consistent with results in the All CZP in PC group in the overall RA pool summarised by the sponsor. However, the results suggest that the frequencies of certain TEAEs in DMARD-naïve patients for whom treatment with CZP are initiated concomitantly may be higher than the frequencies in patients who are not DMARD-naïve when CZP is

initiated. The safety profile of concomitant treatment with CZP in DMARD-naïve subjects of Study C-EARLY may be less favourable than the safety profile of CZP described in the PI, which is based on the overall RA pool and post-marketing data. In particular it is noted that the rate of hepatic events in Study C-EARLY appears to be higher than that reported in previous RA controlled trials and the mortality rate in the Early RA subpool analysis appears to be higher than that reported for the Overall RA pool. Comment has been sought from the sponsor on these issues.

Data deficiencies

There were data deficiencies with respect to clinical studies supporting the alternative dosage regimen of 400 mg every 4 weeks, the duration of efficacy data did not exceed one year and ACR20 results were not reported on.

Conditions of registration

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

- The following study reports must be submitted to the TGA, in addition to those identified and/or agreed in the RMP/ASA, as soon as possible after completion, for evaluation as a Category 1 submission(s):
  - Study C-EARLY Period 2

Questions for the sponsor

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

1. Clarify the status of the submission in Canada as it is unclear if the submission has been considered by Health Canada or if, as in the US, a broader indication for RA was initially approved.
2. Provide comment on whether the plasma concentration results observed in Study C-EARLY and Study C-OPERA are comparable to those from previous RA studies including studies in support of the alternative dosing regimen of 400mg every 4 weeks.
3. Comment on the clinical significance of the primary efficacy endpoint result in Period 1 of Study C-EARLY.
4. Provide comment on the finding of the higher mortality rate in the all certolizumab treated subjects in all studies in the early RA subpool compared with the overall RA pool.
5. Please provide an analysis of hepatic adverse events and increases in LFTs in Period 1 of Study C-EARLY.
6. Please provide an analysis of the drug-related TEAEs in Period 1 of Study C-EARLY. Specifically, whether a drug-related TEAE was considered by the sponsor to be related to certolizumab or methotrexate or both drugs.

Delegate's considerations

The primary issues with the submission are as follows:

1. The acceptability of only one pivotal study to support the proposed indication.
2. Whether the result of the primary efficacy outcome from Study C-EARLY is considered clinically significant.

3. The proposed indication may include first-line use of certolizumab without concomitant methotrexate but the pivotal study did not include this patient population.
4. In Study C-EARLY, the mandated withdrawal of patients who did not improve sufficiently is not mentioned in the draft PI.
5. The efficacy of the alternative treatment regimen has not been demonstrated in this submission but no reason for a difference in efficacy and safety in DMARD-naïve patients has been identified.
6. The variation in adverse event profile across studies and analyses.

Proposed action

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

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

> *'Cimzia in combination with MTX is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs.'*

Request for ACPM advice

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

1. The sufficiency of Study C-EARLY and the supporting Study C-OPERA to support the proposed indication given the novel primary efficacy outcome?
2. Are the results for the primary and secondary efficacy outcomes in Study C-EARLY considered clinically significant in this patient population?
3. When read in the context of previously approved RA indications, could the proposed indication imply that first-line use of certolizumab without concomitant methotrexate is efficacious?
4. Subjects in Study C-EARLY were withdrawn at various points if a response was not achieved. Should the PI include this information in order to guide prescribers considering stopping certolizumab therapy?
5. Does the committee have any concerns regarding the wording of the dosage and administration instructions for this indication?
6. Does the committee have any concerns regarding the safety profile for certolizumab in DMARD-naïve patients? In particular, does the committee have any concerns with respect to hepatic events and mortality?

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

Question 1

· Clarify the status of the submission in Canada as it is unclear if the submission has been considered by Health Canada or if, as in the US, a broader indication for RA was initially approved.

In Canada as in the US, a broader indication was initially approved.

Question 2

- Provide comment on whether the plasma concentration results observed in Study C-EARLY and Study C-OPERA are comparable to those from previous RA studies including studies in support of the alternative dosing regimen of 400mg every 4 weeks.

The plasma concentrations at steady state in Study C-EARLY (RA0055) are comparable to those observed in the pivotal studies (Studies C87027; C87050) which supported the approval of 200 mg Q2W dosing regimen for current approved RA indication (see Table 2, below).

Table 2. Plasma CZP trough concentrations (µg/mL) for all subjects and those with overall anti-CZP antibody negative status for Studies RA0055 Period 1, C87027, C87050 and C87014

		RA0055 Period 1 (PKS1)[a]		C87027 (Safety Set)[a]		C87050 (Safety Set)[a]		C87014 (RS)[b]
	CZP Dose	200mg Q2W+MTX		200mg Q2W+MTX		200mg Q2W+MTX		400mg Q4W+MTX
Visit	Statistics	All Subjects N=659	Overall (-) Status N=596	All Subjects N=392	Overall (-) Status N=350	All Subjects N=248	Overall (-) Status N=596	All Subjects N=126
W12	n	606	547	369	329	229	213	106
	GeoMean	21.879	24.705	17.412	20.647	15.720	18.001	13.73
W24	n	542	495	254	225	171	159	115
	GeoMean	19.099	21.678	17.038	19.723	15.048	17.234	11.60
W36	n	529	483	234	206	-	-	-
	GeoMean	17.743	20.608	15.013	17.848	-	-	-
W52	n	500	459	252	225	-	-	-
	GeoMean	17.589	20.575	15.438	18.439	-	-	-

CI = confidence interval; CSR = clinical study report; CZP = certolizumab pegol; GeoMean = geometric mean; MTX = methotrexate; N = number of subjects; n = number of observations;
PKS1 = Pharmacokinetic Analysis Set 1; Q2W = every 2 weeks; Q4W = every 4 weeks; RS = Randomised Set; W = Week; a) overall Status: overall anti-CZP antibody negative status, defined as ≤ 2.4units/mL at each visit during the Treatment Period, excluding the Safety Follow-up Visit; b) antibody status data not available.

Study C87014 is the pivotal study which supported the approval of 400 mg Q4W dosing regimen with MTX (without the additional CZP 400mg loading dose at Week 2). As expected the C_{trough} for the 400 mg Q4W dosing regimen is lower than that of 200 mg Q2W (see Table 2 above). Those results are in line with simulation based on basic pharmacokinetic principles for a 1-compartment model at steady state. The simulation shows that with the 400 mg Q4W dose regimen, plasma concentrations are not expected to fall below the 200 mg Q2W trough concentration until approximately Day 22 of the 28-day dose interval. Following the subsequent 400 mg dose, it is expected that the plasma concentrations will exceed the CZP 200 mg Q2W trough concentration after approximately 2 days, so in total the plasma concentrations with the CZP 400 mg Q4W dose regimen are expected to be above the 200 mg Q2W trough concentration for approximately 20 days out of the 28 day dose interval (71% of the dose interval).

Of note Study C-OPERA, a Japanese study was provided as additional supportive results. The plasma concentrations seen in this study with 200 mg Q2W were in line with the results seen in Japanese adult RA patients with inadequate response to MTX. In Japan both dose regimens are approved for maintenance for the treatment of RA (including inhibition of progression of bone structural damage). Due to the difference in ethnicity, the results are not provided in this table and are available in the Study RA0096 CSR.

Finally, the sponsor would like to indicate that in the Doseflex study in adult RA patients with inadequate response to MTX, for the maintenance dose regimens, the clinical response was similar for the 200 mg Q2W and 400mg Q4W dosing regimens.[11]

Question 3

- Comment on the clinical significance of the primary efficacy endpoint result in Period 1 of Study C-EARLY.

The sponsor considers that the difference in the proportions of subjects that reached the stringent endpoint of sustained remission (defined as DAS28 (ESR) < 2.6 at the Week 40 and Week 52 Visits, at Week 52) of 13.9% (OR of 2.283 (95% CI: 1.503, 3.468)) in favour of CZP + MTX is clinically significant. The sponsor considers a 10% difference as clinically meaningful based on the clinical judgment of expert members of the Steering Committee for the study (an opinion provided prior to study unblinding); since this was a novel endpoint, published data supporting this did not exist. It is reasonable that this difference, and more to the point, the actual difference of 13.9%, is clinically meaningful, given the totality of the data from Study RA0055. The primary endpoint assesses signs and symptoms and a laboratory marker of inflammation; however, as the assessor pointed out, the primary endpoint result was supported by positive results for multiple secondary endpoints covering not only signs and symptoms, but also physical functioning, progression of structural damage and health outcomes. The positive response across multiple measures of diverse aspects of RA indicates that the primary endpoint result can be considered clinically meaningful. This is supported by the CHMP, which stated that sustained remission is a clinically important endpoint and considered that the sustained remission results in Study RA0055 were 'clinically meaningful' (Assessment Report, EMA/CHMP/825080/2015).[12]

Sustained remission rates have not been reported for early RA studies with other anti-TNFα drugs; however, a closely related endpoint, DAS28 remission at (or near) Week 52, has been reported for etancercept;[13] infliximab;[14] adalimumab;[15] and golimumab.[16] The increases in the proportions of patients who achieved DAS28 remission during treatment with these anti-TNFα drugs in combination with MTX above MTX monotherapy have ranged from 16% to 22%. The 16% increase at Week 52 with CZP + MTX versus PBO + MTX in Study RA0055 is comparable with these results. The comparability of the Study RA0055 Week 52 remission rate with those for other anti-TNFα drugs that are approved for this indication provides additional assurance that the Study RA0055 results for the related, but more stringent, sustained remission primary endpoint are clinically meaningful.

[11] Furst D et al. Two dosing regimens of certolizumab pegol in patients with active rheumatoid arthritis. Arthritis Care Res (Hoboken). 2015 Feb;67(2):151-60.
[12] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). EMA/CHMP/825080/2015: Assessment report for Cimzia International non-proprietary name: certolizumab pegol. Procedure No. EMEA/H/C/001037/II/0045. 19 November 2015.
[13] Emery P et al. Comparison of methotrexate monotherapy and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet. 2008;372:375-82.
[14] St Clair E et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum. 2004;50(11):3432–43.
[15] Breedveld F et al. The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum. 2006;54(1):26–37.
[16] Emery P et al. Golimumab, a Human Anti-Tumor Necrosis Factor α Monoclonal Antibody, Injected Subcutaneously Every Four Weeks in Methrotrexate-Naïve Patients With Active Rheumatoid Arthritis. Twenty-Four-Week Results of a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Golimumab Before Methotrexate as First-Line Therapy for Early-Onset Rheumatoid Arthritis. Athritis Rheum. 2009;60:2272-83.

Conclusion

CZP + MTX more than doubled the proportion of subjects who achieved the stringent endpoint of sustained remission (DAS28 (ESR) < 2.6 at the Week 40 and Week 52) compared with PBO + MTX. That magnitude of increase, in conjunction with significant improvements in multiple aspects of RA seen in Study RA0055 indicates that the sustained remission response is clinically significant.

Question 4

- Please provide comment on the finding of the higher mortality rate in the all certolizumab treated subjects in all studies in the early RA subpool compared with the overall RA pool.

In general the profile of fatal TEAEs is similar between the subpool of subjects with RA ≥ 1 year, and the subpool of subjects with RA < 1 year (note that the overall RA pool includes the subjects with RA < 1 year; therefore, the appropriate comparison is between the mutually exclusive subpools RA < 1 year and RA ≥ 1 year, rather than between the subpool RA < 1 year and the overall RA pool). The incidences of fatal cardiac disorders, neoplasia, nervous system disorders, and TEAEs in the primary SOC of Investigations were the same or similar in the subpools. There was a higher incidence of fatal infections (0.7% versus 0.2%) and fatal general disorders (death/sudden death and febrile disorders); 0.5% versus 0.1%) in the early RA subpool. Further details are provided in Table 3, below.

Table 3. Summary of deaths, All Data Pool (Safety Population)

	RA regardless of duration All CZP in All Studies N=4049	RA ≥1 year All CZP in All Studies N=3648	RA <1 year All CZP in All Studies N=401
Total duration of exposure (years)	**8663.4**	**7976.4**	**687.0**
Patient-years at risk[a]	**9277.3**	**8426.6**	**737.1**
Mortality Rate	**0.63**	**0.58**	**1.22**
Primary System Organ Class:	**n (%) IR (95% CI)**	**n (%) IR (95% CI)**	**n (%) IR (95% CI)**
Any TEAEs leading to death	**58 (1.4) 0.63 (0.47, 0.81)**	**49 (1.3) 0.58 (0.43, 0.77)**	**9 (2.2) 1.22 (0.56, 2.32)**
Cardiac disorders	19 (0.5) 0.20 (0.12, 0.32)	17 (0.5) 0.20 (0.12, 0.32)	2 (0.5) 0.27 (0.03, 0.98)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	13 (0.3) 0.14 (0.07, 0.24)	11 (0.3) 0.13 (0.07, 0.23)	2 (0.5) 0.27 (0.03, 0.98)
Infections and infestations	10 (0.2) 0.11 (0.05, 0.20)	7 (0.2) 0.08 (0.03, 0.17)	3 (0.7) 0.41 (0.08, 1.19)
Nervous system disorders	7 (0.2) 0.08 (0.03, 0.16)	6 (0.2) 0.07 (0.03, 0.15)	1 (0.2) 0.14 (0.00, 0.76)
General disorders and administration site conditions	4 (0.1) 0.04 (0.01, 0.11)	2 (0.1) 0.02 (0.00, 0.09)	2 (0.5) 0.27 (0.03, 0.98)
Respiratory, thoracic and mediastinal disorders	2 (0.0) 0.02 (0.00, 0.08)	2 (0.1) 0.02 (0.00, 0.09)	0
Vascular disorders	2 (0.0) 0.02 (0.00, 0.08)	2 (0.1) 0.02 (0.00, 0.09)	0
Hepatobiliary disorders	1 (0.0) 0.01 (0.00, 0.06)	1 (0.0) 0.01 (0.00, 0.07)	0
Injury, poisoning and procedural complications	5 (0.1) 0.05 (0.02, 0.13)	5 (0.1) 0.06 (0.02, 0.14)	0
Investigations	1 (0.0) 0.01 (0.00, 0.06)	0	1 (0.2%) 0.14 (0.00, 0.76)
Musculoskeletal and connective tissue disorders	1 (0.0) 0.01 (0.00, 0.06)	1 (0.0) 0.01 (0.00, 0.07)	0

CI=confidence interval; CZP=certolizumab pegol; incl=including; IR=incidence rate; RA=rheumatoid arthritis
Note: Data are displayed as number of subjects (percentage of subjects) and incidence of new cases per 100 patient-years.
[a] Patient-years at risk was calculated as the Total Study Medication Duration replacing the maintenance dosing interval (14 or 28 days) by 84 days censored by date of last clinical contact.

CI = confidence interval; CZP = certolizumab pegol; incl = including; IR = incidence rate; RA = rheumatoid arthritis Note: Data are displayed as number of subjects (percentage of subjects) and incidence of new cases per 100 patient years; a) patient-years at risk was calculated as the Total Study Medication Duration replacing the maintenance dosing interval (14 or 28 days) by 84 days censored by date of last clinical contact.

The number of subjects who experienced fatal TEAEs by time of occurrence (that is, duration of exposure) in the overall RA pool, the subpool of subjects with RA ≥ 1 year, and the subpool of subjects with RA < 1 year has been analysed. The previous conclusion of the RA ISS that there was no trend toward an increasing incidence of deaths over time in the overall RA pool appears to apply to the early RA subpool, that is, there is no clear pattern of consistent increase in deaths with increasing duration of exposure to CZP. Further details are provided in Table 4, below.

Table 4. Summary of TEAEs leading to death by time of occurrence; All Data Pool (Safety Population)

Time of Occurrence	N per time interval			Number (%) subjects who experienced an AE leading to death per interval		
	RA regardless of duration	RA ≥1 year	RA <1 year	RA regardless of duration	RA ≥1 year	RA <1 year
>0 to <3 months	4049	3648	401	10 (0.2)	8 (0.2)	2 (0.5)
≥3 to <6 months	3886	3487	378	6 (0.2)	5 (0.1)	1 (0.3)
≥6 to <12 months	3449	3035	325	8 (0.2)	7 (0.2)	1 (0.3)
≥12 to <18 months	1960	1766	147	4 (0.2)	4 (0.2)	0
≥18 to <24 months	1655	1530	119	6 (0.4)	6 (0.4)	0
≥24 to <36 months	1466	1355	106	10 (0.7)	6 (0.4)	4 (3.8)
≥36 to <48 months	1334	1234	95	4 (0.3)	3 (0.2)	1 (1.1)
≥48 to <60 months	1219	1128	88	9 (0.7)	9 (0.8)	0
≥60 months	941	844	71	2 (0.2)	2 (0.2)	0

Note: A total of 59 subjects in the overall RA pool are noted in this table; however, only 58 subjects in the All Data Pool died as of the 30 Nov 2011 data cut off. Subject 1 experienced 1 fatal TEAE that began in the > 0 to <3 months' time interval and 2 fatal TEAEs that began in the ≥ 3 to < 6 months' time interval; therefore, this subject is counted in both time intervals.

A thorough analysis of fatal cases in the early RA subpool has been performed. Nine subjects in the early RA subpool who received CZP experienced 13 TEAEs leading to death. The mean age of these subjects was 61.9 years (range 50 to 78), greater than the mean ages for the entire early RA subpool (51.9 years, Early RA Subpool) and the overall RA pool (53.2 years). Most of the subjects had significant medical history or concomitant conditions which may have contributed to or caused their deaths. Furthermore, Investigators concluded that CZP was not or was unlikely to be related to the deaths of 6 of these subjects, while CZP was possibly related to the deaths of 3 of the subjects. These subjects/events were as follows: Subject 1 (pyrexia, colon cancer, metastasis to liver, metastasis to lung; CZP dose of 200 mg Q2W), Subject 2 (disseminated tuberculosis; CZP dose of 400 mg Q2W), and Subject 3 (pneumonia; CZP dose of 400 mg Q2W). In the first 2 cases, the sponsor agrees that a role for CZP cannot be excluded. In Subject 3, the Investigator assessed fatal pneumonia as possibly related to CZP; however, the subject had only been exposed to CZP for 19 days, and he had significant other disease burden as well as exacerbating factors according to the narrative.

Fatalities occurred at doses of 200 mg Q2W (4 subjects; note that 3 of these subjects had initially received 400 mg Q2W for varying durations), 400 mg Q2W (4 subjects) and 400 mg Q4W (1 subject). The durations of exposure (in days) to CZP at the time of onset of the fatal TEAEs were 0, 19 (these 2 events with durations of exposure of 0 and 19 occurred in the same subject), 63, 125, 252, 767, 837, 842, 943, and 1407 (4 events in 1 subject, all of which occurred after 1407 days exposure to CZP).

Conclusion

The profile of fatal TEAEs (that is, incidences of fatal TEAEs by primary SOC) is comparable between the early RA subpool and the subpool of subjects with RA ≥ 1 year. There is no particular category of fatal TEAE overrepresented in the early RA subpool, which suggests that risk of CZP treatment is not significantly different in the early RA subpool. Furthermore, the mortality in the early RA subpool relative to the subpool of subjects with RA ≥ 1 year can be explained when the details pertaining to the fatal cases,

especially comorbid conditions, are considered. Most of the 9 subjects in the early RA subpool who died were older and had significant medical history or concomitant conditions which may have contributed to or caused their deaths. In addition, in the investigator's opinion, 6 cases were not or were unlikely to be related to CZP. Overall the review indicates that the fatality risk in the early RA subpool is not significantly different from that in the subpool of subjects with RA ≥ 1 year.

Question 5

- Does the committee have any concerns regarding the wording of the dosage and administration instructions for this indication?

Hepatic adverse events

The assessor has expressed concern that the proportion of subjects in the certolizumab group in the SS1 of Study C-EARLY with any hepatic event (13.1%) was higher than the proportion of subjects in the All CZP in PC group with any hepatic event (5.8%). As shown in Table 5 (below) there was also a higher proportion of hepatic events in the PBO + MTX group in Period 1 of Study RA0055 compared to the PBO group in the RA PC Data Pool. Table 5 also shows that the difference in incidences of any hepatic event between the CZP + MTX group and the PBO + MTX group is small in both Study RA0055 and the PC Data Pool (1.1% and 2.2%, respectively), suggesting comparable relative risks. Finally, the incidence rates per 100 patient-years of hepatic events in the CZP + MTX group in Study RA0055 (15.54) is similar to that in the All CZP in PC group in the PC Data Pool (13.97).

Table 5. Incidence and Incidence rate of hepatic events in Study RA0055 and the PC Data Pool (SS1 and Safety Population, respectively)

Study/Pool	N	PBO[a] Incidence (%) Incidence rate[c] (95% CI)	N	CZP[a] Incidence (%) Incidence rate[c] (95% CI)	ARR[d]
RA0055	217	12.0% 14.64 (9.57, 21.46)	659	13.1% 15.54 (12.43, 19.19)	-1.1%
PC Data Pool	1137	3.6% 11.28 (8.10, 15.31)	2965	5.8% 13.97 (11.96, 16.22)	-2.2%

ARR = absolute risk reduction; CI = confidence interval; CZP = certolizumab pegol; MTX = methotrexate; PBO = placebo; PC = placebo-controlled; SS1 = Safety Set 1; a) PBO + MTX in Study RA0055 and PBO for the PC Data Pool; b) CZP+MTX in RA0055 and All CZP in PC for the PC Data Pool; c) Incidence rate is the number of new cases per 100 patient-years and the associated 95% confidence interval; d) Absolute risk reduction = incidence in the PBO group minus incidence in the CZP group.

Changes in liver function parameters

The incidences of all post-Baseline marked elevations in liver function tests (LFTs) were low (< 7.0%) and similar between the CZP + MTX and PBO + MTX groups.

Very high elevations (that is, ≥ 10 x ULN and ≥ 20 x ULN) of AST and ALT were reported in no more than 1 subject per group (≤ 0.5%). The incidence of elevations in ALT of ≥ 3 x ULN was greater than in AST of ≥ 3 x ULN in both groups (6.5% versus 2.0% for CZP + MTX and 6.9% versus 1.4% for PBO + MTX). Elevations in alkaline phosphatase of ≥ 1.5 x ULN were low (2.6% for CZP + MTX and 3.7% for PBO + MTX). Elevations in bilirubin of ≥ 1 x ULN were observed in 5.5% of subjects in the CZP + MTX group and 4.6% of subjects in the PBO + MTX group; however, few subjects had elevations ≥ 1.5 x ULN (< 1.5% for either group). No subjects had both elevations of bilirubin ≥ 1 x ULN and AST or ALT ≥ 3 x ULN. No subjects met the criteria for Hy's law (bilirubin ≥ 2 x ULN and AST or ALT ≥ 3 x ULN).

In the instances where there was an elevation of ALT or AST, these elevations were generally transient and returned to normal or non-clinically significant values. All subjects were DMARD-naïve at Screening but treated with MTX during the study (escalated to the

maximum tolerated dose (maximum 25 mg/week and minimum 15 mg/week by Week 8), which can contribute to elevations in ALT or AST.

Conclusion

The overall increase in the incidence of hepatic events is similar in both treatment groups in Study C-EARLY. When correcting for exposure, the occurrence of hepatic events is similar in Study C-EARLY as compared to the RA PC studies. This suggests that the increase might be due to the study design of Study C-EARLY (rapid up-titration of MTX in DMARD-naïve subjects with early RA) rather than an increased risk in the early RA population. The current approved label already covers the ADR 'Hepatitis (includes hepatic enzyme increased)' as being with a frequency of common.

Question 6

- Does the committee have any concerns regarding the safety profile for certolizumab in DMARD-naïve patients? In particular, does the committee have any concerns with respect to hepatic events and mortality?

All TEAEs that were considered by the Investigators to be related to study drug were compared to adverse reactions listed in the British SmPC for MTX that was sourced from Europe;[17] or the Australian label for Cimzia, and then further classified by UCB study physicians into one of the following categories:

- TEAE is related to CZP only
- TEAE is related to MTX only
- TEAE is related to both CZP and MTX

The incidence and event rate of TEAEs in the following post-hoc categories are presented:

- Related to CZP only
- Related to MTX only
- Related to both CZP and MTX (note that if a drug-related TEAE was not listed in the SmPC for MTX and/or the label for CZP, it was classified as related to both CZP and MTX, since the Investigator had considered it to be related to study drug).

Also note that in the category 'Related to CZP only', there were 18 PBO + MTX subjects who experienced 19 TEAEs considered related to CZP only, even though these subjects did not receive CZP. The events were identified and were consistent with adverse reactions listed in the label for CZP. No further action to remove events from the table was performed to account for the fact that CZP was never administered.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Cimzia injection containing 200 mg/mL of certolizumab pegol to have an overall positive benefit–risk profile for the amended indication:

> *'Cimzia in combination with MTX is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with MTX or other DMARDs'*

In making this recommendation the ACPM:

[17] Summary of Product Characteristics (SPC) for Methotrexate 2.5 mg tablets. Datapharm Communications Limited; electronic Medicines Compendium (eMC). Last updated 18 Jun 2015.

- noted that the proposed indication may include first-line use of certolizumab without MTX, however there was no CZP monotherapy treatment arm in the clinical studies.
- noted that CZP + MTX combination therapy may have clinical benefit over certolizumab monotherapy especially in patients with anti-drug antibodies.
- commented that the term 'progressive' overlapped with the term 'severe' in the proposed indication and may exclude patients with early stage active disease without progressive tissue damage, therefore this term may not be needed.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Specific Advice

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

1. The sufficiency of Study C-EARLY and the supporting C-OPERA study to support the proposed indication given the novel primary efficacy outcome?

   Yes, the novel primary efficacy outcome DAS28 (ESR) was considered a valid primary efficacy outcome. The provision of one pivotal study (Study C-EARLY) and one supporting study (Study C-OPERA) was considered sufficient evidence to support the proposed indication.

2. Are the results for the primary and secondary efficacy outcomes in Study C-EARLY considered clinically significant in this patient population?

   Yes, the primary and secondary efficacy outcomes in Study C-EARLY are clinically significant for this patient population.

3. When read in the context of previously approved RA indications, could the proposed indication imply that first-line use of certolizumab without concomitant methotrexate is efficacious?

   Yes, the proposed indication could imply that first-line use of certolizumab without concomitant methotrexate is efficacious in case methotrexate is not tolerated or contraindicated. Whilst Study C-EARLY did not include a CZP monotherapy treatment arm the committee did not consider it necessary to specifically exclude this patient population from the proposed indication. However, the PI should state there was a lack of evidence to support the use of certolizumab monotherapy in this population.

4. Subjects in Study C-EARLY were withdrawn at various points if a response was not achieved. Should the PI include this information in order to guide prescribers considering stopping certolizumab therapy?

   Yes, the withdrawal of non-responders in Study C-EARLY should be mentioned in the PI.

5. Does the committee have any concerns regarding the wording of the dosage and administration instructions for this indication?

   The committee noted the two dosing regimens and has no concerns regarding the wording of the dosage and administration instruction for this indication.

6. Does the committee have any concerns regarding the safety profile for certolizumab in DMARD naïve patients? In particular, does the committee have any concerns with respect to hepatic events and mortality?

   The committee noted the adverse event profile, including the hepatic events and risk of mortality; however this did not raise safety concerns that would preclude

registration and was broadly consistent with the known safety profile of certolizumab.

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, the TGA approved the registration of Cimzia certolizumab pegol (rbe) 200 mg/mL solution for injection pre-filled syringe, as indicated to include the following:

> *'Cimzia in combination with methotrexate is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs.'*

The full indications are now:

> *'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 (see Dosage and Administration).*
>
> *Cimzia in combination with methotrexate is indicated for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs*
>
> *Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.*
>
> *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).'*

Specific conditions of registration applying to these goods

The following study reports must be submitted to the TGA as soon as possible after completion, for evaluation as a Category I submission:

· Study C-EARLY Period 2

Attachment 1. Product information

The PI for Cimzia approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, 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

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au