Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Certolizumab pegol

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

First round report: January 2016
Second round report: March 2016

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 the Extract from the Clinical Evaluation Report

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

Contents

List common of abbreviations

Abbreviation	Definition
ACPA	Anticyclic citrullinated peptide antibody
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20% response
ACR50	American College of Rheumatology 50% response
ACR70	American College of Rheumatology 70% response
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibody
ANCOVA	Analysis of Covariance
ANCOVA LINEAR	Analysis of Covariance with linear extrapolation for missing data
ANCOVA LOCF	Analysis of Covariance using last observation carried forward for missing data
ANCOVA OC	Analysis of Covariance using observed cases
AST	Aspartate aminotransferase
BMI	Body Mass Index
CCDS	Company Core Data Sheet
CCP	Cyclic citrullinated peptide
CDAI	Clinical Disease Activity Index
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CMI	Consumer medicine information
COX-2	Cyclo-oxygenase-2
CRP	C-reactive protein
CSR	Clinical Study Report

Abbreviation	Definition
CZP	Certolizumab pegol
DAS28	Disease activity score-28 joint count
DAS28 (ESR)	Disease activity score-28 joint count erythrocyte sedimentation rate
DMARD(s)	Disease-modifying anti-rheumatic drug(s)
eCRF	Electronic Case Report form
ER(s)	Event rate(s)
ES1	Enrolled set Period 1
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FAS1	Full analysis set Period 1
GCP	Good clinical practice
h	Hour
HAQ-DI	Health Assessment Questionnaire-Disability Index
ICH	International Conference on Harmonisation
ILD	Interstitial lung disease
IQ	Interquartile
IR(s)	Incidence rate(s)
ITP	Idiopathic thrombocytopenic purpura
IXRS	Interactive Voice/Web Response System
KL-6	Sialylated carbohydrate antigen KL-6
LDA	Low disease activity
LOCF	Last observation carried forward
LS	Least square
LTBI	Latent tuberculosis infection

Abbreviation	Definition
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Affairs
MMRM	Mixed effect model for repeated measures
mTSS	Modified total Sharp score
MTX	Methotrexate
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
OC	Observed case
PBO	Placebo
PC	Placebo-controlled
PCS	Physical Component Summary
PEG	Polyethylene glycol
PI	Product information
PKS1	Pharmacokinetic set Period 1
PPF	Pre-submission planning form
PPS	Per-protocol set
PPS1	Per-protocol set Period 1
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT(s)	Preferred term(s)
PtAAP	Patient's Assessment of Arthritis Pain
PtGADA	Patient's Global Assessment of Disease Activity
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RA	Rheumatoid arthritis

Abbreviation	Definition
RAD1	Radiographic set Period 1
RF	Rheumatoid Factor
RMP	Risk Management Plan
RS1	Randomised set Period 1
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous/subcutaneously
SD	Standard deviation
SDAI	Simplified Disease Activity Index
SE	Standard error
SJC	Swollen joint count
SOC	System Organ Class
SPC	Summary of Product Characteristics
SS1	Safety set Period 1
TB	Tuberculosis
TEAE(s)	Treatment-emergent adverse event(s)
TJC	Tender joint count
TNF	Tumour necrosis factor
US	United States
USA	Unites States of America

1. Introduction

This is a submission to extend the rheumatoid arthritis indication of Cimzia, certolizumab pegol.

1.1. Drug class and therapeutic indication

Certolizumab pegol is a biological product. It is a recombinant, humanised antibody Fab' fragment that is expressed in an *Escherichia coli* expression system and then subsequently purified and conjugated to polyethylene glycol (PEG).[1]

The approved indications are:

- *'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]

The proposed additional rheumatoid arthritis indication is:

> *'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.'*

Comment: The proposed indication is for first line use of certolizumab pegol (CZP) with methotrexate (MTX) in patients with severe, active and progressive rheumatoid arthritis. In relation to the currently approved indications, it is noted that CZP is indicated for use in RA as monotherapy in case of a contraindication or intolerance to MTX.[1] It follows that patients who have a contraindication to MTX would not have been treated with MTX, and the indication remains silent with regard to using other DMARDs before CZP. Therefore, this currently approved RA indication appears to imply the option of first line use of CZP monotherapy.

[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.

The sponsor indicates that the 2010 European League Against Rheumatism (EULAR) recommendations were current at the time the protocol for Study C-EARLY was written. The 2010 EULAR recommendations include the recommendation that DMARD-naïve patients with poor prognostic markers might be considered for combination therapy of MTX plus a biological agent.[2] It is noted that the 2013 update of the 2010 EULAR recommendations for the management of RA with non-biological and biological DMARDs does not include this recommendation.[3]

It is noted that the currently approved RA indications in the United States of America (USA), European Union (EU) and Canada are not identical to the currently approved RA indications in Australia.[4,5,6] The current EU Summary of Product Characteristics (SPC) includes RA indications that are similar, but not identical, to the RA indications in the currently approved Australian PI.[1,5]

The United States (US) and Canadian product information documents for Cimzia are silent in relation to first line use of CZP in combination with MTX in the treatment of patients with RA. In the US, the RA indication is 'Cimzia is indicated for the treatment of adults with moderately to severely active rheumatoid arthritis (RA).[4] This indication appears to infer that CZP could be used as first line treatment in the management of RA with or without other concomitant medication. One of the RA indications in the Canadian Product Monograph also suggests that CZP in combination with MTX can be used as first line treatment in RA:

'Cimzia (certolizumab pegol) in combination with methotrexate (MTX) is indicated for: reducing signs and symptoms, inducing major clinical response, and reducing the progression of joint damage as assessed by X-ray, in adult patients with moderately to severely active rheumatoid arthritis (RA).'[6]

1.2. Dosage forms and strengths

The following dosage forms and strengths are currently registered:

Table 1. Dosage forms and strengths currently registered in Australia

AUST R	Active ingredient	Trade name	Strength	Dosage form	Pack/ container
154726	Certolizumab pegol	Cimzia	200 mg/mL	injection	2 pre-filled syringes/pack

The product is supplied with a cotton swab, which is described as a device on the pre-submission planning form (PPF).

No new dosage forms or strengths are proposed.

[2] Smolen J et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Ann Rheum Dis 2010; 69: 964-975.

[3] Smolen J et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014; 73: 492-509.

[4] UCB Inc. US prescribing information for Cimzia (certolizumab pegol). Revised 10/2015. Reference ID: 3834410. US Food and Drug Administration, Silver Spring.

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

[6] UCB Canada Inc. Canadian product monograph for Cimzia (certolizumab pegol solution for injection in a single-use pre-filled glass syringe 200 mg/mL. Date of approval: 2 October 2015. Health Canada, Ottawa.

1.3. Dosage and administration

The currently approved dosage and administration recommendations pertaining to all approved indications are as follows:

- *'Loading dose:*

  The recommended loading dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) initially (Week 0) and at Weeks 2 and 4.

- *Maintenance dose:*
  - *Rheumatoid arthritis:*

    After the loading dose, the recommended maintenance dose of Cimzia for adult patients with rheumatoid arthritis is 200 mg every 2 weeks via subcutaneous injection. Alternatively, Cimzia 400 mg every 4 weeks has been shown to be safe and effective.

    No additional benefit has been observed with doses above a total dose of 400 mg/monthly (see Clinical Trials Section).
  - *Psoriatic arthritis:*

    After the loading dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Alternatively Cimzia 400 mg every 4 weeks can be considered.
  - *Ankylosing spondylitis:*

    After the loading dose, the recommended dose of Cimzia for adult patients with ankylosing spondylitis is 200 mg every 2 weeks or 400 mg every 4 weeks.'[1]

For the above indications, available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continuation of therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment.

Cimzia treatment should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. After proper training in injection technique, patients may self-inject with Cimzia if their physician determines that it is appropriate and with medical follow-up as necessary.

- *'Children and adolescents*:

  There is no experience in children or adolescents below 18 years of age.

- *Elderly:*

  No dose adjustment is required. Population pharmacokinetic analyses showed no effect of age.

- *Renal impairment:*

  There are insufficient data to provide dosing recommendations in moderate and severe renal impairment (see Pharmacokinetic properties).

- *Hepatic impairment:*

  Specific clinical studies have not been performed to assess the effect of hepatic impairment on the pharmacokinetics of Cimzia.'[1]

No changes to the Dosage and Administration section are proposed in relation to the proposed new indication relating to RA.

Comment: The currently approved dosage and administration recommendations for RA include an alternative dosage regimen of 400 mg every four weeks.[1] No clinical studies are

provided in this submission to support the efficacy and safety of this dosage regimen in the proposed indication. This sponsor is requested to clarify why such data are not provided to support this dosage regimen in the proposed indication.

2. 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 CZP 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 CZP 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's 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.

Comment: The sponsor's clinical rationale is accepted.

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.[1,7,8,9,10]

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.[8] 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.[9] These respective indications remain silent on the use of other DMARDs and previous use of DMARDs,

[7] Pfizer Australia Pty Limited. Australian product information document for Enbrel (etanercept (rch)). Date of most recent amendment: 7 December 2015.

[8] AbbVie Pty Ltd. Australian product information document for Humira (adalimumab). Date of most recent amendment: 31 August 2015, Version 33. TGA, Canberra.

[9] Janssen Cilag Pty Ltd. Australian product information document for Remicade powder for injection (infliximab). Date of most recent amendment: 10 November 2015. TGA, Canberra.

[10] 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.

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.[7] 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.[7] 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.[10]

3. Contents of the clinical dossier

3.1. Scope 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 (C-OPERA) dated 23 April 2014
- Integrated Summary of Safety:
  - Integrated RA safety pooling (data cut off: 30 Nov 2011) listings
  - Integrated RA safety pooling (data cut off: 30 Nov 2011) tables
- Reference to Periodic Safety Update Report (PSUR) for the period covering 7 March 2013 to 6 March 2014
- 27 literature references
- An introduction document, Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Synopses of individual studies and literature references.

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 (C-EARLY) Period 1 dated 14 August 2015
- Interim CSR for Study RA0096 (C-OPERA)
- Integrated Summary of Safety:
  - Integrated RA safety pooling (data cut off: 30 Nov 2011) listings
  - Integrated RA safety pooling (data cut off: 30 Nov 2011) tables
- Reference to the PSUR for the period covering 7 March 2013 to 6 March 2014
- 27 literature references
- An introduction document, Clinical Overview (Amendment 1, 28 August 2015), Clinical Overview (30 January 2015), Summary of Clinical Efficacy (Amendment 1, 28 August 2015) Summary of Clinical Efficacy (15 January 2015), Summary of Clinical Safety (Amendment 1, 28 August 2015), Summary of Clinical Safety (12 January 2015), Synopses of individual studies and literature references.

Comment: The 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.

3.2. 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.

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

3.3. 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 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 Good Clinical Practice, 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 (Good Clinical Practice (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.

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

4. Pharmacokinetics

Comment: The pharmacokinetics of CZP are described in the currently approved PI.[1] The sponsor proposes no changes to the Pharmacology section of the PI.

4.1. Studies providing pharmacokinetic data

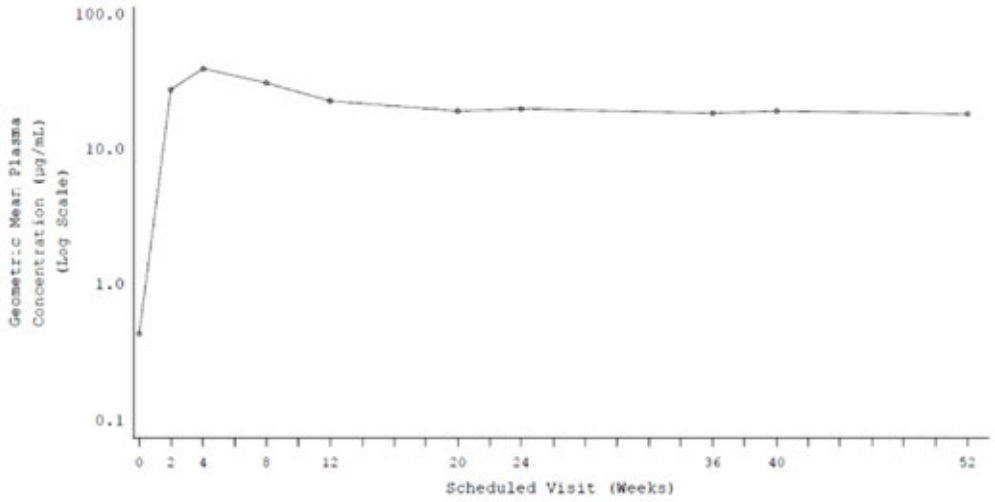
There are no pharmacokinetic studies included in the submission. Study C-EARLY and Study C-OPERA both provided data in relation to plasma CZP concentrations and immunogenicity data.

4.2. Summary of pharmacokinetics

4.2.1. Study C-EARLY

During Period 1 of Study C-Early, in the CZP + MTX treatment group 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, as shown below in Figure 1.

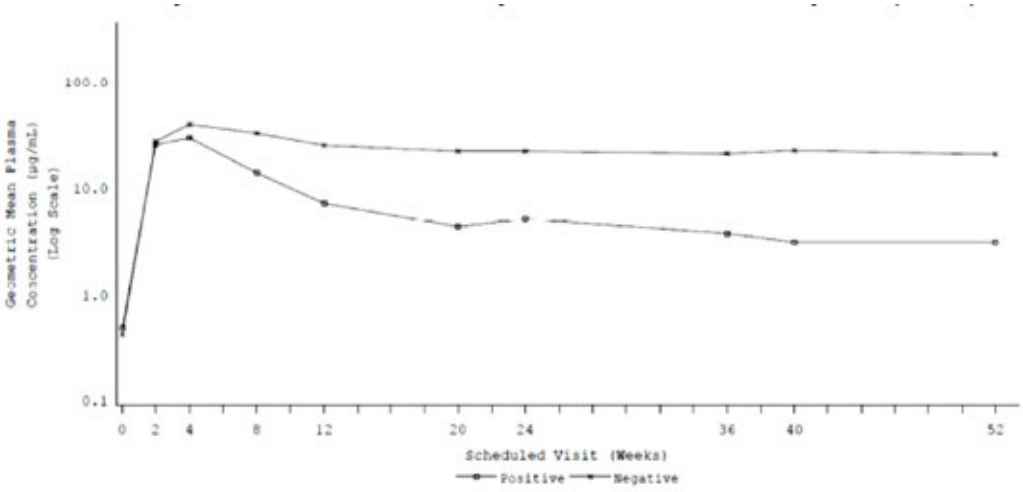
Figure 1. Study C-EARLY, Period 1: Plot of geometric mean CZP plasma concentrations (µg/mL), actual values by visit (PKS1)



Note: Values below the limit of quantification of 0.41µg/mL were set to half the limit of quantification.

Overall, 9.6% of subjects (n = 63) were positive for anti-CZP antibodies (> 2.4 units/mL) and this resulted in notably lower geometric mean plasma CZP concentrations than in subjects who were negative for anti-CZP antibodies at the measurement time points from Week 8 to Week 52 (shown in Figure 2, below). The number of subjects contributing to each measurement time point decreased over Period 1 of the study.

Figure 2. Study C-EARLY, Period 1: Plot of geometric mean CZP plasma concentrations (µg/mL) by overall anti-CZP antibody status, actual values by visit (PKS1)

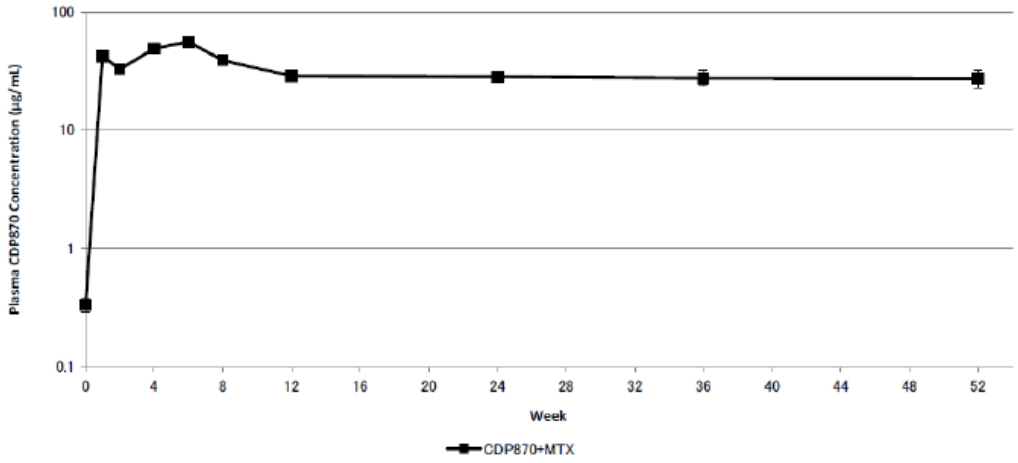


Note: Values below the limit of quantification of 0.41µg/mL were set to half the limit of quantification.
Note: A subject was overall positive to anti-CZP antibodies if the level was >2.4units/mL on at least 1 visit in Period 1 (no samples were taken after the last/Withdrawal Visit). A subject was overall negative to anti-CZP antibodies if the level was ≤2.4units/mL at all visits in Period 1 (no samples were taken after the last/Withdrawal Visit).

4.2.2. Study C-OPERA

During the Treatment Period of Study C-OPERA, the geometric mean CZP plasma concentrations were stable from Week 12 (shown in Figure 3, below). 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 (shown in Figure 4, below). Over the Treatment Period, 8.8% of subjects (n = 14) who received CZP + MTX had anti-CZP antibodies at one or more measurement time points.

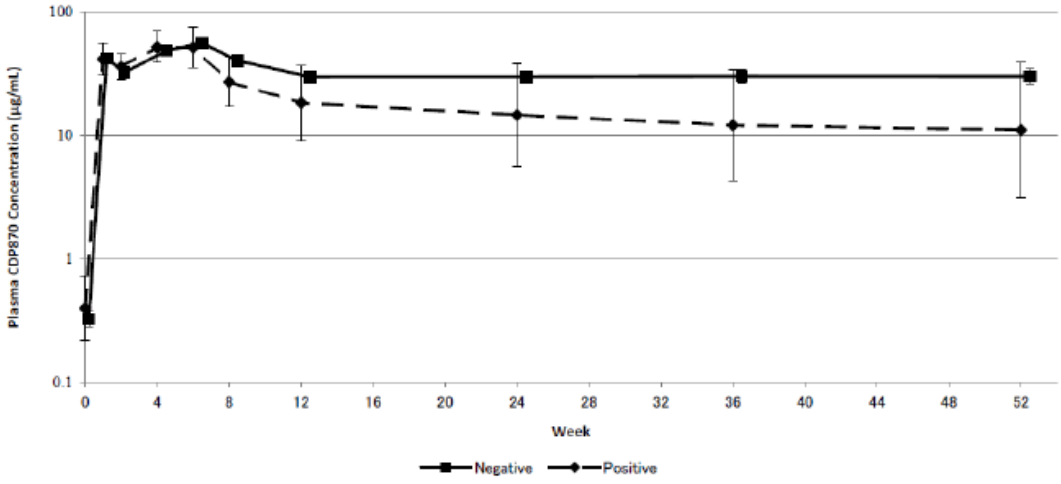
Figure 3. Study C-OPERA, Treatment Period: Overall geometric mean CZP plasma concentrations (µg/mL) with 95% CIs during the Treatment Period following a dose of CZP 200 mg Q2W (semi-log plot, OC, PKS) (400 mg loading doses administered at Weeks 0, 2, and 4)



CI=confidence interval; CDP870=CZP=certolizumab pegol; MTX=methotrexate; OC=observed case; PKS=Pharmacokinetic Analysis Set, Q2W=every 2 weeks

Note: Data represent the geometric mean and the 95% CI on a semi-logarithmic scale.

Figure 4. Study C-OPERA, Treatment Period: Geometric mean CZP plasma concentrations (µg/mL) with 95% CIs by anti-CZP antibody status during the Treatment Period following a dose of CZP 200 mg Q2W (semi-log plot, OC, PKS) (400 mg loading doses administered at Weeks 0, 2, and 4)



CI=confidence interval; CDP870=CZP=certolizumab pegol; OC=observed case; PKS=Pharmacokinetic Analysis Set; Q2W=every 2 weeks

Note: Data represent the geometric mean and the 95% CI on a semi-logarithmic scale.

Immunogenicity results from both studies are described in the safety section later in this document.

Comment: In the PI it is indicated that there is an approximate three-fold increase in clearance that results from the presence of antibodies to CZP.[1] The above results in anti-CZP antibody positive subjects are consistent with this information.

4.3. Evaluator's overall 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.

5. Pharmacodynamics

There are no pharmacodynamic studies included in the submission.

6. 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.

Comment: 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 PK of MTX and the pharmacokinetics of CZP were reported to have been similar to the pharmacokinetics of CZP observed in healthy subjects.[1]

7. Clinical efficacy

7.1. Pivotal efficacy studies

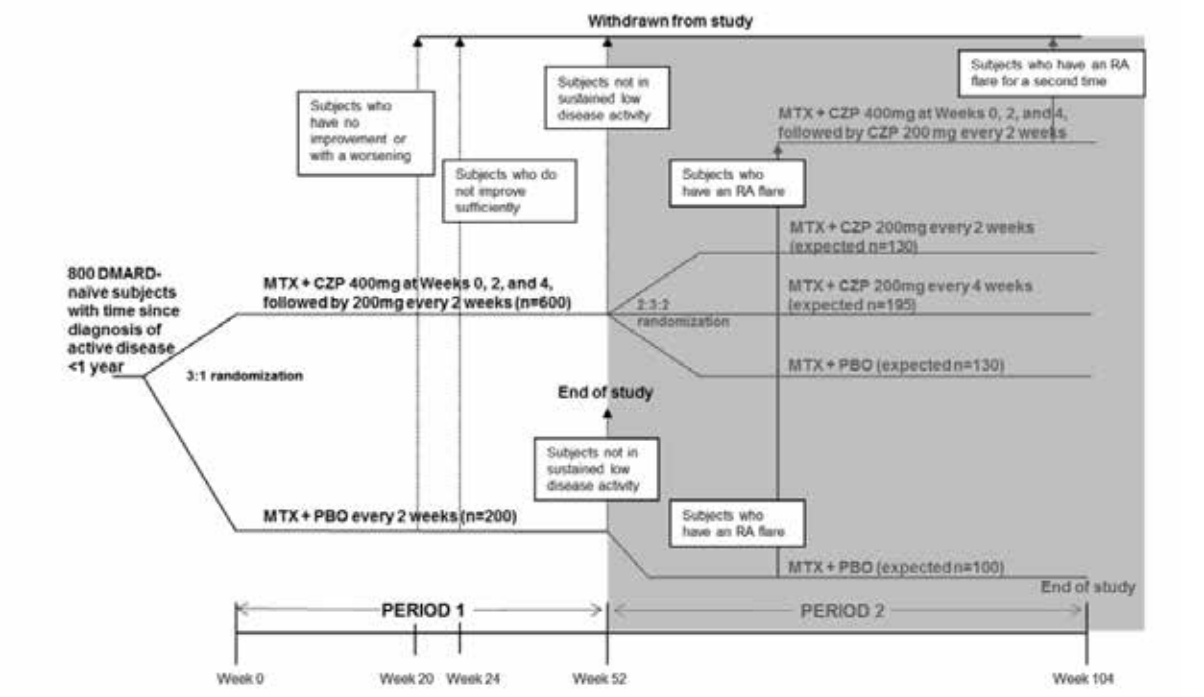
7.1.1. Study C-EARLY (Study RA0055, Period 1)

7.1.1.1. Study design, objectives, locations and dates

Study C-EARLY was a Phase III, randomised, double-blind, placebo-controlled study, undertaken in multiple centres. The 181 study centres were in Europe, Australia, Latin America and North America.

The study had two periods, Period 1 (Week 0 to Week 52) and Period 2 (Week 52 to Week 104) as shown in Figure 5, below. There was a Screening Visit (Week -2/4 to 0). The results pertaining to Period 1 are covered by the submitted CSR. Period 2 was reported to be ongoing when this CSR was being written and the sponsor indicates that the results of Period 2 will be reported in a separate CSR.

Figure 5. Study C-EARLY, study design



CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; MTX=methotrexate; PBO=placebo; RA=rheumatoid arthritis

The aim of the study in Period 1 was to evaluate the efficacy and safety of CZP 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. For context, in Period 2, the aim of the study was to investigate the effects of reducing the frequency of CZP administration compared with stopping CZP administration in subjects who had achieved sustained LDA during initial treatment with CZP.

For Period 1, the first subject was enrolled on 25 January 2012. The last subject completed Period 1 on 29 August 2014. The duration of this study period was 2 years and 5.5 months.

The primary objective for Period 1 was to show that initial treatment with CZP and MTX is more efficacious than initial treatment with placebo (PBO) and MTX based on the achievement of sustained remission at Week 52, which was defined as Disease activity score-28 joint count

erythrocyte sedimentation rate (DAS28 (ESR)) < 2.6 at both the Week 40 Visit and the Week 52 Visit.

The key secondary efficacy objective was to demonstrate that CZP + MTX was superior to PBO + MTX in achieving sustained LDA at Week 52, defined as DAS28 (ESR) ≤ 3.2 at both the Week 40 Visit and the Week 52 Visit.

Other secondary objectives were to compare the efficacy of that CZP + MTX and PBO + MTX in relation to radiographic progression, clinical response, patient-reported outcomes and productivity within and outside the home, respectively.

The study also had other efficacy objectives based on exploratory measures, PK and immunological objectives and a safety objective.

7.1.1.2. Inclusion and exclusion criteria

The main inclusion criteria were:

- Male or female aged at least 18 years old at the Screening Visit
- A positive RF or positive ACPA result at Screening
- 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
  - C-reactive protein (CRP) ≥ 10 mg/L at Screening and/or erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour (h) at Screening and Baseline
- 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
- DMARD-naïve at Screening and Baseline (except anti-malarials)

The main exclusion criteria were:

- Female subjects who were breastfeeding, pregnant, or planned to become pregnant during the study or within 6 months of the last dose of study medication
- The presence of a secondary, non-inflammatory musculoskeletal condition which was considered to interfere with the evaluation of the effect of the study medication on the subject's RA
- A diagnosis of any other inflammatory arthritis or Steinbrocker IV functional capacity
- The use of prior medication of specific drug classes within specified periods
- The presence of one or more medical history exclusions including malignancy, blood dyscrasias, congestive heart failure, demyelinating disease of the central nervous system, active infection, active or latent tuberculosis (TB) or high risk of being infected with *Mycobacterium tuberculosis*.

Comment: The proposed indication is:

> *'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.'*
>
> Adult-onset RA was defined by the 2010 ACR/EULAR classification criteria. It is not clear if Australian rheumatologists use these criteria.
>
> The sponsor indicates that the inclusion criteria of the study selected a subset of moderate to severe DMARD-naïve subjects at higher risk for rapid progression.

Based on the information provided by the sponsor, a DAS28 (ESR) value of > 3.2 to ≤ 5.1 reflects moderate disease activity and a DAS28 (ESR) value of > 5.1 reflects severe/high disease activity. The sponsor highlights that risk of rapid progression may be indicated by a CRP level ≥ 6 mg/L and ESR ≥ 28 mm/h, and that DAS28 > 4.02 and a swollen joint count ≥ 3 are predictive of rapid progression. The sponsor indicates that ACPA and RF are variables that are predictive of the degree of radiological progression over the first year of RA and that CPR and ESR are correlated with severity. The sponsor also indicates that very active disease and early structural damage are prognostic indicators of a higher likelihood of rapid, progressive disease and that erosions indicate progressive disease. Active RA disease was defined in the inclusion criteria as shown above.

The sponsor is requested to clarify the definition of severe, active, progressive RA in the proposed indication.

The study population was chosen to reflect patients with early progressive active RA. The proposed indication does not specify a timeframe since diagnosis in which concomitant CZP + MTX can be initiated. In this study subjects were to have had 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. It is acknowledged that it is unlikely that adult patients with severe, active and progressive rheumatoid arthritis would not have had any previous DMARD treatment if the time since the diagnosis of RA was more than one year. Nonetheless, to reflect the study population in Study C-EARLY, consideration should be given to amending the proposed indication to specify that patients are to have a time since RA diagnosis of less than one year.

7.1.1.3. Study treatments

Study treatments were:

- CZP + MTX: CZP 400 mg at Weeks 0, 2 and 4 + MTX followed by CZP 200 mg every 2 weeks + MTX
- PBO + MTX: PBO 2 syringes at Weeks 0, 2 and 4 + MTX followed by PBO 1 syringe every 2 weeks + MTX

MTX was initiated at randomisation (Week 0) at a dosage of 10 mg/week. The dosage was to be escalated by 5 mg every two weeks to a maximum dosage of 25 mg/week, achieved by Weeks 6 to 8. Titration of the dose took into consideration the subject's medical history, medical conditions and concomitant therapies. 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. After the escalation period (Week 0 to Week 8), subjects were to receive MTX 15 mg/week or higher. If the subject did not tolerate MTX 15 mg/week after Week 8, a number of steps could be taken including a temporary reduction in MTX to 10 mg/week for 2 weeks. The subject was withdrawn from the study if he/she was not tolerating a MTX dosage of 15 mg/week when it was reintroduced.

CZP or PBO were administered until Week 50 and MTX was continued and taken at Week 51.

CZP was supplied in a 200 mg/mL pre-filled syringe and was administered by subcutaneous (SC) injection. PBO was supplied in a pre-filled syringe of 0.9% saline solution and was administered by SC injection. MTX was supplied as 2.5 mg tablets and were administered orally.

Subjects were withdrawn from the study at Week 20, if they had not achieved an improvement in disease activity, defined as a DAS28 (ESR) ≤ 0. The Week 52 assessments were undertaken at the Withdrawal Visit.

A sufficient improvement in disease activity was defined as Low Disease Activity (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. In Sweden, an additional evaluation was done at Week 36 and if a subject was not in LDA, he/she was withdrawn and the Week 52 assessments were undertaken. Based on a local protocol amendment, the definition of sufficient improvement in disease activity was different in Sweden (DAS28 (ESR) ≤ 3.2 and/or improvement in DAS28 (ESR) ≥ 1.2 points compared with Baseline and a DAS28 (ESR) < 5.1) compared with the definition above used in other countries.

At Week 52, in all centres, subjects who were in sustained LDA, and who had been randomised to CZP + MTX in Period 1, were re-randomised to a standard maintenance dose of CZP + MTX (CZP 200 mg every 2 weeks + MTX), a reduced frequency dosing of CZP + MTX (CZP 200 mg every 4 weeks/PBO one syringe every 4 weeks (with CZP and PBO administration to be staggered two weeks apart) + MTX) or CZP stopped dosing + MTX (PBO one syringe every 2 weeks + MTX) for Period 2 of the study. Subjects who were randomised to PBO + MTX in Period 1, and who were in sustained LDA at Week 52, continued PBO + MTX treatment in Period 2 (as shown in Figure 5, above). Subjects who were not at least in sustained LDA at Week 52 stopped participation in the study and the Week 52 assessments were performed.

If subjects were on anti-malarial medication, this medication was ceased at the Screening Visit.

Prohibited medications during the study were non-biologic DMARDs other than MTX, biologic DMARDs except the study medication, live or attenuated vaccines (not allowed 8 weeks prior to Baseline or during the study), any experimental therapy, intra-articular hyaluronic acid, and intra-articular corticosteroids except as rescue medication.

During the study, rescue medication for RA, according to specified doses and conditions, was permitted, as were medications other than those that were prohibited, and medicinal formulations of folic acid or leucovorin. Rescue medications were intra-articular corticosteroids, analgesics or opioids, NSAIDs/cyclo-oxygenase-2 (COX-2) inhibitors, topical anaesthetic creams and licensed NSAID creams.

Comment: The results of Study C-EARLY may not be generalisable to the target population of the proposed indication. Subjects in Study C-EARLY who did not tolerate at least 15 mg MTX/week during the first 8 weeks of the study were withdrawn from the study, and MTX was titrated according to a protocol-defined regimen. If CZP + MTX were to be initiated concomitantly in clinical practice, it is possible that the ongoing dose of MTX after titration could be less than 15 mg weekly. However, given the target patient population of the proposed indication have severe, active and progressive RA, it is anticipated that the dose of MTX prescribed in the majority of patients would, if tolerated, be the maximum recommended dose. If CZP and MTX were to be initiated concomitantly, it is also possible that Australian prescribers may not titrate MTX in exactly the same way as was done in this study.

It is not clear to the clinical evaluator how many subjects in each treatment group were withdrawn from the study because they did not tolerate at least 15 mg MTX/week during the first 8 weeks of the study. The sponsor is requested to clarify the location of this information in the CSR or provide this information.

Subjects in Sweden were more likely to be withdrawn from the study than subjects in other countries as the definition of sufficient improvement in disease activity was more stringent and an additional evaluation was undertaken at Week 36 and subjects not in LDA were withdrawn. This may have biased the results. However, only 15 subjects were randomised in Sweden and therefore comprise only a small proportion (1.7%) of the overall randomised subject population. The sponsor is requested to confirm this.

7.1.1.4. Efficacy variables and outcomes

Efficacy variables related to the signs and symptoms of RA, the inhibition of progression of structural damage, physical functioning, tiredness/fatigue, productivity at the workplace and within the household and health-related quality of life.

The main efficacy variable was DAS28 (ESR). The components of the DAS28 (ESR) were tender joint count (TJC), swollen joint count (SJC), ESR (mm/h), and the Patient's Global Assessment of Disease Activity (PtGADA) (visual analog scale in mm). The DAS28 (ESR) was calculated using the following formula copied from the amended CSR for Study C-EARLY (Ra0055) Period 1:

$$0.56 \times \sqrt{(TJC)} + 0.28 \times \sqrt{(SJC)} + 0.70 \times \text{lognat (ESR)} + 0.014 \times PtGADA$$

The DAS28 (ESR) calculations were undertaken by the interactive voice/web response system (IXRS) at the Week 0, 20, 25, 36 (Sweden only), 40 and 52 Visits. The DAS28 (ESR) determined the subject's treatment. The ESR value was entered into the IXRS by the unblinded study centre personnel who had performed the measurement. Study centre personnel also entered into the IXRS the Patient's Global Assessment of Disease Activity (PtGADA) measurement, the SJC and TJC.

Efficacy variables related to the key secondary efficacy outcomes and secondary outcomes that the sponsor proposes to report in the PI were:

- Van der Heijde modified total Sharp score (mTSS)
- Joint erosion score
- Joint narrowing score
- American College of Rheumatology (ACR) 50% response (ACR50), ACR 70% response (ACR70)
- Health Assessment Questionnaire: Disability Index (HAQ-DI)
- Patient's Assessment of Arthritis Pain (PtAAP)

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 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 efficacy outcomes that the sponsor proposes to report in the PI are:

- ACR50 response at Week 52 in relation to Baseline
- The change from Baseline in HAQ-DI at Week 52
- The change from Baseline in mTSS at Week 52
- The change from baseline in DAS28 (ESR) by week
- The proportion of subjects in remission based on DAS28 (ESR) < 2.6 at Week 12, Week 24 and Week 52
- The proportion of subjects achieving LDA (DAS28 (ESR) ≤ 3.2) at Week 12, Week 24 and Week 52
- The proportion of subjects with ACR50 at Week 12, Week 24 and Week 52
- The proportion of subjects with ACR70 at Week 12, Week 24 and Week 52
- The change from Baseline in joint erosion score at Week 52
- The change from Baseline in joint space narrowing score at Week 52

- The change from Baseline in PtAAP at Week 52
- The proportion of subjects reaching normative physical function (HAQ-DI score ≤ 0.5)
- The proportion of subjects with radiographic non-progression (mTSS ≤ 0.5) from Baseline at Week 52

There were additional secondary clinical variables and patient-reported variables assessed at Week 12, Week 24 and Week 52/Withdrawal Visit as well as a number of other efficacy outcomes.

Comment: It appears that DAS28 (ESR) was chosen by the sponsor as the primary efficacy variable as the aim of the study was to evaluate the efficacy and safety of CZP + MTX as first line treatment in inducing and sustaining clinical remission, and in limiting radiographic progression, in DMARD-naïve adults with active early RA. Sustained remission, the primary efficacy outcome, was defined using DAS28 (ESR).

The primary efficacy outcome is stringent. The primary efficacy variable is consistent with the tools to measure efficacy (primary and secondary endpoints) described in the Points to Consider on Clinical Investigation of Medicinal Products Other than NSAIDs for Treatment of Rheumatoid Arthritis.[11]

7.1.1.5. Randomisation and blinding methods

At Baseline (Week 0), subjects were randomly assigned to either CZP + MTX or PBO + MTX in a ratio of 3:1. Randomisation was stratified by time since the diagnosis of RA at Baseline (≤ 4 months, > 4 months). Randomisation was undertaken centrally and used an IXRS.

The sponsor, investigator, study centre personnel, and vendor staff who were involved in the study, were blinded to treatment assignment. There were a number of exceptions. Of note, if a subject was unable to self-administer CZP (or PBO), or did not have someone to assist with study drug administration, the subject could attend the study centre to have the study medication administered but the person performing the administration was unblinded because the viscosity of CZP and PBO were different. These unblinded study centre personnel were also required to determine the ESR. Also of note, the laboratory staff who analysed the CRP concentration and recorded the ESR values received from study centres were also not blind to the treatment assignment.

Unblinding occurred in Period 1 after the Week 52 database lock which occurred after all subjects had completed the Week 52 assessments and, if applicable, safety follow-up phone call 10 weeks after the last dose.

There were 3 global protocol amendments, as described in Table 2, below.

[11] Committee for Proprietary Medicinal Products. Points to Consider on Clinical Investigation of Medicinal Products Other than NSAIDs for Treatment of Rheumatoid Arthritis. CPMP/EWP/556/95 rev 1/Final. Replaces CPMP/EWP/556/95 (adopted by the TGA February 2001). Effective: 29 January 2007. TGA, Canberra.

Table 2. Study C-EARLY, global protocol amendments

Protocol version	Summary of main changes
Original protocol dated 25 October 2011	
Global protocol amendment 1 27 July 2012	· Incorporation of updated detection and monitoring policy · Stipulation of contraception use after the last dose of study treatment was extended · The exclusion criterion was extended for female subjects who were breast feeding, pregnant, or who planned to become pregnant during the study or within 6 months following the last dose of study treatment. · Clarification of the length of the screening period, the packaging and labelling of MTX and the re-screening of subjects
Global protocol amendment 2 6 February2013	· The PBO + MTX arm of Period 1 was prolonged in Period 2 to Week 104 · Updates to the statistical section following the development of the SAP · In sections related to Period 2, PBO + MTX nomenclature was replaced with MTX + CZP stopped dosing · Serious AE reporting details were changed
Global protocol amendment 3 13 January 2014	· Additional endpoints were added for Period 1 and Period 2 · Additional subgroups were considered for analyses · Predictability analyses were added · A 'completer' analysis set for Period 1 was added and associated sensitivity analyses were added · Details of multiple comparisons/multiplicity were added · TB language was expanded and inorganic phosphorus was changed to phosphorous in laboratory analyses

There were 6 local protocol amendments, of note the definition of sufficient improvement in disease activity was different in Sweden (see section: Study treatments for this study, above) and in both France and Sweden, additional laboratory parameter monitoring in relation to MTX was added to the protocol.

Comment: As unblinded study centre personnel performed the ESR measurement and entered the ESR value into the IXRS, and the laboratory staff who recorded the ESR values received from study centres were also not blind to the treatment assignment, this may be a potential source of bias. The sponsor is requested to comment.

Not all subjects were subject to exactly the same protocol as local protocol amendments were made in a number of countries. It is possible that this may have

introduced bias. For example, in France, an exclusion criterion was amended to exclude subjects with a known allergy to MTX or its excipients, gluten hypersensitivity or intolerance due to the presence of gluten.

7.1.1.6. Analysis populations

The analysis sets for Period 1 are described in Table 3, below.

Table 3. Study C-EARLY, analysis population sets

Analysis Set	Population
Enrolled Set 1 (ES1)	All subjects who had given informed consent
Pharmacokinetic Set 1 (PKS1)	Subjects in the ES1 who had received at least one dose of CZP and had provided at least one PK sample.
Randomised Set 1 (RS1)	All subjects randomised into Period 1.
Safety Set 1 (SS1)	All subjects in RS1 who had received at least one dose of study medication (CZP or PBO).
Full Analysis Set Period 1 (FAS1)	All subjects who had both a valid Baseline and valid post-Baseline efficacy measurement within Period 1 for the primary efficacy assessment of DAS28 (ESR).
Radiographic Set Period 1 (RAD1)	Subjects in the FAS1 who had provided valid radiographs (radiographs with a non-missing mTSS score) at Baseline and at Week 52 or at the Withdrawal Visit.
Per-Protocol Set Period 1 (PPS1)	Subjects in the FAS1 who did not have any important protocol deviations that would have influenced the validity of the data.
Completer Set Period 1 (CS1)	Subjects in the FAS1 who had completed to Week 52.

7.1.1.7. Sample size

For the primary efficacy outcome in Period 1, the expected percentages of subjects in sustained DAS28 (ESR) remission at Week 52 were 50% for the standard maintenance dose of CZP + MTX group and 30% in the PBO + MTX group. It was estimated by the sponsor that 600 subjects in the CZP + MTX treatment group and 200 subjects in the PBO + MTX treatment group would result in 99% power to detect a difference given an alpha = 0.05 and a 3:1 randomisation. The sponsor indicates that to compute this superiority sample size and power, a 2-group continuity-corrected chi-square test with a 2-sided alpha value of 0.05 was used.

The sponsor planned to enrol a total of 800 subjects in the study.

Comment: The sponsor indicates, in the Clinical Overview, that there was no precedent on which to directly base assumptions regarding the proportions of subjects in each treatment group expected to be in sustained DAS28 (ESR) remission at Week 52.

Only 500 subjects in the CZP + MTX group and 143 subjects in the PBO + MTX group completed Week 52. In addition, the actual proportions of subjects in sustained DAS28 (ESR) remission at Week 52 (PBO + MTX 15.0%, CZP + MTX 28.9%) were lower than assumed for the sample size calculation and the difference between the

groups was smaller. Despite the reduced power, there was a statistically significant difference between the treatment groups based on the results of the primary analysis of the primary efficacy outcome.

7.1.1.8. Statistical methods

Hypothesis testing was performed in a hierarchical order to control the overall study-wise Type 1 error rate at 5%. The pre-defined order was as follows and each hypothesis test was performed at a 2-sided 95% alpha level:

1. Primary efficacy outcome: sustained DAS28 (ESR) remission at Week 52
2. Key secondary efficacy outcome: sustained DAS28 (ESR) LDA at Week 52
3. ACR50 response at Week 52 in relation to Baseline
4. Change from Baseline in HAQ-DI at Week 52
5. Change from Baseline in mTSS at Week 52

For the other efficacy outcomes, no adjustment for multiple comparisons was made. The sponsor highlights that significance testing was performed, and presented, only for descriptive purposes.

No interim analyses were undertaken for Period 1. As the study had two parts with different objectives and different randomisation schemes, and the analysis of the Period 1 data included data from all subjects after they had terminated Period 1, the analysis of the Period 1 data was not considered to be an interim analysis by the sponsor.

Non-responder imputation (NRI) was used for analyses of sustained remission rates and LDA rates and for a number of dichotomous variables. A subject with missing data for a given assessment time point was counted as a non-remitter or non-responder. A subject with Week 40 and Week 52 Visits that met certain criteria were also counted as a non-remitter or non-responder. If rescue medication was required, efficacy data collected at assessments immediately after such medication use were treated as missing for that visit.

For subjects who withdrew before Week 52 and who had radiographs at their Withdrawal Visit, linear extrapolation was used to estimate the mTSS score at Week 52.

Last observation carried forward (LOCF) was used to impute missing data for a number of the efficacy variables.

For the DAS28 (ESR) calculation, missing individual item scores were imputed. If an individual component score was missing, the DAS28 (ESR) was set to missing. ESR = 1 was substituted into the DAS28 calculation if ESR = 0. For the TJC and SJC assessments, if there were missing observations at a specific measurement time point the remaining observations were assessed and weighted by dividing by the number of non-missing values and multiplying by 28. If more than 50% of the tenderness grades or swelling grades, respectively, were missing, then the total TJC or SJC was set to missing.

The FAS1 was used to summarise the efficacy data from Period 1 except for the radiographic analyses which were based on the RAD1.

Comment: Information about the hierarchical test procedure was added to the protocol in global protocol amendment 3. This amendment to the protocol was made before the end of the study.

Efficacy analyses: Primary efficacy outcome

For the primary efficacy outcome, the primary Week 52 analysis was undertaken using a logistic regression model including terms for treatment, region and the stratification factor, time since RA diagnosis at Baseline. From this model, the odds ratio measuring treatment effect was

estimated and was presented with the 95% 2-sided CI and p-value. This analysis was performed on the FAS1. Non-responder imputation was used. The PPS1 (with imputation) and CS1 (with imputation) were used for sensitivity analyses on the primary efficacy outcome. Subgroup analyses were also undertaken for the primary efficacy outcome.

Key secondary efficacy outcome

For the key secondary efficacy outcome, analysis was undertaken using a logistic regression model including terms for treatment, region and time since RA diagnosis at Baseline. The odds ratio measuring treatment effect was estimated and was presented with the 95% 2-sided CI and p-value. This analysis was performed on the FAS1. Non-responder imputation was used. CS1 (with imputation) was used for the sensitivity analysis. A subgroup analysis by time since RA diagnosis at Baseline was undertaken.

Other secondary efficacy outcomes in the pre-defined hierarchical hypothesis testing

In relation to the other secondary efficacy outcomes included in the pre-defined hierarchical hypothesis testing:

ACR50 response at Week 52 in relation to Baseline: was analysed using a logistic regression model including terms for treatment, region and time since RA diagnosis at Baseline. The odds ratio measuring treatment effect was estimated and was presented with the 95% 2-sided CI and p-value. Non-responder imputation was used. A subgroup analysis by time since RA diagnosis at Baseline was undertaken.

Change from Baseline in HAQ-DI at Week 52: was analysed using an Analysis of Covariance (ANCOVA) model with terms for treatment, region and time since RA diagnosis at Baseline as factors and Baseline value as a covariate. The difference in LS means and the 95% 2-sided CIs were presented.

C*hange from Baseline in mTSS at Week 52*: the data were analysed using an ANCOVA model on the ranks with terms for treatment, region and time since RA diagnosis at Baseline as factors and rank Baseline value as a covariate. The Hodges-Lehmann point estimate of shift and 95% exact CI were used to estimate the treatment effect. The p-value was presented also. A subgroup analysis for time since RA diagnosis at Baseline was undertaken. A sensitivity analysis using an ANCOVA on the actual values was also performed.

Other secondary efficacy outcomes

These were analysed primarily using ANCOVA models or logistic regression models except Work Productivity Survey – Rheumatoid Arthritis (WPS-RA); a boot-strap method was used for treatment comparisons of this efficacy variable.

Treatment effect was estimated for most of the efficacy outcomes using the odds ratio and 95% CI or the difference in LS means with 95% CI. For the change from Baseline in joint erosion score at Week 52 and change from Baseline in JSN score at Week 52, respectively, the treatment effect was estimated by the Hodges-Lehmann point estimate of shift and corresponding 95% exact CI. The ratio of geometric LS means and 95% CI was used to estimate treatment effect at Weeks 12, 24 and 52 for CRP and ESR, respectively.

Other efficacy outcomes: statistical analysis methods used were generally those used for the secondary efficacy outcomes. For a number of the other efficacy outcomes, the results were summarised only.

Safety analyses

Of note, TEAEs were defined as AEs starting on or after the date of administration of the first study medication and up to 70 days after the most recent dose of CZP or PBO. TEAEs were reported as treatment-related if the relationship to the study medication was assessed as 'related' or the relationship to the study medication was missing and of severity 'severe' if the

severity had been assessed as severe or if the information was missing. Adverse event data were classified according to MedDRA SOC, HLT and PT and were summarised.

There was one amendment to the statistical analysis plan (SAP). Changes to the SAP included:

- the number of regions was reduced for statistical reasons
- the calculated time since diagnosis was specified for use rather than the IXRS value
- additional analyses were included that had not been specified in the protocol

After this amendment to the SAP, a number of changes were made to the planned analyses. These changes included:

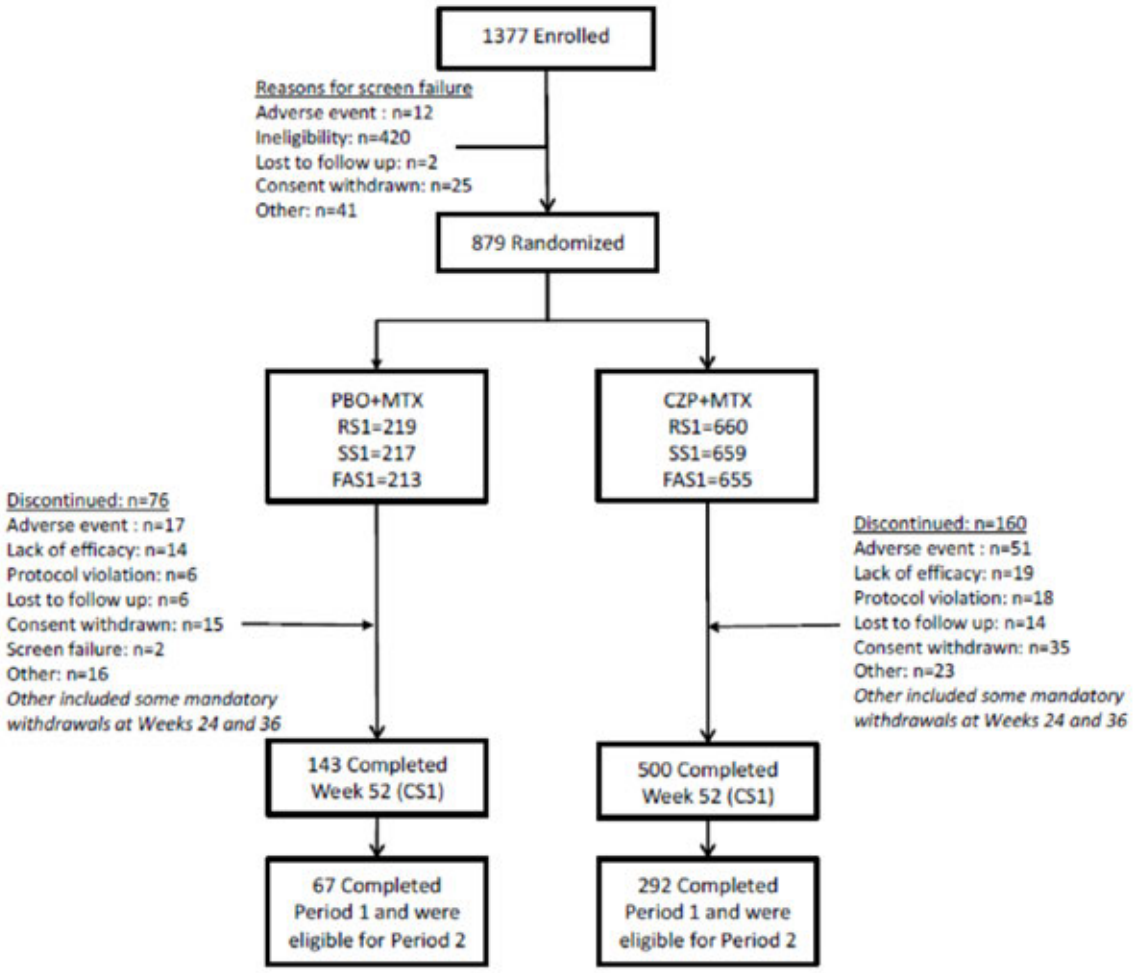
- the addition of an analysis estimating the mTSS scores at Week 52 for all subjects by linear extrapolation.
- for the radiographic variables, asymptotic (Moses) CIs were used instead of exact CIs for the Hodges-Lehmann estimate of shift
- for subjects who met the withdrawal criteria in the protocol but were not withdrawn, these subjects were to be excluded from the PPS1 but the efficacy data collected after the specified time of withdrawal were not set to missing.
- Post-hoc analyses were performed on the primary efficacy outcome based on sub-regions

Comment: It appears that subjects only had X-rays of the hands, wrists and feet, to calculate the mTSS score, at Baseline (Week 0) and Week 52/Withdrawal. With regard to the additional analysis undertaken using the RAD1 in which the Week 52 mTSS scores of all subjects were estimated by linear extrapolation of the post-Baseline mTSS scores, the sponsor is requested to clarify if this means that the Week 0 mTSS score was used to extrapolate the Week 52 score for each subject. It is not clear to the clinical evaluator how such an extrapolation would be undertaken and the sponsor is requested to provide clarification. The sponsor is also requested to clarify if there was a comparison undertaken of the change in mTSS score from Baseline between those subjects who had a change in mTSS score at Week 52 based on a Week 52 radiograph and those subjects for whom the change in mTSS score at Week 52 was estimated, stratified by treatment group. If such a comparison was undertaken, please clarify the location of the results in the CSR.

7.1.1.9. Participant flow

Participant flow is shown in Figure 6, below.

Figure 6. Study C-EARLY, Period 1: Participant flow



CS1=Completer Set Period 1; CZP=certolizumab pegol; FAS1=Full Analysis Set Period 1; LDA=low disease activity; mand w/d=mandatorily withdrawn subjects; MTX=methotrexate; PBO=placebo; RS1=Randomized Set 1; SS1=Safety Set 1

Note: Subjects completed Week 52 if they had a Week 52 Visit. Subjects completed Period 1 if they had a Week 52 Visit and were eligible for Period 2 (ie, in sustained LDA).

Note: Subjects 05991 and 06934 were randomized in error, were not dosed, and withdrawn shortly afterwards as screen failures. These 2 subjects were included in the RS1.

Of 1377 subjects who were enrolled in the study, 880 subjects were randomised. 3 subjects were randomised in error and did not receive study medication. 2 of these subjects were included in the RS1 and one subject was excluded from any output because of incomplete data on informed consent. Excluding this subject, of the 879 randomised subjects, 660 subjects were randomised to receive CZP + MTX and 219 subjects were randomised to receive CZP + MTX at Week 0. In the CZP + MTX group 500 randomised subjects (75.8%) completed Week 52 compared with 143 subjects (65.3%) in the PBO + MTX 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% (n = 292) and 30.6% (n = 67) in the PBO + MTX group.

The proportion of randomised subjects who discontinued was 34.7% (n = 76) in the PBO + MTX group compared with 24.2% (n = 160) in the CZP + MTX group. The proportion of subjects who discontinued due primarily to adverse events was similar in the two treatment groups (PBO + MTX 9.1% (n = 20), CZP + MTX 8.5% (n = 56)). Mandatory withdrawals based on the IXRS were higher in the PBO + MTX group than the CZP + MTX group at Week 20 (PBO + MTX 1.4% (n = 3), CZP + MTX 0.5% (n = 3)), Week 24 (PBO + MTX 4.1% (n = 9), CZP + MTX 1.4% (n = 9)) and Week 52 (PBO + MTX 32.9% (n = 72), CZP + MTX 29.8% (n = 197)). In Sweden, where an

additional assessment was undertaken at Week 36, only one subject (0.5% of all randomised subjects in the treatment group) in the PBO + MTX group was withdrawn compared with five (0.8% of all randomised subjects in the treatment group) in the CZP + MTX group.

The subjects contributing to each analysis set are shown in Table 4, below.

Table 4. Study C-EARLY, Period 1: Populations analysed (all subjects screened)

	Number of subjects						
	RS1	SS1	FAS1	PPS1	RAD1	CS1	PKS1
All subjects	879	876	868	809	691	643	659
PBO+MTX	219	217	213	201	163	143	0
CZP+MTX	660	659	655	608	528	500	659

CS1=Completer Set Period 1; CZP=certolizumab pegol; FAS1=Full Analysis Set Period 1; MTX=methotrexate; PBO=placebo; PKS1=Pharmacokinetic Set 1; PPS1=Per Protocol Set Period 1; RAD1=Radiographic Set Period 1; RS1=Randomized Set 1; SS1=Safety Set 1

Comment: The sponsor is requested to clarify the proportion of subjects in each treatment group who received the scheduled study treatment up to Week 52 but were not eligible for Period 2.

The sponsor is requested to clarify if the CS1 includes subjects who discontinued and had a Withdrawal Visit in place of the Week 52 visit.

With regard to the results for mandatory IXRS withdrawals at key visits, results in tables in amended CSR and tables in other documents differ. The sponsor is requested to clarify why the results are different.

The numbers of subjects by discontinuation reason 'adverse event' are not identical in the participant flow diagram in the amended CSR of Study C-EARLY (PBO + MTX n = 17, CZP + MTX n = 51) (see Figure 6 above) compared with a table in the amended Period 1 table set for Study C-EARLY (PBO + MTX n = 20, CZP + MTX n = 56). The sponsor is requested to clarify why the results are different.

The proportion of subjects who completed Period 1 varied between regions (Eastern Europe 57.2% (n = 123), Western Europe and Australia 50.6% (n = 127), North America 23.1% (n = 71), Latin America 39.6% (n = 42)).

7.1.1.10. Major protocol violations/deviations

The proportions of subjects in each treatment group who had at least one important protocol deviation were similar in the two treatment groups (PBO + MTX 18.3% (n = 40); CZP + MTX 16.4% (n = 108)). The proportions of subjects in each treatment group with important protocol deviations for safety, efficacy, and conduct, respectively, were also similar. Major protocol deviations included medication compliance, incorrect treatment and violation of exclusion criteria and inclusion criteria.

The sponsor highlights that the CRP values for 160 CRP test results were unblinded unintentionally but considers that these findings are not important protocol deviations as the Investigator would not have been able to have determined with certainty the study treatment the subject was receiving based on the CRP value.

Comment: The sponsor's rationale as to why it considers the unblinding of the CRP values is not an important protocol deviation seems reasonable.

Subjects with important protocol deviations for efficacy were excluded from the PPS. Therefore the effect of these deviations can be seen by comparing the results for the primary efficacy outcome in the FAS1 and the PPS1.

It is noted that a number of subjects had protocol deviations that related to not meeting aspects of the criteria for active disease in the inclusion criteria.

7.1.1.11. Baseline data

Based on the SS1, the mean (SD) age of all subjects (N = 876) was 50.6 (13.5) years. The age range was 18 years to 90 years and the median 52.0 years. All subjects were at least 18 years of age at the time of Screening. Only 15.1% of subjects (n = 132) were aged 65 years or older. The majority of subjects were women (76.7% (n = 672)), 'white' (86.3% (n = 756) and of non-Hispanic or Latino ethnic origin (79.0% (n = 692)). Approximately half of the subjects were in Europe and Australia (53.0% (n = 464)) and half in Latin and North America (47.0% (n = 412)).

The majority of subjects (75.9% (n = 665)) had a calculated time to diagnosis of RA ≤ 4 months. The calculated time was the time from the date of first diagnosis or first symptoms of RA to the date of Baseline. The proportion of subjects with a time since first diagnosis of RA ≤ 4 months in the IXRS was lower (71.1% (n = 623)). The sponsor indicates that the randomisation (IXRS) stratification factor of time since RA diagnosis was not accurate after adjusting for a window of ± 7 days for 95% of subjects, therefore, calculated time since RA diagnosis was used in the analyses. The median calculated time since first diagnosis of RA was 1.63 months (range 0.0, 98.9; mean 2.87 (4.27)). One subject had a time since RA diagnosis of 98.9 months and was excluded from the PPS1. The median calculated time since first symptoms of RA was 6 months in both treatment groups (PBO + MTX: range 0, 83, mean (SD) 9.6 (11.9), CZP + MTX: range 0, 509, mean (SD) 12.3 (32.2)).

Overall, 6.1% (n = 53) had a history of at least one extra-articular feature of RA and 6.7% (n = 59) had at least one extra-articular feature of RA at Screening.

The demographic attributes of subjects in the SS1 were generally similar between the PBO + MTX and CTP + MTX groups. Of note, there was a higher proportion of females in the PBO + MTX group compared with the CZP + MTX group (PBO + MTX 80.2% (n = 174), CZP + MTX 75.6% (n = 498)) and vice versa for males (PBO + MTX 19.8% (n = 43), CZP + MTX 24.4% (n = 161)). A higher proportion of subjects in the PBO + MTX group had a body mass index (BMI) of ≥ 30 (PBO + MTX 35.5% (n = 77), CZP + MTX 31.4% (n = 207)). The baseline characteristics of subjects in the SS1 were generally similar between the PBO + MTX and CZP + MTX groups also. Overall, 96.8% (n = 848) of subjects were RF positive (≥14 IU/mL) and 84.0% (n = 736) were ACPA positive (≥ 7 IU/mL). The median RF value (IU/mL) was higher in the PBO + MTX group than in the CZP + MTX group (PBO + MTX: median 108.50 (range 11.0, 2295.0), mean (SD) 244.09 (345.77), CZP + MTX: median 95.00 (range 3.5, 5421.0), mean (SD) 210.02 (365.60)). Median ACPA values (IU/mL) were similar in the two groups (PBO + MTX: median 243.60 (range 0.2, 14072.2), mean (SD) 724.20 (1444.33), CZP + MTX: median 203.10 (range 0.2, 7608.9), mean (SD) 511.91 (867.96)). The baseline data based on the FAS1 were consistent with those based on the SS1.

A summary of the baseline characteristics of RA of the subjects are shown in Table 5, below. Baseline characteristics of RA were also generally comparable in the two groups based on the FAS1. The majority of all subjects (96.5% (n = 838)) had high DAS28 (ESR) disease activity, defined as a DAS28 (ESR) > 5.1. Based on all subjects, the mean (SD) DAS28 (ESR) score was 6.722 (0.897) and the mean (SD) SJC and TJC values, each based on 28 joints, were 12.53 (5.52) and 15.76 (6.47), respectively. The median HAQ-DI at baseline was 1.750 in the PBO + MTX and 1.625 in the CZP + MTX group. The range was the same in each group (0.00, 3.00). At Baseline, the median mTSS was 2.8 (range 0, 161; mean (SD) 8.5 (17.5)) in the PBO + MTX group and 3.0 (range 0, 130; mean (SD) 7.2 (13.8)) in the CZP + MTX 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 (range 0, 69, mean (SD) 4.4 (8.0)) and median JSN value was 0.0 (range 0, 94; mean (SD) 3.1 (7.8)). The majority of subjects had erosions at Baseline (77.8% (n = 675)).

Based on the RAS1, the results for the baseline radiographic assessments (mTSS, erosion score, JSN and presence of erosions) were similar to those based on the FAS1.

Table 5. Study C-EARLY, Period 1: Summary of Baseline characteristics of RA (FAS1)

	PBO+MTX N=213	CZP+MTX N=655	All subjects N=868
DAS28(ESR)			
n	213	655	868
Mean (SD)	6.797 (0.907)	6.697 (0.893)	6.722 (0.897)
Median	6.855	6.704	6.753
Min, max	4.44, 9.07	3.89, 9.04	3.89, 9.07
DAS28(ESR) disease activity, n (%)			
Moderate: >3.2 to ≤5.1	10 (4.7)	20 (3.1)	30 (3.5)
High: >5.1	203 (95.3)	635 (96.9)	838 (96.5)
SJC (based on 28 joints)			
n	213	655	868
Mean (SD)	13.04 (5.64)	12.37 (5.48)	12.53 (5.52)
Median	13.00	12.00	12.00
Min, max	4.0, 28.0	2.0, 28.0	2.0, 28.0
TJC (based on 28 joints)			
n	213	655	868
Mean (SD)	16.22 (6.45)	15.61 (6.48)	15.76 (6.47)
Median	16.00	15.00	15.00
Min, max	4.0, 28.0	4.0, 28.0	4.0, 28.0
PtGADA			
n	213	655	868
Mean (SD)	65.3 (22.6)	65.3 (21.8)	65.3 (22.0)
Median	67.0	69.0	69.0
Min, max	2, 100	0, 100	0, 100
PhGADA			
n	213	653	866
Mean (SD)	68.6 (17.0)	67.5 (16.2)	67.7 (16.4)
Median	72.0	70.0	70.0
Min, max	12, 100	3, 100	3, 100
PtAAP			
n	213	654	867
Mean (SD)	66.4 (22.9)	66.0 (22.3)	66.1 (22.4)
Median	71.0	71.0	71.0
Min, max	2, 100	0, 100	0, 100
HAQ-DI			
n	213	654	867
Mean (SD)	1.688 (0.647)	1.610 (0.607)	1.629 (0.618)
Median	1.750	1.625	1.750
Min, max	0.00, 3.00	0.00, 3.00	0.00, 3.00
mTSS			
n	212	651	863
Mean (SD)	8.5 (17.5)	7.2 (13.8)	7.5 (14.8)
Median	2.8	3.0	3.0
Min, max	0, 161	0, 130	0, 161

Table 5. (continued) Study C-EARLY, Period 1: Summary of Baseline characteristics of RA (FAS1)

	PBO+MTX N=213	CZP+MTX N=655	All subjects N=868
Erosion score			
n	212	651	863
Mean (SD)	4.7 (8.3)	4.3 (7.9)	4.4 (8.0)
Median	1.5	1.5	1.5
Min, max	0, 68	0, 69	0, 69
JSN			
n	212	651	863
Mean (SD)	3.8 (10.4)	2.9 (6.8)	3.1 (7.8)
Median	0.0	0.0	0.0
Min, max	0, 94	0, 76	0, 94
Presence of erosions, n (%)			
Yes	169 (79.3)	506 (77.3)	675 (77.8)
No	43 (20.2)	145 (22.1)	188 (21.7)
Missing	1 (0.5)	4 (0.6)	5 (0.6)
BRAF-MDQ total score			
n	211	652	863
Mean (SD)	32.6 (15.7)	31.8 (15.4)	32.0 (15.5)
Median	32.0	32.0	32.0
Min, max	0, 70	0, 70	0, 70
CDAI			
n	213	653	866
Mean (SD)	42.64 (12.87)	41.28 (12.52)	41.62 (12.61)
Median	42.80	40.80	41.20
Min, max	10.4, 74.9	14.2, 73.5	10.4, 74.9
SDAI			
n	213	653	866
Mean (SD)	44.79 (13.91)	43.46 (13.56)	43.79 (13.65)
Median	44.84	42.50	43.32
Min, max	10.5, 91.5	16.4, 89.7	10.5, 91.5
CRP (mg/L)			
n	213	655	868
Mean (SD)	21.49 (27.91)	21.73 (29.47)	21.67 (29.08)
Median	10.51	11.14	11.10
Min, max	0.3, 243.2	0.2, 231.1	0.2, 243.2
ESR (mm/h)			
n	213	655	868
Mean (SD)	50.76 (22.23)	50.18 (24.67)	50.32 (24.08)
Median	44.00	42.00	43.00
Min, max	10.0, 135.0	2.0, 150.0	2.0, 150.0

BRAF-MDQ=Bristol Rheumatoid Arthritis Fatigue-Multidimensional Questionnaire; CDAI=Clinical Disease Activity Index; CRP=C-reactive protein; CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; ESR=erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; HAQ-DI=Health Assessment Questionnaire-Disability Index; JSN=joint space narrowing; Min=minimum; max=maximum; mTSS=modified total Sharp score; MTX=methotrexate; PBO=placebo; PhGADA=Physician's Global Assessment of Disease Activity; PtAAP=Patient's Assessment of Arthritis Pain; PtGADA=Patient's Global Assessment of Disease Activity; RA=rheumatoid arthritis; SD=standard deviation; SDAI=Simplified Disease Activity Index; SJC=swollen joint count; TJC=tender joint count

Note: The TJC and SJC each have a possible range of scores from 0 to 28 with lower scores indicating less tenderness and swelling, respectively. The PtGADA, PhGADA, and PtAAP each have a possible range of scores from 0 to 100 with higher scores indicating a worse state. The HAQ-DI total score has a possible range from 0 to 3 with lower scores indicating less disability (ie, physical functioning). The mTSS has a possible range from 0 to 448 with lower scores meaning less structural damage in the hands and feet. The total joint erosion score has a possible range from 0 to 280 with lower scores meaning less joint erosion in the hands and feet. The total JSN score has a possible range from 0 to 168 with lower scores meaning less JSN in the hands and feet. The BRAF-MDQ total score has a possible range from 0 to 70 with higher scores indicating worse fatigue.

Based on FAS1, CRP and ESR values at baseline were, respectively, comparable in the two treatment groups (CRP (mg/mL): PBO + MTX mean (SD) 21.49 (27.91), median 10.51 (range 0.3, 243.2), CZP + MTX mean (SD) 21.73 (29.47), median 11.14 (range 0.2, 231.1); ESR (mm/h): PBO + MTX mean (SD) 50.76 (22.23), median 44.00 (range 10.0, 135.0), CZP + MTX mean (SD) 50.18 (24.67), median 42.00 (range 2.0, 150.0)).

Based on the SS1, 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. Nearly all subjects reported use of any prior medication (93.9% (n = 823)). One subject in each treatment group had a history of prior use of anti-malarial medication. A concomitant medication was taken on at least one day in common with the study medication by nearly every subject (98.7% (n = 865)). The proportions of subjects in each treatment group using concomitant medication based on anatomical main groups and pharmacological subgroups were generally similar and any differences between the groups were not notably large. Of note, a higher proportion of subjects in the CZP + MTX group were receiving concomitant medication that fell within the Anatomic Therapeutic Chemical Level 3 code 'beta-lactam anti-bacterials, penicillins' (PBO + MTX 9.7% (n = 21); CZP + MTX 15.8% (n = 104)) which the sponsor highlights is to be expected as CZP is associated with an increased risk of infection. For many of the specific concomitant medications, only one subject in the study was taking the medication. Non-steroidal anti-inflammatory and anti-rheumatic products were used concomitantly by 68.2% (n = 148) of subjects in the PBO + MTX group and 69.8% (n = 460) of subjects in the CTP + MTX group. Folic acid was used by 74.2% (n = 650) of subjects overall and the proportion of subjects using folic acid was the same in each treatment group.

Based on FAS1, the majority of subjects (83.6% (n = 726)) did not use rescue medication during the study. Of the 142 subjects who did, the proportions of subjects in each group were comparable (PBO + MTX 16.0% (n = 34), CTP + MTX 16.5% (n = 108)). The proportions of subjects using rescue medication from a specific drug class were also similar.

During the study no subjects used prohibited medications.

Relative to the first injection, a similar proportion of subjects in each treatment group received the study treatment in compliance with the protocol, having a compliance ratio between 0.8 and 1.0 (PBO + MTX 84.8% (n = 184), CZP + MTX 82.7% (n = 545)). The compliance ratio was calculated as the study duration in days minus the total number of days deviated from schedule divided by the study duration in days.

Comment: The proposed indication relates to patients with severe, active and progressive RA. It is noted that although the inclusion criteria allowed subjects with moderate and severe RA (based on DAS 28(ESR) > 3.2) to enter the study, the majority of subjects (96.5% (n = 838)) had severe RA based on DAS28 (ESR) > 5.1. Subjects were required to have had active RA disease as defined in the inclusion criteria of the study (see Section 7.1.1.2). With regard to the definition of active disease in the inclusion criteria, the mean and median number of swollen and tender joints at Screening, and the mean and median DAS28 (ESR), CRP and ESR values, respectively, at Screening do not appear to be presented in the submission. The sponsor is requested to provide comment on this point.

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. In the overall study population, at Baseline, the mean number of swollen joints and tender joints, the mean DAS 28(ESR), the mean and median CRP values and ESR values, were all notably higher than the cut-off values for these

parameters used to define active disease for the inclusion criteria. The mean ACPA and RF values were also much higher than the cut-off values used to determine that a subject was RF positive (≥ 14 IU/mL) and ACPA positive (≥ 7 IU/mL), respectively.

It is not clear what proportion of subjects in each treatment group had RA that was severe and active and progressive. The sponsor is requested to clarify the location of this information in the CSR or provide it.

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.

By region, not all demographic and baseline characteristics were similar in each of the treatment groups. Of note, for the region Eastern Europe, a notably higher proportion of subjects has a RF > 42 IU/mL in the PBO + MTX group compared with the CZP + MTX group (PBO + MTX 76.8% (n = 43), CZP + MTX 61.0% (n = 97)).

The calculated time to diagnosis was the time from the date of first diagnosis, or first symptoms of RA, to the date of Baseline. The dates of the subjects' first symptoms of RA may be subject to recall bias.

It is possible that some subjects were receiving non-pharmacological management of RA, such as exercise therapy. As this was a randomised trial, it is likely that the proportions of subjects in each treatment group who were receiving non-pharmacological management of RA were similar. It is unlikely that a small difference in the proportion of subjects in each group receiving non-pharmacological treatments would have had an appreciable impact on the results of the primary efficacy outcome. The sponsor is requested to clarify if subjects were permitted to receive non-pharmacological management of RA and, if so, whether there was a difference in the proportion of subjects in each treatment group receiving such therapy at Baseline.

7.1.1.12. Results for the primary efficacy outcome

Based on the FAS1 with NRI, the proportion of subjects who were in DAS28 (ESR) remission (DAS28 (ESR) < 2.6) at both the Week 40 and Week 52 Visits, defined as sustained remission at Week 52, was higher in the CZP + MTX group compared with the PBO + MTX and the difference was statistically significant (PBO + MTX (N = 213): 15.0% (n = 32), CZP + MTX (N = 655): 28.9% (n = 189); odds ratio CZP + MTX/PBO + MTX 2.283, 95% CI (1.503, 3.468); p < 0.001).

The sponsor indicates that a ≥ 10% difference between the groups in sustained remission at Week 52 is clinically meaningful based on the expert opinion of the members of the study's Steering Committee.

The results of the sensitivity analyses based on the PPS1 and CS1 with NRI were supportive of the results of the primary analysis (PPS1: PBO + MTX (n = 201): 15.4% (n = 31), CZP + MTX (n = 608): 29.4% (n = 179); odds ratio CZP + MTX/PBO + MTX 2.289, 95% CI (1.494, 3.509); p < 0.001; CS1: PBO + MTX (N = 143): 22.4% (n = 32), CZP + MTX (N = 500): 37.8% (n = 189); odds ratio CZP + MTX/PBO + MTX 2.109, 95% CI (1.359, 3.272); p < 0.001). The sponsor highlights that the results of these sensitivity analyses suggest that the respective impacts on the primary efficacy outcome of subjects in the FAS1 who had protocol violations, and subjects who did not complete the study to Week 52, did not bias the results.

The results of a sensitivity analysis using the IXRS stratification factor for time since RA were very similar to the results of the primary analysis using calculated time since RA diagnosis.

Based on the FAS1 with NRI, a lower proportion of subjects who were anti-CZP antibody positive on at least one visit during Period 1 (excluding the Safety Follow-up Visits) were in sustained remission at Week 52 compared with subjects who were anti-CZP antibody negative

at all Visits in Period 1 (excluding the Safety Follow-up Visits) (anti-CZP antibody positive: 14.3% (n = 9), anti-CZP antibody negative: 30.4% (n = 180)).

Based on the FAS1 with NRI, the results of subgroup analyses for the primary efficacy outcome, by time since RA diagnosis at Baseline (≤ 4 months, > 4 months), gender (male, female), region (Europe and Australia, Latin and North America), age (< 65 years, ≥ 65 years), RF (≤ 42 IU/mL, > 42 IU/mL), albumin (< 42 g/L, ≥ 42 g/L) and presence of erosions at Baseline (yes/no), were generally consistent with the results of the primary analysis with a higher proportion of subjects in the CZP + MTX group in sustained remission at Week 52 compared with the PBO + MTX group. The difference between the two groups was not statistically significant for all strata in each subgroup analysis. Of note, by region, a higher proportion of subjects in the CZP + MTX group were in sustained remission at Week 52 in region 'Europe and Australia' (38.4% (n = 136)) compared with region 'Latin and North America' (17.6% (n = 53)). Based on a post-hoc analysis by region/country, and based on the FAS1, for the region 'Latin America', a higher proportion of subjects in the PBO + MTX group were in sustained remission at Week 52 compared with the CZP + MTX group (PBO + MTX 32.0% (n = 8), CZP + MTX 26. 3% (n = 21)). Baseline assessments of RA variables and RA history were generally comparable across the treatment groups for subjects in the Latin America region based on the FAS1.

Comment: DAS28 (ESR) remission (DAS28 (ESR) < 2.6) at both the Week 40 and Week 52 Visits, is a novel primary efficacy outcome. The sponsor highlights that sustained remission is not based on a universally accepted duration and indicates that sustained remission at a three month interval, as indicated in the primary efficacy outcome, is based on the EULAR recommendation to adjust treatment every one to three months until achievement of remission or LDA. This seems reasonable.

A number of possible sources of bias may have affected the results of the primary outcome. NRI may introduce uncertainty into the results as the imputed values may not represent the truth. It would be expected that treating missing data as not being in sustained DAS28 (ESR) remission at Week 52 would bias the results toward the null and underestimate the difference between the treatment groups. Other possible sources of bias are protocol violations and discontinued subjects. However, the results of the sensitivity analyses based on the PPS1 and CS1 were supportive of the results of the primary analysis suggesting that subjects who had protocol deviations, and subjects who discontinued and for whom results were imputed using NRI, did not appear to notably change the results for the primary efficacy outcome, as highlighted by the sponsor. NRI is conservative as subjects may respond over time. The fact that not all countries involved in the study used the same protocol may also have introduced bias.

The sponsor indicates that a ≥ 10% difference between the groups in sustained remission at Week 52 is clinically meaningful based on the expert opinion of the members of the study's Steering Committee. This conclusion seems reasonable.

The results of the statistical comparisons of the two treatment groups in relation to the individual components of the DAS28 (ESR), specifically, change from Baseline in SJC at Week 52, change from Baseline in TJC at Week 52, ratio of ESR at Week 52 to Week 0 and change from Baseline in PtGADA at Week 52, were supportive of the results of the primary analysis of the primary efficacy outcome.

With regard to the subgroup analysis results for Latin America, it is difficult to know if the smaller proportion of subjects in the CTZ + MTX group, compared with the PBO + MTX group, who achieved sustained remission at Week 52 represents the truth as the numbers of subjects in each treatment group in the FAS1 from this region were relatively small (PBO + MTX n = 25, CZP + MTX n = 80).

7.1.1.13. Results for other efficacy outcomes

Secondary outcomes that were included in the hierarchical test procedure: The key secondary efficacy outcome and the other three select secondary efficacy outcomes that were included in the hierarchical test procedure all reached statistical significance.

Key secondary efficacy outcome: sustained DAS28 (ESR) LDA at Week 52

Based on the FAS1 with NRI, the proportion of subjects who had DAS28 (ESR) ≤ 3.2 at both the Week 40 and Week 52 Visits, defined as sustained LDA at Week 52, was higher in the CZP + MTX group compared with the PBO + MTX and the difference was statistically significant (PBO + MTX (n = 213): 28.6% (n = 61), CZP + MTX (n = 655): 43.8% (n = 287); odds ratio CZP + MTX/ PBO + MTX 1.957, 95% CI (1.384, 2.767); p < 0.001).

The sponsor indicates that it considers the result clinically meaningful. The subjects who met the primary efficacy outcome also met this efficacy outcome. The results of the sensitivity analysis based on CS1 were supportive of the results based on the FAS1.

ACR50 response at Week 52 in relation to Baseline

Based on the FAS1 with NRI, the proportion of subjects who had an ACR50 response at Week 52 was higher in the CZP + MTX group compared with the PBO + MTX and the difference was statistically significant (PBO + MTX (n = 213): 52.6% (n = 112), CZP + MTX (n = 655): 61.8% (n = 405); odds ratio CZP + MTX/PBO + MTX 1.446, 95% CI (1.052, 1.989); p = 0.023).

Change from Baseline in HAQ-DI at Week 52

Based on the FAS1 with LOCF, at Week 52, the change from Baseline was greater in the CZP + MTX group compared with the PBO + MTX group and the difference was statistically significant (PBO + MTX (n = 210): LS mean (SE) -0.819 (0.044), CZP + MTX (n = 645): LS mean (SE) -0.997 (0.028); CZP + MTX-PBO + MTX LS mean (SE) -0.177(0.049), 95% CI (-0.27, -0.082); p-value < 0.001).

The sponsor indicates that it considers the change from Baseline in the CZP + MTX group clinically meaningful. A minimum clinically important difference (MCID) was defined as an improvement of at least 0.22 points from Baseline.

Change from Baseline in mTSS at Week 52

At Week 52, there were small mean increases from Baseline in mTSS based on the RAD1 with linear extrapolation (PBO + MTX (n = 163): mean (SD) 1.8 (4.3), median (range) 0.5 (-9, 20), CZP + MTX (n = 528): mean (SD) 0.2 (3.2), median (range) 0.0 (-26, 26); CTP + MTX minus PBO + MTX difference (Hodges-Lehmann point estimate of shift) -0.978, 95% CI (-1.005, -0.500); p-value < 0.001).

The above p-value was estimated using ANCOVA on the ranks with treatment, region and time since RA diagnosis at Baseline (≤ 4 months, > 4 months) as factors and Baseline rank as a covariate. A sensitivity analysis using an ANCOVA on the actual values and the same imputation method had similar results to the results above.

An additional analysis was undertaken using the RAD1 in which the Week 52 mTSS scores of all subjects were estimated by linear extrapolation of the post-Baseline mTSS scores. The results of this analysis were very similar to the above results based on the RAD1 in which mTSS score was estimated by linear extrapolation of the post-Baseline score only for subjects who withdrew before Week 52 and had radiographs taken at their Withdrawal Visit.

Comment: The sponsor indicates that it considers the result for the key secondary efficacy outcome to be clinically meaningful. This seems reasonable.

A clinically meaningful change from Baseline in the mTSS appears to be > 0.5 (deterioration). Based on this definition, there was no clinically meaningful

deterioration in the mTSS in the CZP + MTX group at Week 52 compared with Baseline.

The target treatment response for clinical practice for the ACR50 is noted to be 40%. This result was achieved in both treatment groups at Week 52, but the proportion of subjects who achieved ACR50 was higher in the CZP + MTX group than the PBO + MTX group, supportive of the results for the primary efficacy outcome.

For HAQ-DI, there was a clinically important difference in both treatment groups. The difference between the treatment groups, although statistically significant, was small.

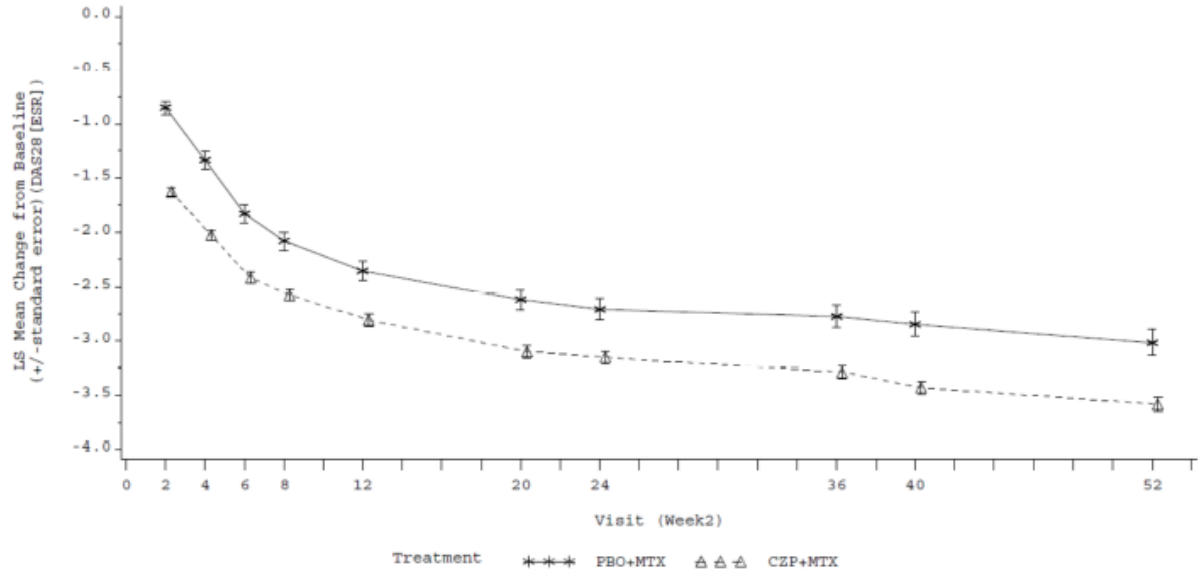
Additional secondary efficacy outcomes and other efficacy outcomes that the sponsor proposes to describe in the PI are summarised below.

Change from Baseline in DAS28 (ESR) by week

This was a secondary efficacy outcome for Week 12, Week 24, Week 52/Withdrawal Visit and another efficacy outcome for Weeks 2, 4, 6, 8, 20, 36 and 40.

Based on the FAS1 with LOCF, there was a greater mean reduction in DAS28 (ESR) from Baseline in the CZP + MTX group compared with the PBO + MTX at each of the above measurement time points (see Figure 7, below). An additional analysis was undertaken based on a mixed effect model for repeated measures (MMRM) to account for missing data. The results of this analysis were supportive of the results of the analysis using LOCF. The sponsor indicates that this suggests that the missing data did not bias the results.

Figure 7. Study C-EARLY, Period 1: Mean change from Baseline in DAS28 (ESR) by visit (FAS1 with LOCF)



CZP=certolizumab pegol; DAS28(ESR)=disease activity score-28 joint count erythrocyte sedimentation rate; FAS1=Full Analysis Set Period 1; LOCF=last observation carried forward; LS Mean=least squares mean; MTX=methotrexate; PBO=placebo

Note: The number of subjects in each treatment group can slightly change across the scheduled visits.

Proportion of subjects with DAS28 (ESR) < 2.6 at Week 12, Week 24, Week 52

The secondary efficacy outcome 'remission' was based on five criteria including DAS28 (ESR) < 2.6. The proportions of subjects in the FAS1 with NRI with DAS28 (ESR) < 2.6 at Week 12, Week 24, and Week 52 were higher in the CZP + MTX group compared with the PBO + MTX

group (Week 12: PBO + MTX (n = 213): 12.2% (n = 26), CZP + MTX (n = 655): 18.9% (n = 124); odds ratio CZP + MTX/ PBO + MTX 1.693, 95% CI (1.035, 2.596); p = 0.035;
Week 24: PBO + MTX (n = 213): 13.1% (n = 28), CZP + MTX (n = 655): 26.1% (n = 171); odds ratio CZP + MTX/ PBO + MTX 2.315, 95% CI (1.488, 3.603); p < 0.001; Week 52: PBO + MTX (n = 213): 26.8% (n = 57), CZP + MTX (n = 655): 42.6% (n = 279); odds ratio CZP + MTX/ PBO + MTX 2.039, 95% CI (1.437, 2.895); p < 0.001).

Proportion of subjects with DAS28 (ESR) ≤ 3.2 at Week 12, Week 24, Week 52

Based on the FAS1 with NRI, the proportion of subjects who achieved LDA (DAS28 (ESR) ≤ 3.2) were higher in the CZP + MTX group compared with the PBO + MTX group at Week 12, Week 24, and Week 52 (Week 12: PBO + MTX (n = 213): 18.8% (n = 40), CZP + MTX (n = 655): 31.6% (n = 207); odds ratio CZP + MTX/ PBO + MTX 1.992, 95% CI (1.353, 2.394); p < 0.001;
Week 24: PBO + MTX (n = 213): 30.5% (n = 65), CZP + MTX (n = 655): 39.7% (n = 260); odds ratio CZP + MTX/PBO + MTX 1.475, 95% CI (1.049, 2.073); p = 0.025; Week 52: PBO + MTX (n = 213): 39.4% (n = 84), CZP + MTX (n = 655): 54.7% (n = 358); odds ratio CZP + MTX/ PBO + MTX 1.867, 95% CI (1.345, 2.591); p < 0.001).

Proportion of subjects with ACR 50 at Week 12, Week 24, Week 52

Based on the FAS1 with NRI, the proportions of subjects who achieved ACR50 at Week 12, Week 24, and Week 52 were higher in the CZP + MTX group compared with the PBO + MTX group. The results at Week 52 are reported above. At Week 12, the proportions of subjects who achieved ACR50 were 40.8% (n = 87) in the PBO + MTX group and 51.0% (n = 334) in the CZP + MTX group (odds ratio CZP + MTX/PBO + MTX 1.494, 95% CI (1.089, 2.049); p = 0.013). At Week 24, the proportions of subjects who achieved ACR50 were 50.2% (n = 107) in the PBO + MTX group and 56.5% (n = 370) in the CZP + MTX group (odds ratio CZP + MTX/PBO + MTX 1.258, 95% CI (0.917, 1.726); p = 0.155).

Proportion of subjects with ACR 70 at Week 12, Week 24, Week 52

Based on the FAS1 with NRI, the proportions of subjects who achieved ACR70 at Week 12, Week 24, and Week 52 were higher in the CZP + MTX group compared with the PBO + MTX group. At Week 12, the proportions of subjects who achieved ACR70 were 19.7% (n = 42) in the PBO + MTX group and 33.1% (n = 217) in the CZP + MTX group (Odds ratio CZP + MTX/ PBO + MTX 1.996, 95% CI (1.370, 2.909); p < 0.001). At Week 24, the proportions of subjects who achieved ACR70 were 29.1% (n = 62) in the PBO + MTX group and 41.1% (n = 269) in the CZP + MTX group (odds ratio CZP + MTX/PBO + MTX 1.679, 95% CI (1.198, 2.355); p = 0.003). At Week 52, the proportions of subjects who achieved ACR70 were 39.9% (n = 85) in the PBO + MTX group and 51.3% (n = 336) in the CZP + MTX group (odds ratio CZP + MTX/ PBO + MTX 1.571, 95% CI (1.142, 2.163); p = 0.006).

Change from Baseline in erosion score at Week 52

Based on the RAD1, using rank ANCOVA with linear extrapolation, the mean increase from baseline in joint erosion score at Week 52 was lower in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX (n = 163): mean (SD) 1.1 (3.0), median (range) 0.5 (-7, 20), CZP + MTX (n = 528): mean (SD) 0.1 (2.1), median (range) 0.0 (-22, 13); CTP + MTX minus PBO + MTX difference (Hodges-Lehmann point estimate of shift) -0.500, 95% CI (-0.508, -0.366); p-value < 0.001).

An additional analysis was undertaken using RAD1 in which the Week 52 joint erosion score of all subjects were estimated by linear extrapolation of the post-Baseline joint erosion score. The results of this analysis were very similar to the above results based on the RAD1 in which joint erosion score was estimated by linear extrapolation of the post-Baseline score only for subjects who withdrew before Week 52 and had radiographs taken at their Withdrawal Visit. The results using an ANCOVA model with linear extrapolation were also similar.

Change from Baseline in JSN score at Week 52

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 + MTX group compared with the PBO + MTX group but the median change was the same in both groups (PBO + MTX (n = 163): mean (SD) 0.7 (2.3), median (range) 0.0 (-7, 15), CZP + MTX (n = 528): mean (SD) 0.1(1.7), median (range) 0.0 (-16, 13); CTP + MTX minus PBO + MTX difference (Hodges-Lehmann point estimate of shift) 0.000, 95% CI (0.000, 0.000); p-value = 0.001).

An additional analysis was undertaken using RAD1 in which the Week 52 JSN score of all subjects were estimated by linear extrapolation of the post-Baseline JSN score. The results of this analysis were consistent with the above results based on the RAD1 in which JSN score was estimated by linear extrapolation of the post-Baseline score only for subjects who withdrew before Week 52 and had radiographs taken at their Withdrawal Visit. The results using an ANCOVA model with linear extrapolation were supportive.

Change from Baseline in PtAAP at Week 52

Based on the FAS1 with LOCF, at Week 52, the change from baseline was greater in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX (n = 210): LS mean (SE) -44.0 (1.7), CZP + MTX (n = 645): LS mean (SE) -48.5 (1.0); CZP + MTX-PBO + MTX LS mean (SE) -4.4 (1.8)), 95% CI (-8.0, -0.8); p-value = 0.016).

Proportion of subjects reaching normal physical function (HAQ-DI ≤ 0.5) at Week 52

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 + MTX group compared with the PBO + MTX group based on the FAS1 with NRI (PBO + MTX (n = 213): 35.7% (n = 76), CZP + MTX (n = 655): 48.1% (n = 315); odds ratio CZP + MTX/PBO + MTX 1.668, 95% CI (1.207, 2.305); p = 0.002).

Radiographic non-progression at Week 52 (change in mTSS ≤ 0.5 from Baseline)

At Week 52 a higher proportion of subjects in the CZP + MTX group compared with the PBO + MTX group had radiographic non-progression, compared with Baseline, based on the RAD1 with linear extrapolation (PBO + MTX (n = 163): 49.7% (n = 81), CZP + MTX (n = 528), 70.3% (n = 371); odds ratio CZP + MTX/ PBO + MTX 2.385, 95% CI (1.664, 3.419); p < 0.001).

Comment: The study was not powered for the comparison of PBO + MTX and CZP + MTX in relation to these secondary efficacy outcomes and there was no adjustment for multiple comparisons. Therefore the results are considered hypothesis-generating and the 95% CI and p-values descriptive only.

For the efficacy outcomes above evaluating disease activity at Week 12, Week 24, Week 52, the results suggest a greater benefit in the CZP + MTX group, compared with the PBO + MTX group, from Week 12 which is sustained at Week 52. A greater mean reduction in DAS28 (ESR) was observed in the CZP + MTX group, compared with the PBO + MTX group, at each of the measurement time points from Week 2.

For a number of the study's secondary and other efficacy outcomes that reported changes from Baseline at different time points in the study, not all of the subjects in the analysis set were included in the analysis at each reported measurement time point despite the use of LOCF to deal with missing data, for example, in describing change from Baseline in DAS28 (ESR) in the FAS1 by week. The sponsor is requested to clarify why this is the case. This may have been a source of bias.

Other secondary efficacy outcomes/other efficacy outcomes

The results for the other secondary efficacy outcomes and other efficacy outcomes were generally supportive of the results of the primary efficacy outcome. These outcomes related to

the signs and symptoms of RA, the inhibition of progression of structural damage, physical functioning, tiredness/fatigue, productivity at the workplace and within the household, and health-related quality of life.

In addition to the efficacy variable DAS28 (ESR) < 2.6, remission, as opposed to sustained remission, was evaluated in the FAS1 with NRI by other efficacy measures (CDAI ≤ 2.8, SDAI ≤ 3.3, the new ACR/EULAR 2011 remission criteria and the new ACR/EULAR 2011 remission criteria simplified for clinical practice). The results for the other efficacy measures were supportive of the results for the primary analysis of the primary efficacy outcome (sustained remission) showing a higher proportion of subjects in the CZP + MTX, compared with the PBO + MTX group, achieving the efficacy outcome at Weeks 12, 25 and 52.

Comment: There was no imputation of missing data for some of the efficacy endpoints which may also have been a source of bias.

Subgroup analyses - secondary and other efficacy outcomes: Analyses of categorical secondary and other efficacy outcomes at Week 52 were undertaken by time since diagnosis of RA (≤ 4 months, > 4 months) based on the FAS1 with NRI. The proportions of subjects meeting the efficacy outcome at Week 52 were similar across the strata and were generally higher in the CZP + MTX group compared with the PBO + MTX group. For some of the efficacy variables at certain measurement time points there were higher proportions of remitters in the PBO + MTX group compared with the CZP + MTX group but the differences between the groups were not large.

Similarly, for continuous secondary and other efficacy variables based on the FAS1 with LOCF, the LS mean decreases from baseline at Week 52 were generally similar across the strata for each variable in each treatment group and were higher in the CZP + MTX group compared with the PBO + MTX group. With regard to radiographic efficacy variables, mTSS, erosion score and JSN score, based on the RAD1 with linear extrapolation, the mean changes from Baseline in the CZP + MTX group were lower than in the PBO + MTX group. The mean changes from Baseline at Week 52 were similar across the strata except for erosion score which was 0.1 (0.8) for the subgroup ≤ 4 months and -0.1 (2.8) for subgroup > 4 months in the CZP + MTX group. The median changes from Baseline at Week 52 for erosion score were, however, 0.00 (Q1: -0.5, Q3: 0.5) in both groups.

Post-hoc analyses: To investigate the consistency of treatment effect across regions, a logistic regression model on the primary efficacy variable with the added term treatment by region interaction was used. The interaction term was found to be significant, therefore, post hoc analyses were performed using subregions. The results of post-hoc analyses of secondary and other efficacy outcomes by region were generally supportive of the results for the primary efficacy outcome.

The baseline values for RA variables were not always similar in each treatment group for the analyses by region/country. For example, in Latin America, a higher proportion of subjects in the PBO + MTX group, compared with the CZP + MTX group, had erosions at Baseline (PBO + MTX 84.0% (n = 21), CZP + MTX 63.8% (n = 51)).

The results of post-hoc analyses undertaken for change from baseline in mTSS at Week 52, using FAS1 with non-missing baseline mTSS score and using a rank ANCOVA, and in which change from Baseline was imputed by different methods, were supportive of the result based on the RAD1 with linear extrapolation.

Post-hoc analyses of ACR20, ACR50 and ACR70 responders by Visit in subjects who had a Baseline DAS28 (ESR) ≥ 6.753, based on FAS1 and using NRI, showed higher proportions of subjects in the CZP + MTX group, compared with the PBO + MTX group, were ACR20, ACR50 and ACR70 responders, respectively, at each visit (Visit 3 (Week 2) to Visit 12 (Week 52)). In this subgroup, the proportions of subjects reaching normative physical function By Visit, based on FAS1 and using NRI, showed higher proportions of subjects in the CZP + MTX group, compared

with the PBO + MTX group, were responders at each of the Visits. Subjects in the CZP + MTX group, compared with the PBO + MTX group, also had a greater decrease from Baseline in HAQ-DI at each of the Visits based on FAS1 using LOCF.

Comment: The post-hoc analyses in subjects with DAS28 (ESR) ≥ 6.753 suggest that even in subjects who had a Baseline DAS28 (ESR) ≥ 6.753 there is a benefit of CZP + MTX over PBO + MTX in relation to ACR20, ACR50 and ACR70 response and physical function. These results, however, are hypothesis-generating.

7.2. Other efficacy studies

7.2.1. Study C-OPERA (Study RA0096)

7.2.1.1. Study design, objectives, locations and dates

Study C-OPERA is an ongoing, Phase III, multi-centre, randomised, double-blind, placebo-controlled, parallel group comparison study. The study was initiated at 73 study sites in Japan. A total of 378 subjects were screened at 70 sites. The first subject was enrolled on 11 October 2011 and the last subject completed the 52-week double-blind Treatment Period on 28 August 2013.

The objective of the study was to compare the efficacy of CZP + MTX, in MTX-naïve subjects with early RA and poor prognostic factors, to PBO + MTX using inhibition of joint damage progression after one year of treatment as the primary efficacy outcome.

This study has the following periods:

- 4-week Screening Period (Day -28 to Day 0)
- 52-week double-blind, placebo-controlled Treatment Period (Week 0 to Week 52)
- 52-week Follow-Up Observation Period (Week 52 to Week 104)
- Rescue Treatment Period (up to Week 104)

This Screening Period and Treatment Period have been completed and the results are reported in the interim CSR included in the submission.

Comment: This study was conducted in only one country, Japan, so the results may not be generalisable to patients in all countries.

7.2.1.2. Inclusion and exclusion criteria

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.

Exclusion criteria included a diagnosis of any other type of inflammatory arthritis, previous receipt of MTX, leflunomide and other biological agents, tuberculosis or a history of tuberculosis, a high risk of infections, the presence of complications associated with a renal disorder, hepatic disorder or severe respiratory disorder, the presence, or a history of, demyelinating disease or NYHA Class III or IV congestive heart failure or malignant tumour, and females who were pregnant or breast feeding.

Comment: The inclusion criteria of Study C-OPERA had some similarities with the inclusion criteria for Study C-EARLY. In Study C-OPERA, subjects were early RA, to have moderate or severe RA based on DAS28 (ESR) ≥ 3.2, and the presence of poor prognostic factors. These criteria are similar to inclusion criteria for Study C-EARLY. In Study C-OPERA, subjects included in the study were MTX-naïve and in

Study C-EARLY subjects included in the study were DMARD-naïve. As it is anticipated that MTX would normally be the first DMARD started in subjects with RA, a subject who is MTX-naïve would probably be DMARD-naïve also.

7.2.1.3. Study treatments

In the Treatment Period, subjects received one of the two following study treatments:

- CZP + MTX: 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 + MTX weekly orally from Week 0
- PBO + MTX: PBO 2 syringes SC at Weeks 0, 2 and 4 followed by PBO 1 syringe SC every 2 weeks from Week 6 to Week 50 +MTX weekly orally from Week 0

During the Treatment Period, MTX was initiated at Week 0 at a dose of 8 mg/week and administration was commenced concomitantly with the start of administration of CZP or PBO. The MTX dose was increased to 12 mg/week at Week 4 and to 16 mg/week at Week 8 if tolerated. Each subject was maintained on the maximum tolerated dose. The dose could be increased, alternatively, at 2 mg every two weeks. MTX was administered weekly as a single dose or as a divided dose of two doses every 12 hours over one day or four doses every 12 hours over two days. The dose of MTX could be decreased or temporarily withdrawn if required. Folic acid could be administered at a dose of < 5 mg/week. Certain other concomitant medications/treatments were permitted during the study with specified restrictions on use.

Subjects who did not achieve an improvement of symptoms at, and after, Week 24 could receive rescue treatment with CZP 200 mg every two weeks up to Week 104. Only the data collected for these subjects prior to commencement of the rescue treatment were included in this interim CSR. Subjects were considered not to have achieved an improvement in their symptoms if they had moderate or higher disease activity, defined as DAS28 (ESR) ≥ 3.2, for four weeks or longer. The dosage of MTX could be changed during the Rescue Treatment Period.

Subjects who completed the Treatment Period could enter the Follow-Up Observation Period during which they received MTX monotherapy.

A follow-up examination was undertaken 10 weeks after final study drug administration for subjects who withdrew from the study during the Treatment Period or who discontinued or terminated rescue treatment. A follow-up examination was also undertaken for subjects in the Follow-Up Observation Period who withdrew in the first 8 weeks of the period and at Week 8 of the Follow-Up Observation Period for those subjects who continued in the Follow-Up Observation Period for more than 8 weeks.

Comment: In Study C-OPERA, the dosage of CZP was the same as in Study C-EARLY. The dose of MTX was a minimum of 8 mg/ week and a maximum of 16 mg/week in Study C-OPERA which is lower than the required concomitant MTX dose in Study C-EARLY (from Week 8 onward a minimum dose of 15 mg/week and a maximum dose of 25 mg/week).

7.2.1.4. Efficacy variables and outcomes

The primary efficacy variable was mTSS.

There were multiple other efficacy variables, including:

- Bone erosion score
- JSN score
- DAS28 (ESR)
- ACR/EULAR remission rate (SDAI-based)
- ACR/EULAR remission rate (Boolean-based).

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:
    - SDAI-based
    - Boolean-based.

DAS28 (ESR) remission was defined as DAS28 (ESR) < 2.6. ACR/EULAR SDAI-based remission was defined as SDAI ≤ 3.3. ACR/EULAR Boolean-based remission was defined as TJC (in 28 joints) ≤ 1, SJC (in 28 joints) ≤ 1, CRP ≤ 1 (mg/dL) and PtGADA ≤ 1 (100 mm visual analog scale converted to cm).

Additional efficacy outcomes were also specified. These outcomes included additional analyses of DAS28 (ESR) remission rate, ACR/EULAR remission rate (SDAI-based and Boolean-based), and analyses of DAS28 (ESR), SDAI, ACR20, ACR50 and ACR70 response rates, disease activity markers, TJC and SJC, HAQ-DI, HAQ-DI remission rate, PtAAP, PtGADA, PhGADA, CRP, ESR, MMP-3 and labour productivity.

X-rays were read centrally by blinded readers. ESR was determined at the study site.

7.2.1.5. Randomisation and blinding methods

A randomised allocation table was prepared for study drug allocation. Subjects, the Investigator and sub-investigator and personnel related to the sponsor were blinded to study drug allocation except for the person in charge of drug concentration measurements, the person in charge of emergency reporting of AEs, persons in charge of study drug administration and persons in charge of packaging the study drugs. The individuals in charge of study drug administration were not permitted to undertake activities related to the analysis of efficacy and safety.

7.2.1.6. Analysis populations

The analysis populations are shown in Table 6, below.

Table 6. Study C-OPERA, Treatment Period: Populations analysed during the Treatment Period (ES)

Treatment group	Analysis sets				
	RS	FAS	PPS	PKS	SS
All subjects	319	316	302	316	316
PBO+MTX	158	157	149	157	157
CZP+MTX	161	159	153	159	159

CZP=certolizumab pegol; ES=Enrolled Set; FAS=Full Analysis Set; MTX=methotrexate; PBO=placebo; PKS=Pharmacokinetic Analysis Set, PPS=Per-Protocol Set; RS=Randomized Set; SS=Safety Set

Subjects were identical in the Full Analysis Set (FAS), Safety Set (SS) and Pharmacokinetic Analysis Set (PKS).

7.2.1.7. Sample size

For the primary efficacy outcome, the sample size calculation was based on an assumed difference in the change from Baseline in mTSS at Week 52 between the treatment groups of

2.57, and a standard deviation in the change from Baseline in mTSS of 6.75 for each treatment group. Based on these assumptions, at least 146 subjects in each treatment group were estimated by the sponsor to be required to detect a difference between the treatment groups with a power of at least 0.90 and a 2-sided significance level of 0.05.

7.2.1.8. Statistical methods

Study C-OPERA was a superiority trial. The primary analysis was undertaken to assess if treatment up to Week 52 with CZP + MTX was superior to PBO + MTX for the primary efficacy outcome.

There were no adjustments made for multiple comparisons. For subgroup analyses of the primary and secondary efficacy outcomes, each subgroup interaction was examined with a significance level of 0.10.

Primary efficacy outcome

The primary analysis of the primary efficacy outcome in the FAS was performed using rank ANCOVA with linear extrapolation for missing data (ANCOVA LINEAR). Measured values were converted to rank scores. Treatment group was used as a factor and Baseline rank score as a covariate. A Hodges-Lehmann point estimate and 95% CI were calculated. An ANCOVA model was also undertaken for the measured values, using the treatment group as a factor and Baseline value as a covariate. The least-square (LS) means for each treatment group, and the difference between the LS means were calculated as were the corresponding 95% CIs. Analyses using rank ANCOVA LINEAR and the PPS, and other ANCOVA models using the FAS (ANCOVA using LOCF for missing data (ANCOVA LOCF) and ANCOVA using observed cases (ANCOVA OC)) and a mixed model repeated measurement method), were also undertaken for the primary efficacy outcome.

As supportive analyses, non-progression (change from Baseline ≤ 0.5) of mTSS, erosion score, and JSN score, at Week 52, were analysed using the FAS and different imputation methods. The 95% CI was calculated by the Clopper Pearson method and a Fisher's exact test was used for the comparison between the treatment groups.

Exploratory analyses were undertaken for yearly progression of mTSS using an ANCOVA and the proportion of subjects with rapid radiographic progression (yearly progression ≥ 5) and the 95% CI by the Clopper Pearson method was calculated.

Secondary efficacy outcomes

For the secondary efficacy outcome, inhibition of joint damage progression at Week 24, the statistical methods used were similar to those used for the primary efficacy outcome.

The DAS28 (ESR) remission rate was analysed as the proportion of subjects with DAS28 (ESR) < 2.6. The 95% CI was calculated by the Clopper Pearson method and a Fisher's exact test was used for the comparison between the treatment groups. This outcome was analysed in the FAS using LOCF and NRI and PPS using LOCF.

The proportion of subjects in ACR/EULAR remission (SDAI-based) was analysed in the FAS using LOCF and NRI and PPS using LOCF. The 95% CI was calculated by the Clopper Pearson method and a Fisher's exact test was used for the comparison between the treatment groups. For the ACR/EULAR remission (Boolean-based) the same analyses were performed as for ACR/EULAR remission (SDAI-based).

Other efficacy outcomes

Analyses of other efficacy were performed in the FAS using LOCF and OC. The statistical methods used depended on the efficacy outcome.

There were three amendments to the study protocol summarised in Table 7, below.

Table 7. Study C-OPERA, protocol amendments

Protocol amendment	Summary of changes
Protocol amendment 1 dated 29 July 2011	· Update to the action required if a subject was found to be hepatitis B core antibody positive · Editorial changes
Protocol amendment 2 dated 7 June 2012	· The protocol was amended to reflect a change in the sponsor of the study · The planned study period was extended
Protocol amendment 3 dated 18 January 2013	· Criteria and procedures for the withdrawal of subjects with hepatitis B virus were updated and specified in greater detail.

A number of planned analyses were updated after the SAP approval. Of note, the formula describing the estimated mTSS yearly progression was corrected and the statistical approach for the supportive and sensitivity analyses of the primary efficacy variable using the mixed model was updated.

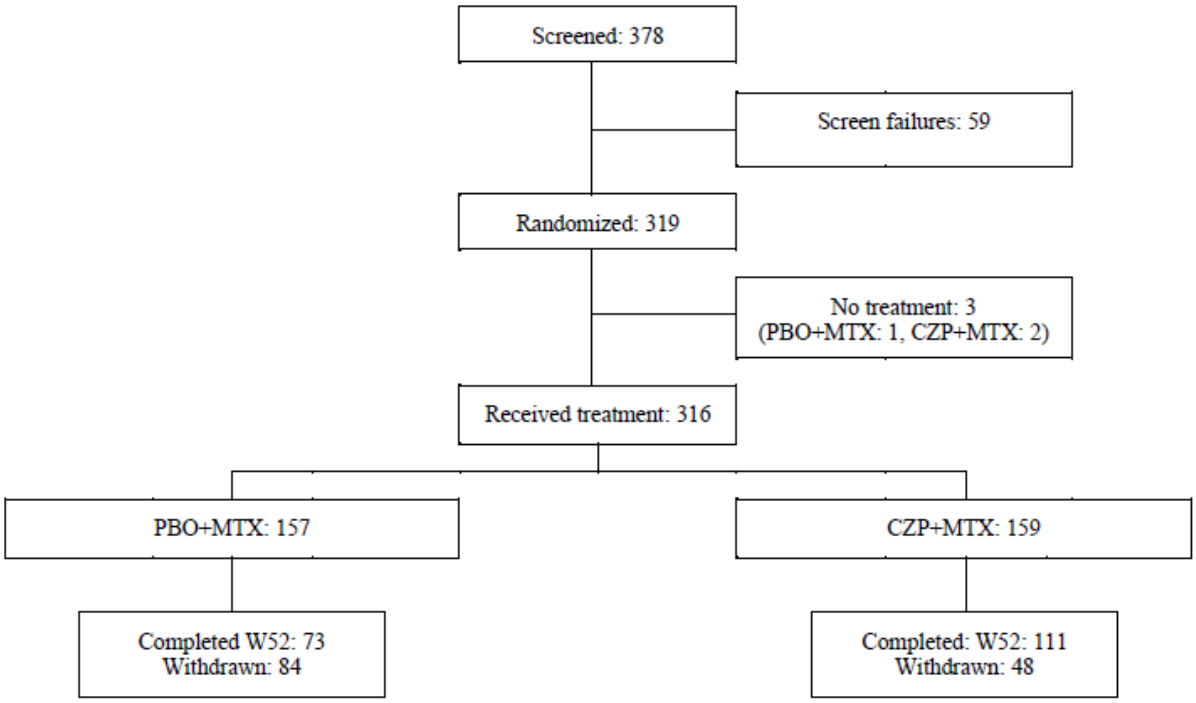
Comment: The sponsor is requested to clarify if the primary analysis of the primary efficacy outcome was only the analysis in the FAS performed using rank ANCOVA with linear extrapolation for missing data (ANCOVA LINEAR) or if the ANCOVA model undertaken for the measured values, using the treatment group as a factor and Baseline value as a covariate, was also a primary analysis of the primary efficacy outcome.

The protocol amendments are unlikely to have affected the results of the Treatment Period. The amendments related to subjects with hepatitis B virus were safety-related amendments. With regard to the update of planned analyses in the SAP, the analyses updated were supportive and sensitivity analyses of the primary efficacy outcome and an exploratory analysis of the primary efficacy outcome. The results of these analyses are hypothesis-generating only.

7.2.1.9. Participant flow

Of 378 subjects screened, 319 were randomised (PBO + MTX: n = 158, CZP + MTX: n = 161). Of the randomised subjects, two subjects in the CZP + MTX and one subject in the PBO + MTX group did not receive the study drug (see Figure 8, below). Of the randomised subjects, 84 (53.2%) withdrew from the study and 73 (46.2%) completed Week 52 in the PBO + MTX group, and in the CZP + MTX group, 48 (29.8%) withdrew from the study and 111 (68.9%) completed Week 52. Lack of efficacy was the main reason for the difference in the proportions of randomised subjects in each group who discontinued the double-blind Treatment Period (discontinuation due to lack of efficacy: PBO + MTX: 44.9% (n = 71) CZP + MTX: 22.4% (n = 36)).

Figure 8. Study C-OPERA: Flowchart of subject disposition



CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; W=Week

Note: Rescue treatment was available for subjects who did not achieve an improvement of symptoms at and after Week 24 (Visit 16). This criterion applied if moderate or higher disease activity (DAS28[ESR] ≥3.2) persisted for 4 weeks or longer.

Comment: Discontinuation of large number of subjects during the Treatment Period, especially from the PBO + MTX group, is an issue as it is likely to have introduced bias both for the OC analyses and the analyses using imputation of missing data (linear extrapolation, LOCF, NRI). If the results of different analyses using different methods on a given efficacy outcome are not consistent, it will be unclear which of the results best represents the truth.

7.2.1.10. Major protocol violations/deviations

In total 17 subjects were excluded from the per-protocol set (PPS) due to deviations from the protocol (PBO + MTX: n = 10, CZP + MTX: n = 9). Of these 17 subjects, the three subjects who did not receive the study medication were excluded from all of the data sets. For the remaining 14 subjects, the majority of the deviations related to early withdrawal leading to a short Treatment Period and frequent deviation from the study drug administration schedule. The numbers of subjects in each group with these deviations were comparable. Subjects who used prohibited concomitant drugs and restricted concomitant drugs during the study were classified as non-responders.

Comment: The protocol deviations are unlikely to have appreciably affected the efficacy and safety results.

7.2.1.11. Baseline data

Based on the FAS, the majority of subjects were female (81.0% (n = 256) and the mean (SD) age was 49.3 (10.5) years (range: 21, 64). All subjects were from Japan and of Asian ethnic background. The mean (SD) value for DAS28 (ESR) was 5.45 (1.15) and 61.5% of subjects (n = 194) had a DAS28 (ESR) value > 5.1. The median anti-CCP antibody value was 190.00 U/mL (range 13.9, 300.0; Q1 72.55, Q3 300.00) and the median RF value was 93.00 U/mL (range: 3, 803; Q1 59.0, Q3 275.0). The median values (Q1, Q3) for tender joint count (68 joints) and

swollen joint count (66 joints) were 11.0 (6.0, 18.5) and 10.0 (6.0, 16.0). CRP values were > 1.0 mg/dL in 38.6% of subjects (n = 122) and ESR values were ≥ 51 mm/h in 29.7% of subjects (n = 94). The mean HAQ-DI value was 1.03 (SD 0.67). The median mTSS value was 1.50 (range 0.0, 120.5; Q1 0.50, Q3 5.50) and median erosion score was 0.50 (range 0.0, 68.0; Q1 0.00, Q3 2.50) and median JSN score was 0.50 (range 0.0, 55.0; Q1 0.00, Q3 2.25). Approximately half of all subjects had bone erosions at Baseline (50.3%, n = 159). Overall 19.0% of subjects (n = 60) had received prior DMARDs and 18.0% (n = 57) were receiving steroids at Baseline. The median time from date of first onset of RA symptoms to Baseline was 3.0 months (range 0, 12; Q1 2.0, Q3 6.0). Overall, 26.3% (n = 83) of subjects had a time from date of first RA symptoms to Baseline of ≥ 6 months.

Demographic and other baseline characteristics were generally comparable in the two treatment groups. The demographic and other baseline characteristics of the PPS were similar to the FAS.

The proportions of subjects with previous medical history System Organ Class (SOC) and preferred terms (PTs) were generally similar between the treatment groups. There were differences in the proportions of subjects in the two treatment groups who had concomitant diseases falling under certain SOCs but the differences were due to small differences in the absolute numbers of subjects with specific concomitant disease PTs. All subjects used concomitant medications during the Treatment Period, and the majority used restricted concomitant medication (PBO + MTX 90.4% (n = 142), CZP + MTX 93.7% (n = 149)). The proportions of subjects who used prohibited concomitant medications were the same in both groups (3.8%). Concomitant MTX use, by average dose, maximum dose and final dose, was similar in the two treatment groups. The use of permitted concomitant oral corticosteroids was also generally comparable between the treatment groups. Treatment compliance was comparable between the treatment groups based on the compliance ratio.

7.2.1.12. Results for the primary efficacy outcome

At Week 52, the mean change from Baseline for the mTSS was smaller in the CZP + MTX group compared with the PBO + MTX group (Mean (SD) change from Baseline at Week 52: PBO + MTX (n = 157): 1.58 (4.86), CZP + MTX (n = 158): 0.36 (2.70)). The median change from Baseline in each treatment group was 0.00 (Median change (range) from Baseline at Week 52: PBO + MTX (n = 157): 0.00 (-3.0, 47.4), CZP + MTX (n = 158): 0.00 (-9.8, 25.1)). The difference between the groups (CZP + MTX minus PBO + MTX), based on the Hodges-Lehmann point estimate of shift, was 0.00 (95 % CI (0.00, 0.00); p < 0.001) (See Table 8, below).

Table 8. Study C-OPERA - Treatment Period: Actual values and changes from Baseline in mTSS, bone erosion and joint specie narrowing scores at Week 52 (FAS, rank ANCOVA, LINEAR)

Parameter	Treatment group				Difference (CZP+MTX vs PBO+MTX)
	PBO+MTX N=157		CZP+MTX N=159		
	Actual	CFB	Actual	CFB	
Primary variable					
mTSS					
Baseline					
n	157	-	159	-	-
Mean (SD)	5.95 (15.30)	-	5.16 (8.76)	-	-
Median (range)	1.50 (0.0-120.5)	-	1.50 (0.0-55.5)	-	-
Week 52					
n	157	157	158	158	-
Mean (SD)	7.53 (16.68)	1.58 (4.86)	5.55 (9.35)	0.36 (2.70)	-
Median (range)	2.50 (0.0-125.7)	0.00 (-3.0-47.4)	1.50 (-1.8-57.0)	0.00 (-9.8-25.1)	-
Primary analysis					
Diff. (95% CI)[a]	-	-	-	-	0.00 (0.00, 0.00)
p-value[b]	-	-	-	-	<0.001
Sensitivity analysis					
LS Mean (SE)[c]	-	1.57 (0.31)	-	0.38 (0.31)	-1.19 (0.44)
Diff. 95% CI[c]	-	-	-	-	(-2.06, -0.32)
Diff. p-value[c]	-	-	-	-	0.007
Subcomponents of the mTSS					
Bone erosion score					
Baseline					
n	157	-	159	-	-
Mean (SD)	2.77 (7.94)	-	2.24 (4.44)	-	-
Median (range)	0.50 (0.0-68.0)	-	0.50 (0.0-39.0)	-	-

ANCOVA=analysis of covariance; CZP=certolizumab pegol; CFB=change from Baseline; CI=confidence interval; Diff.=difference; FAS=Full Analysis Set; LS Mean=least square means; MTX=methotrexate; mTSS=modified total Sharp score; PBO=placebo, SD=standard deviation; SE=standard error

[a] The Hodges-Lehmann point estimate of shift and 95% CI was used.

[b] The ANCOVA on the ranks with treatment as factors and Baseline rank as covariate was used.

[c] The ANCOVA model with the following factors: treatment and Baseline value was used.

Table 8. (continued) Study C-OPERA - Treatment Period: Actual values and changes from Baseline in mTSS, bone erosion and joint specie narrowing scores at Week 52 (FAS, rank ANCOVA, LINEAR)

Parameter	Treatment group				Difference (CZP+MTX vs PBO+MTX)
	PBO+MTX N=157		CZP+MTX N=159		
	Actual	CFB	Actual	CFB	
Week 52					
n	157	157	158	158	-
Mean (SD)	3.56 (8.58)	0.79 (2.23)	2.40 (4.76)	0.15 (1.30)	-
Median (range)	1.00 (-0.5-68.5)	0.00 (-3.0-15.1)	0.63 (0.0-38.5)	0.00 (-4.1-9.8)	-
Diff. (95% CI)[a]	-	-	-	-	0.00 (0.00, 0.00)
p-value[b]	-	-	-	-	<0.001
Joint space narrowing score					
Baseline					
n	157	-	159	-	-
Mean (SD)	3.18 (8.58)	-	2.92 (5.76)	-	-
Median (range)	0.50 (0.0-55.0)	-	0.50 (0.0-32.5)	-	-
Week 52					
n	157	157	158	158	-
Mean (SD)	3.97 (9.81)	0.80 (3.59)	3.16 (6.22)	0.22 (2.15)	-
Median (range)	1.00 (0.0-57.2)	0.00 (-1.5-37.7)	0.50 (-2.5-32.5)	0.00 (-6.5-22.9)	-
Diff. (95% CI)[a]	-	-	-	-	0.00 (0.00, 0.00)
p-value[b]	-	-	-	-	0.006

ANCOVA=analysis of covariance; CZP=certolizumab pegol; CFB=change from Baseline; CI=confidence interval; Diff.=difference; FAS=Full Analysis Set; LS Mean=least square means; MTX=methotrexate; mTSS=modified total Sharp score; PBO=placebo, SD=standard deviation; SE=standard error

[a] The Hodges-Lehmann point estimate of shift and 95% CI was used.

[b] The ANCOVA on the ranks with treatment as factors and Baseline rank as covariate was used.

[c] The ANCOVA model with the following factors: treatment and Baseline value was used.

Sensitivity analyses and supportive analyses

Overall, the results of the sensitivity analyses for the primary efficacy outcome were supportive of the results of the primary analysis.

The results for the analyses of the sub-components of the mTSS, bone erosion and JSN score, were generally supportive of the result for the primary analysis of the primary efficacy outcome. It is noted that, using ANCOVA model with treatment and baseline value as factors, and based on observed cases in the FAS, there was higher LS mean increase from Baseline in JSN score at Week 52 in the CZP + MTX group compared with the PBO + MTX group but the changes in both groups were small (LS mean change (SE): PBO + MTX (n = 73): 0.10 (0.11), CZP + MTX (n = 112): 0.17 (0.09)).

Subgroup analyses were generally supportive of the results for the primary efficacy outcome with lower mean changes from Baseline at Week 52 for the mTSS in the CZP + MTX group compared with the PBO + MTX group for nearly all strata across each of the subgroup parameters. For a number of the subgroup strata, the results of the LS mean differences for the comparison CZP + MTX minus PBO + MTX were negative and the results of the Hodges Lehmann point estimate of shift for the comparison were > 0.00. However, the lower limits of the 95% CIs for the latter results were 0.00.

The proportion of subjects in the FAS with non-progression of joint damage at Week 52, based on a change from Baseline in mTSS ≤ 0.5 and using linear extrapolation for missing data, was higher in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX (n = 157): 70.7% (n = 111), 95% CI (62.9, 77.7), CZP + MTX (n = 158): 82.9% (n = 131), 95% CI (76.1, 88.4); Difference (CZP + MTX versus PBO + MTX): p = 0.011). The results were similar using LOCF for missing data. Based on observed cases, the proportions of subjects with mTSS non-progression at Week 52 were almost identical. The results of the subgroup analyses were generally supportive.

Exploratory analyses

Mean yearly progression in mTSS at Week 52 was lower in the CZP + MTX group, compared with the PBO + MTX group, and the proportion of subjects with rapid radiographic progression (yearly progression in mTSS ≥ 5) was lower in the CZP + MTX group compared with the PBO + MTX group.

Comment: In a Table in the CSR for Study C-OPERA, it is not clear to the clinical evaluator why one subject in the CZP + MTX group in the FAS did not contribute to the change from Baseline analyses for mTSS, bone erosion and JSN, even though linear extrapolation was used to impute missing data. The sponsor is requested to clarify this point.

The mean changes from Baseline in MTSS at Week 52 in both groups were small relative to the possible range of mTSS values (0 to 448). The median changes were 0.00. As non-progression of joint damage is defined as a change from Baseline in mTSS ≤ 0.5, from the mean results of the primary analysis of the primary efficacy outcome, there was no progression of joint damage in the CZP + MTX at Week 52, compared with Baseline, and clinically significant progression in the PBO + MTX group as the mean change from Baseline in mTSS was > 0.5. However, the median results suggest no progression at Week 52, compared with Baseline, in either group.

Potential sources of bias include imputation of missing data and the possibility that, for the analyses based on observed cases, the subjects remaining in the study may have differed from those subjects who discontinued the study. Despite these potential sources of bias, the results of the sensitivity and supportive analyses for the primary efficacy outcome were generally supportive of the results of the primary analysis.

7.2.1.13. Results for secondary efficacy outcomes

Inhibition of joint damage progression (mTSS) at Week 24

Based on the FAS and using linear extrapolation for missing data and the rank ANCOVA, the mean change from Baseline for the mTSS at Week 24 was smaller in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX (n = 157): mean (SD) 0.86 (2.37), median 0.00 (Q1 0.00, Q3 1.00), CZP + MTX (n = 158): mean (SD) 0.26 (1.55), median 0.00 (Q1 0.00, Q3 0.00)). The difference between the groups (CZP + MTX - PBO + MTX), based on the Hodges-Lehmann point estimate of shift, was 0.00 (95 % CI (0.00, 0.00); p = 0.003). Based on the PPS the results these were consistent as were the results using the rank ANCOVA and observed cases in the FAS, and the FAS with LOCF for missing data, respectively.

The proportion of subjects in the FAS with non-progression of joint damage at Week 24, based on a change from Baseline in mTSS ≤ 0.5 and using linear extrapolation for missing data, was higher in the CZP + MTX group compared with the PBO + MTX group (PBO + MTX (n = 157): 74.5% (n = 117) 95% CI (67.0, 81.1), CZP + MTX (n = 158): 87.3% (n = 138)), 95% CI (81.1, 92.1); difference (CZP + MTX versus PBO + MTX): p = 0.004).

DAS28 (ESR) remission rate at Week 24 and Week 52

Based on the FAS and using LOCF for missing data, higher proportions of subjects in the CZP + MTX group met DAS28 (ESR) remission criteria (DAS28 (ESR) < 2.6) at Week 24 and Week 52, respectively, compared with the PBO + MTX group (Week 24: PBO + MTX (n = 157): 30.6% (n = 48), 95% CI (23.5, 38.4), CZP + MTX (n = 159): 52.8% (n = 84), 95% CI (44.8, 60.8); p < 0.001; Week 52: PBO + MTX (n = 157): 36.9% (n = 58), 95% CI (29.4, 45.0), CZP + MTX (n = 159): 57.2% (n = 91), 95% CI (49.2, 65.0); p < 0.001). The results based on the PPS were supportive as were the results of an analysis using the FAS and NRI.

The results of subgroup analyses were generally supportive.

ACR/EULAR remission rate at Week 24 and Week 52

Based on the FAS and using LOCF for missing data, higher proportions of subjects in the CZP + MTX group met ACR/EULAR remission criteria, both SDAI-based and Boolean-based, at Week 24 and Week 52 (ACR/EULAR remission criteria (SDAI-based) Week 24: PBO + MTX (n = 157): 29.3% (n = 46), 95% CI (22.3, 37.1), CZP + MTX (n = 159): 48.4% (n = 77), 95% CI (40.4, 56.5); p < 0.001; Week 52: PBO + MTX (n = 157): 33.8% (n = 53), 95% CI (26.4, 41.7), CZP + MTX (n = 159): 57.9% (n = 92), 95% CI (49.8, 65.6); p < 0.001; ACR/EULAR remission criteria (Boolean-based) Week 24: PBO + MTX (n = 157): 22.3% (n = 35), 95% CI (16.0, 29.6), CZP + MTX (n = 159): 36.5% (n = 58) 95% CI (29.0, 44.5); p = 0.007; Week 52: PBO + MTX (n = 157): 28.0% (n = 44) 95% CI (21.2, 35.7), CZP + MTX (n = 159): 45.3% (n = 72) 95% CI (37.4, 53.4); p = 0.002) (see Table 9, below). The results based on the PPS were supportive as were the results of an analysis using the FAS and NRI.

Table 9. Study C-OPERA, Treatment Period: Percentage of subjects meeting ACR/EULAR SDAI-based

Remission rate	Week 24			Week 52		
	PBO+MTX N=157 n (%) 95% CI[a]	CZP+MTX N=159 n (%) 95% CI[a]	p-value[b]	PBO+MTX N=157 n (%) 95% CI[a]	CZP+MTX N=159 n (%) 95% CI[a]	p-value[b]
SDAI-based						
Remission	46 (29.3) (22.3, 37.1)	77 (48.4) (40.4, 56.5)	<0.001	53 (33.8) (26.4, 41.7)	92 (57.9) (49.8, 65.6)	<0.001
Boolean-based						
Remission	35 (22.3) (16.0, 29.6)	58 (36.5) (29.0, 44.5)	0.007	44 (28.0) (21.2, 35.7)	72 (45.3) (37.4, 53.4)	0.002

ACR=American College of Rheumatology; CZP=certolizumab pegol; CI=confidence interval; CRP=C-reactive protein; EULAR=European League Against Rheumatism; FAS=Full Analysis Set; LOCF=last observation carried forward, MTX=methotrexate; PBO=placebo PtGADA=Patient Global Assessment of Disease Activity; SDAI=Simplified Disease Activity Index; SJC=swollen joint count; TJC=tender joint count; VAS=visual analog scale

Note: The SDAI-based remission was defined as SDAI ≤3.3. The Boolean-based remission was defined as subjects meeting all of the following criteria: TJC (in 28 joints) ≤1, SJC (in 28 joints) ≤1, CRP ≤1 (mg/dL), and PtGADA ≤1 (100mm VAS data converted to cm).

[a] The 95% CI for remission rate was used.

[b] Fisher's exact test with CZP+MTX and PBO+MTX was used.

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 PBO + MTX group compared with the MTX group.

Comment: The p-values described 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.

Where analyses based on observed cases suggested a better outcome in the PBO + MTX group for a given efficacy outcome this may be due to the fact that subjects who were not improving at Week 24 were discontinued and started on rescue treatment and those who remained in the PBO + MTX may have been subjects who were going to do better or who had different baseline characteristics than those who required rescue treatment. Therefore, it is difficult to interpret the results of such analyses as bias may have been introduced by those who discontinued.

7.2.1.14. Results for the other efficacy outcomes

The results of other efficacy analyses undertaken for the Treatment Period were generally supportive of the results of the primary analysis of the primary efficacy outcome.

Comment: For each efficacy outcome, the results at the majority of the measurement time points, based on the FAS using LOCF and the FAS using OC, respectively, suggested a better outcome in the CZP + MTX group compared with the PBO + MTX group. The results may, however, be biased due to the imputation of results in the LOCF analysis, and, in the OC analysis, the inclusion of data in the analysis at a given time point for only the subjects remaining in the study and contributing data to that measurement time point.

7.3. Analyses performed across trials (pooled analyses and meta-analyses)

Not applicable.

7.4. Evaluator's conclusions on clinical efficacy for pivotal study indication

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. 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), SJC, TJC, CRP, ESR, RF and 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 ACR/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 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 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.[12] 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.[1] 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 dosage of CZP of 400 mg every four weeks plus MTX will be efficacious in the target group to which the proposed

[12] 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.

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.

8. Clinical safety

8.1. Studies providing evaluable safety data

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

8.1.1. Pivotal efficacy studies

In Period 1 of Study C-EARLY, the pivotal efficacy study, the following safety data were collected:

- General adverse events (AEs) were assessed by:
  - giving the subject the opportunity to report AEs spontaneously
  - asking an open-ended question, at each study visit, enquiring whether the subject had noticed anything unusual about their health since their last visit
  - review of self-assessment procedures, such as diary cards, by the investigator.
- AEs of particular interest were serious infections, including opportunistic infections, malignancy, including lymphoma, congestive heart failure, demyelinating-like disorders, aplastic anaemia, pancytopenia, thrombocytopenia, neutropenia and leukopenia, serious bleeding events, lupus and lupus-like illness, and serious skin reactions.
- Samples for laboratory tests, specifically haematology, biochemistry and urinalysis, were collected at Screening, Baseline, Weeks 4, 6, 8, 12, 20, 24, 36, 40 and 52/Withdrawal Visit. Samples for ESR and CRP were also collected at these Visits as well as at Week 2. Immunology samples were collected for analysis at Screening and Weeks 20, 24 and 52/Withdrawal Visit.
- Vital sign measurements were undertaken at Screening, Baseline, Weeks 2, 4, 6, 8, 12, 20, 24, 36, 40 and 52/Withdrawal Visit.
- ECGs were performed at Baseline and at the Week 52/Withdrawal Visit.
- Physical examinations were performed at Screening, Baseline, Weeks 2, 4, 6, 8, 12, 20, 24, 36, 40 and 52/Withdrawal Visit.
- Subjects were evaluated for symptoms and signs of active TB every 12 weeks and for risk of exposure to TB as part of the physical examination. Chest X-rays were undertaken 3 months prior to first study medication administration and at Week 52 (unless prohibited by local law or not recommended by the local guidelines).
- Pregnancy testing at Screening, Baseline, Weeks 4, 8, 12, 20, 24, 36, 40 and 52/Withdrawal Visit.
- TB testing within one month prior to first administration of the study medication and at Week 52 using the QuantiFERON test, Elispot test or purified protein derivative skin test.

8.1.2. Non-pivotal efficacy studies

Study C-OPERA provided data on treatment-emergent adverse events (TEAEs), treatment-related TEAEs, serious TEAEs, TEAES leading to discontinuation, deaths, AEs of interest (infections, malignancies, cardiac events, vascular events, neurological events, auto-immune

disorders, injection site reactions, systemic hypersensitivity reactions, serious bleeding events, serious skin reactions, interstitial lung disease, hepatic disorders), clinical laboratory parameters, vital sign measurements and physical examination findings.

8.2. Patient exposure

8.2.1. Study C-EARLY, Period 1

Based on the 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, above).

Comment: 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.

8.2.2. Study C-OPERA

Based on the 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; Q1 9.68, 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, above).

Comment: 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.

8.3. Adverse events

8.3.1. All adverse events (irrespective of relationship to study treatment)

8.3.1.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1 (PBO + MTX (n = 217), CZP + MTX (n = 659)), the proportion of subjects with any treatment-emergent adverse event (TEAE) was higher in the CZP + MTX group (79.7% (n = 525)) compared with the PBO + MTX group (72.8% (n = 158)). The incidence rate (IR) was 195.66 per 100 subject-years in the PBO + MTX group and 250.77 per 100 subject-years in the CZP + MTX group.

Most of the TEAEs were of mild or moderate severity. Severe TEAEs were reported in a higher proportion of subjects in the PBO + MTX group (9.2% (n = 20)) compared with the CZP + MTX group (7.1% (n = 47)). TEAEs requiring a dose change of MTX were reported in a higher proportion of subjects in the CZP + MTX group (11.1% (n = 73)) compared with the PBO + MTX group (6.5% (n = 14)).

Of note, pancytopenia, thrombocytopenia, hypersensitivity and interstitial lung disease were respectively reported in two subjects in the CZP + MTX group. No subjects in the PBO + MTX group were reported with these AEs during Period 1 of the study. Single subjects were reported with bone marrow toxicity, cardiac arrest, hepatocellular injury, anaphylactic shock, exfoliative rash in the CZP + MTX group. There were no such cases in the PBO + MTX group. Hepatotoxicity was reported in one subject in each treatment group. Parotid gland enlargement and salivary gland enlargement were reported in four subjects and one subject, respectively in the CZP + MTX group and no subjects in the PBO + MTX group.

Injection site reactions were more common in the CZP + MTX group (5.8% (n = 38)) compared with the PBO + MTX group (1.8% (n = 4)). The IR of events falling under the Infections and infestations SOC, per 100 subject-years, was higher in the CZP + MTX group (71.77 per 100 subject years, 95% CI (63.85, 80.40)) compared with the PBO + MTX group (52.70 per 100 subject years, 95% CI (41.52, 65.96)). There were subjects in the CZP + MTX group who had 'neutrophil count decreased' (n = 4) and 'White blood cell decreased' (n = 3) but no such cases in the PBO + MTX group.

The IRs for the TEAEs headache and alanine aminotransferase (ALT) increased were notably higher in the CZP + MTX group compared with the PBO + MTX group (Headache: PBO + MTX: 4.31 per 100 subject years, 95% CI (1.86, 8.48), CZP + MTX: 7.88 per 100 subject years, 95% CI (5.75, 10.54); ALT increased: PBO + MTX: 4.80 per 100 subject-years, 95% CI (2.20, 9.12), CZP + MTX: 7.24 per 100 subject years, 95% CI (5.21, 9.78)).

Comment: The TEAEs, and the proportions of subjects with specific TEAEs, reported in Study C-Early, are generally consistent with the adverse events described in in the draft PI in the tables entitled 'Summary of adverse events regardless of causality for event incidence ≥ 1% in the all CZP group and exceeding that of the placebo group reported during placebo-controlled RA clinical trials' and 'Adverse drug reactions in RA clinical trials and post-marketing'. However, 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, 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.

The proportions of subjects in the CZP + MTX group in Period 1 of Study C-EARLY with ALT increased (6.4%), AST increased (3.0%), and hepatic enzyme increased (2.4%), respectively, are higher than the proportions of subjects who received CZP +/- MTX with these TEAEs (1.8%, 1.2%, 1.1%, respectively) reported in the 'Summary of adverse events regardless of causality for event incidence ≥ 1% in the all CZP group and exceeding that of the placebo group reported during placebo-controlled RA clinical trials' in the PI.[1] The proportions of subjects with these TEAEs in the PBO + MTX group in Period 1 of Study C-EARLY were also higher than the proportions reported in the PI.[1] It is possible that this difference is related to a difference in the doses of MTX administered in Period 1 of Study C-EARLY compared with the other RA studies on which the current table is based, or to the fact that subjects in Study C-EARLY were DMARD-naïve.

With regard to other quantitative safety-related information in relation to RA in the 'Adverse effects' section, the results of Study C-EARLY are generally consistent. Differences in the frequencies of adverse effects of note, the PI states that 'Adverse reactions were reported in 34.0% of patients treated with Cimzia and 24.9% of patients treated with placebo in rheumatoid arthritis controlled clinical trials.'[1] In the SS1 of Study C-EARLY, drug-related TEAEs were reported in 42.2% of subjects treated with CZP + MTX and 31.8% of subjects treated with PBO + MTX. The PI states 'The proportion of patients who discontinued treatment due to adverse events during the controlled trials was 4.4% for patients treated with Cimzia and 2.7% for patients treated with placebo.' In Study C-EARLY, the proportions of subjects in the SS1 who discontinued study medication and were withdrawn from the study were 8.6% in the CZP + MTX group and 9.2% in the PBO + MTX group. The proportions of subjects in both the PBO + MTX and CZP + MTX groups that were 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%).[1]

It is noted that the case of salivary gland enlargement and cases of parotid gland enlargement in the CZP + MTX group were reported as not related to the study drug, suggesting that the occurrence of these adverse events in the CZP + MTX group, but not in the PBO + MTX group, may have been due to confounding factors not equally distributed between the treatment groups through the randomisation process, or to chance.

Of subjects who were exposed to CZP and who were positive for anti-CZP antibody at any time during Period 1, 90.5% (n = 57) had any TEAE during Period 1 compared with 78.5% of subjects (n = 468) who were exposed to CZP but remained negative for anti-CZP antibody during Period 1. Of note, 30.2 % (n = 19) of subjects who were anti-CZP antibody positive had TEAEs falling in the skin and subcutaneous tissue disorders SOC compared with 16.8% (n = 100) of subjects who were anti-CZP antibody negative.

Severe TEAEs were reported in a higher proportion of subjects who had a positive overall anti-CZP antibody status (14.3% (n = 9)) compared with subjects who had a negative overall anti-CZP antibody status (6.4% (n = 38)).

Comment: The currently approved PI for Cimzia indicates that no association has been seen between antibody development and the development of adverse events.[1] Only 63 subjects in Study C-EARLY were positive to anti-CZP antibody at any time during Period 1 and the absolute numbers of subjects reported with TEAEs were much lower than the absolute numbers of subjects who were reported with TEAEs and were negative to anti-CZP antibody at any time during Period 1. It is, therefore, difficult to interpret if there is a true difference in TEAE occurrence associated with anti-CZP antibody status.

8.3.1.2. Other studies

Based on the SS, in the Treatment Period of Study C-OPERA, nearly all subjects in each treatment group had at least one TEAE (PBO + MTX: 94.3% (n = 148), CZP + MTX: 96.2% (n = 153)). The IR per 100 patient-years was higher in the CZP + MTX group compared with the PBO + MTX group but the event rate (ER) per 100 patient years was similar (PBO + MTX: IR 556.89 per 100 patient-years, 95% CI (470.78, 654.18), ER 547.38 per 100 patient years, CZP + MTX: IR 601.93 per 100 patient years, 95% CI (510.33, 705.22), ER 541.26 per 100 patient years). A higher proportion of subjects in the PBO + MTX group had one or more TEAEs of severity severe (PBO + MTX: 5.1% (n = 8), CZP + MTX: 2.5% (n = 4)).

Of note, a higher proportion of subjects in the CZP + MTX group, compared with the PBO + MTX group, were reported with conjunctivitis allergic (PBO + MTX: 0.6% (n = 1), CZP + MTX: 2.5%(n = 4)), nausea (PBO + MTX: 15.9% (n = 25), CZP + MTX: 22.0% (n = 35)), gastroenteritis (PBO + MTX: 5.1% (n = 8), CZP + MTX: 9.4% (n = 15), cell marker increased (PBO + MTX: 0.6%(n = 1), CZP + MTX: 5.0% (n = 8)), hepatic enzyme increased (PBO + MTX: 0.6%(n = 1), CZP + MTX group: 3.1% (n = 5)), dizziness (PBO + MTX: 0.6%(n = 1), CZP + MTX: 2.5%(n = 4)), interstitial lung disease (PBO + MTX: 0.6%(n = 1), CZP + MTX: 3.1% (n = 5)), rash (PBO + MTX: 1.3%(n = 2), CZP + MTX: 6.9% (n = 11)), and epidermal necrosis (PBO + MTX: (n = 0), CZP + MTX: 0.6%(n = 1)). The IRs were also higher in the CZP + MTX group, compared with the PBO + MTX group, for these TEAEs.

In the SOCs in which TEAEs during the Treatment Period were reported in ≥ 10% of subjects in any treatment group, the proportions of subjects in each treatment group with TEAEs falling under the respective SOCs were generally similar by exposure interval.

Comment: After Week 24 the numbers of subjects remaining in the study decreased as increasing numbers of subjects discontinued the study in both treatment groups, particularly the PBO + MTX group so it is difficult to interpret the results by exposure interval after Week 24 as the subjects remaining in the study are likely to differ from those who discontinued the study.

It seems unusual that the TEAE IR is higher than the TEAE ER in both the PBO + MTX group and the CZP + MTX group. The sponsor is requested to clarify why this would be the case.

8.3.2. Treatment-related adverse events (adverse drug reactions)

8.3.2.1. Pivotal studies

In Period 1 of Study C-EARLY, the proportion of subjects in the SS1 with drug-related TEAEs was higher in the CZP + MTX group (42.2% (n = 278)) compared with the PBO + MTX group (31.8% (n = 69)).

Of note, in the CZP + MTX group, the 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 + MTX group were also reported to be related to the study drug.

8.3.2.2. Other studies

During the Treatment Period of Study C-OPERA, a similar proportion of subjects in each treatment group, based on the SS, had one or more drug related TEAEs (PBO + MTX: 66.9% (n = 105); CZP + MTX: 71.1% (n = 113)). Drug related TEAE preferred terms falling under the Investigations SOC were reported in a higher proportion of subjects in the CZP + MTX group (12.6% (n = 20)) compared with the PBO + MTX group (7.6% (n = 12)). The proportions of subjects with drug-related TEAEs falling under other SOCs were generally similar.

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

Comment: With regard to drug related TEAEs, from the information in the amended CSR, drug-related TEAEs are related to CZP/PBO and/or MTX in Study C-EARLY. In Study C-OPERA, it appears that the drug-related TEAEs are related to either CZP or PBO as CZP and PBO are described as the study drugs (investigational product and reference product) in the study protocol (amendment 3). The sponsor is requested to confirm this interpretation is correct.

It is noted that, in the amended Clinical Overview, the sponsor indicates that a case of bone marrow toxicity reported in Study C-EARLY was considered to be related to MTX although it is not reported as related in one of the amended tables for Period 1 of Study C-EARLY. In the amended Clinical Overview it is also indicated that 5.3% of subjects in the CZP + MTX group (n = 35) and 5.5% of subjects in the PBO + MTX group (n = 12) had adverse events associated with MTX use. The sponsor is requested to clarify the location of the supporting data that specifies the study drug to which a TEAE is related.

The drug-related TEAEs reported in Period 1 of Study C-EARLY are generally consistent with the adverse effects and their frequencies reported in the 'Adverse Effects' section, or with the safety information in the 'Precautions' section, of the current PI for Cimzia.[1] Of note, are the following adverse effects that are reported in the frequency category rare (≥ 1/10000 to < 1/1000) in the PI but were reported at higher frequencies in subjects in the CZP + MTX group in Period 1 of Study C-EARLY: pancytopenia (0.3%, n = 2), interstitial lung disease (0.3%, n = 2), erythema nodosum (0.2%, n = 1), skin exfoliation (0.2%, n = 1), and Raynaud's phenomenon (0.2%, n = 1). Alopecia is listed in the frequency category uncommon (≥ 1/1000 to < 1/100) in the PI but was reported in 2.0% of subjects (n = 13) in CZP + MTX group in Period 1 of Study C-EARLY.

Related TEAEs reported in the CZP + MTX group in Period 1 of Study C-EARLY that do not appear to be described in the current PI or draft PI include diarrhoea 1.8% (n = 12), vomiting 1.1% (n = 7), asthenia 0.6% (n = 4), drug intolerance 1.5% (n = 10), and fatigue 0.6% (n = 4). It is possible that some of these TEAEs may be related to MTX only or are reported as related to the study drug as the relationship to the study drug was missing and the TEAE was, therefore, counted as related. It is not clear if Table 12 in the current PI (also contained in the draft PI) is describing adverse reactions in RA clinical trials and post-marketing related to CZP only or CZP with or without concomitant MTX.

It is noted that the proportions of subjects with drug related TEAEs falling within certain SOCs were higher in both treatment groups in Study C-OPERA compared

with Study C-EARLY, for example the Gastrointestinal disorders SOC and the Infections and infestations SOC, even though the mean weekly MTX dose was higher in both treatment groups in Study C-EARLY. These differences may reflect the different study populations in the two studies. The sponsor is requested to provide comment.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Pivotal studies

In Period 1 of Study C-EARLY, one subject (0.5%) in the PBO + MTX group and two subjects (0.3%) in the CZP + MTX group had TEAEs leading to death. The subject in the PBO + MTX group had respiratory failure leading to death. In the CZP + MTX 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 + MTX group and 0.52 deaths per 100 subject-years in the PBO + MTX group.

The proportion of subjects in each group who had serious TEAEs was similar (PBO + MTX: 9.2% (n = 20), CZP + MTX: 10.6% (n = 70)). The IR per 100 subject years was also similar (PBO + MTX: 10.74 per 100 subject years, 95% CI (6.56, 16.59), CZP + MTX: 12.06 per 100 subject years, 95% CI (9.40, 15.23)). The ERs were, in general, supportive of the IRs but the rates were higher as the rate included the number of individual occurrences of the TEAE.

Of note, there were serious TEAEs reported only in the CZP + MTX group including cases of serious anaemia (n = 3 (0.5%)), pancytopenia (n = 2 (0.3%)), single cases of cardiac failure and cardiac arrest (0.2% respectively), various gastrointestinal disorders reported in single subjects (Gastrointestinal disorders SOC: n = 9 (1.4%)), hepatobiliary disorders (Hepatobiliary disorders SOC: n = 3 (0.5%)). The proportions of subjects, IRs per 100 subject years, and ERs per 100 subject years, of serious TEAEs falling under the Infections and infestations SOC were comparable between the treatment groups (PBO + MTX: 3.2% (n = 7), IR 3.69 per 100 subject years, 95% CI (1.48, 7.61), ER 4.15 per 100 subject years, CZP + MTX: 3.0% (n = 20), IR 3.34 per 100 subject-years, 95% CI (2.04, 5.15), ER 4.30 per 100 subject-years).

A greater proportion of subjects in the CZP + MTX group had serious TEAEs falling under the Injury, poisoning and procedural complications SOC (PBO + MTX: 0.5% (n = 1), IR 0.52 per 100 subject-years, 95% CI (0.01, 2.90)), CZP + MTX: 1.2% (n = 8), IR 1.33 per 100 subject-years, 95% CI (0.57, 2.62)). The majority of specific TEAE preferred terms were reported in single subjects.

The IR of serious TEAEs was higher in the subjects who were positive for anti-CZP antibody (IR 17.22 per 100 subject-years, 95% CI (7.87, 32.69)) compared with subjects who were negative for anti-CZP antibody (IR 11.55 per 100 subject-years, 95% CI (8.83, 14.83)).

Comment: Although TB is included as an adverse reaction in the PI for Cimzia, the reported death was of note due to the case's history.[1] The case had had a negative screening chest X-ray and negative QuantiFERON test result two months before the onset of the serious adverse events. No risk factors were identified for TB. This is concerning. It would appear that the subject was either infected with *Mycobacterium tuberculosis* after the screening tests or the presence of infection was not identified by these tests. The specific circumstances of this case are not described in the currently approved Australian PI for Cimzia. This case may have ramifications for the frequency of screening for TB required in patients being treated with CZP. In the PI, periodic evaluation for TB risk factors and testing for

latent infection is recommended but a recommended frequency of such evaluations is not specified. The sponsor is requested to provide comment in relation to this case and in relation to the frequency of periodic evaluation for TB risk factors and testing for latent infection. Infections including TB and serious opportunistic infections are included as an important identified risk in the summary of ongoing safety concerns in the RMP for CZP as shown in Table 10, below.

Table 10. Certolizumab pegol; sponsor's summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Infections including TB and serious opportunistic infections Moderate to severe congestive heart failure (NYHA Class III/IV) Hypersensitivity reactions Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma Demyelinating-like disorders Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia Lupus and lupus-like illness Immunogenicity including sarcoidosis New onset or worsening of psoriasis (palmoplantar pustular psoriasis) and related conditions Hepatobiliary events including hepatitis, hepatitis B virus reactivation, hepatic enzyme increased, and cholestasis
Important potential risks	Cardiac ischaemia and cerebrovascular ischaemia Serious bleeding events
Missing information	Pregnancy and lactation Children and adolescents Live vaccines Long-term use is psoriatic arthritis Long-term use in axial spondyloarthritis Use in patients with hepatitis C/HIV+

NYHA=New York Heart Association. TB=tuberculosis.

8.3.3.2. Other studies

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 (PBO + MTX: 8.9% (n = 14), CZP + MTX: 8.2% (n = 13)). The SAEs were generally single reports in one or other of the treatment groups. There was no notable difference between the treatment groups based on the reported serious TEAEs and drug-related serious TEAEs except that benign lung neoplasm and cervix carcinoma were reported in subjects in the CZP + MTX group as serious drug-related TEAEs.

Of note, of the subjects in the SS who had any serious TEAE (n = 13), all were negative for anti-CZP antibody.

Comment: The sponsor is asked to comment if CZP + MTX is considered to induce or promote the growth of benign or malignant neoplasms. It appears that none of the neoplasms reported in Study C-EARLY were considered related to the study drug. Specific neoplasms, both benign and malignant, are described as adverse reactions in Table 12 of the currently approved PI.[1]

8.3.4. Discontinuation due to adverse events

8.3.4.1. Pivotal studies

In Period 1 of Study C-EARLY, one subject in the CZP + MTX group discontinued due to a fatal AE. The proportion of subjects in each group who discontinued due to TEAEs was similar (PBO + MTX: 9.2% (n = 20), CZP + MTX: 8.6% (n = 57)) as was the IR per 100 subject years (PBO + MTX: 10.60 per 100 subject years, 95% CI (6.48, 16.38), CZP + MTX: 9.60 per 100 subject years, 95% CI (7.27, 12.44)). By SOC, the proportions of subjects who discontinued were similar in the two treatment groups, or higher in the PBO + MTX group compared with the CZP + MTX group, and the IRs were consistent. Of note, in the CZP + MTX group two subjects with pancytopenia, two subjects with interstitial lung disease, and six subjects with TEAEs falling in the Gastrointestinal disorders SOC, respectively, discontinued the study due to these TEAEs compared with no subjects in the PBO + MTX group. TEAEs reported in single subjects in the CZP + MTX group, and leading to discontinuation of the study, included bone marrow toxicity, anaphylactic shock, pulmonary tuberculosis, tuberculosis gastrointestinal and cardiac failure. No subjects in the PBO + MTX group were reported to have discontinued the study due to these TEAEs.

8.3.4.2. Other studies

During the Treatment Period of Study C-OPERA., a similar proportion of subjects in each treatment group, based on the SS, had one or more TEAEs leading to discontinuation of the study drug (PBO + MTX: 4.5% (n = 7), CZP + MTX: 5.7% (n = 9)). Of note, 5 subjects (3.1%) discontinued CZP + MTX due to interstitial lung disease compared to one subject (0.6%) in the PBO + MTX group.

8.4. Laboratory tests

8.4.1. Liver function

8.4.1.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1, the changes from Baseline at each measurement time point for liver function parameters were not notably different between the treatment groups. Mean and median changes from Baseline were generally small in both groups. The median change from Baseline in bilirubin remained at 0.00 in the PBO + MTX but in the CZP + MTX group it increased to 1.71 at Week 20 and remained at that value to the Last/Withdrawal Visit.

The proportions of subjects in each treatment group who had shifts from normal values at Baseline to high values at the end of Period 1 for each of the liver function parameters were, in general, similar.

Comment: Blood bilirubin increased is an adverse reaction reported in the PI for Cimzia.[1]

8.4.1.2. Other studies

The proportion of subjects in the CZP + MTX group with a shift from normal GGT value at Baseline to a high value at Week 52, was higher than in the PBO + MTX group (PBO + MTX: 8.2% (n = 6), CZP + MTX 13.5% (n = 15)). There were no other changes of liver function test parameters of note during the Treatment Period of Study C-OPERA.

8.4.2. Kidney function

8.4.2.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1, the changes from Baseline at each measurement time point for kidney function parameters were not notably different between the treatment groups. Mean and median changes from Baseline were generally small in both groups. The mean and median changes from Baseline in creatinine values were higher in the CZP + MTX group, compared with the PBO + MTX group, at each measurement time point. For urea, creatinine, and urate, the proportions of subjects who had normal values at Baseline and high values at the end of Period 1 were higher in the CZP + MTX group compared with the PBO + MTX, however, the differences were not large and were based on small absolute numbers of subjects (urea: PBO + MTX: 1.4% (n = 3), CZP + MTX: 2.4% (n = 16); creatinine: PBO + MTX: 0.5% (n = 1), CZP + MTX: 1.2% (n = 8); urate: PBO + MTX: 1.8% (n = 4), CZP + MTX: 3.0% (n = 20)).

8.4.2.2. Other studies

There were no changes of renal function test parameters of note during the Treatment Period of Study C-OPERA.

8.4.3. Other clinical chemistry

8.4.3.1. Pivotal studies

The changes from Baseline at each measurement time point for other clinical chemistry parameters were not notably different between the treatment groups in Period 1 of Study C-Early. Mean and median changes from Baseline were generally small in both groups.

There were no notable differences in the proportions of subjects in each treatment group who had shifts from normal values at Baseline to low or high values at the end of Period 1 in other chemistry parameters.

8.4.3.2. Other studies

During the Treatment Period of Study C-OPERA, of note, at the Last/Withdrawal visit, the mean and median KL-6 values were higher in the CZP + MTX group compared with the PBO + MTX group (KL-6 (U/mL): PBO + MTX: mean 34.2 (62.6), median 27.0 (range -179, 351), CZP + MTX: mean 87.8 (218.5), median 37.0 (range -97, 2149)). Also of note, the mean creatine kinase value was above the upper limit of the normal range in the CZP + MTX group at one measurement time point (Week 36) but the median value was within the normal range and the proportion of subjects in the CZP + MTX with a shift from normal total cholesterol value at Baseline to a high value at Week 52 was higher than in the PBO + MTX group (PBO + MTX: 8.2% (n = 6), CZP + MTX: 13.5% (n = 15)).

Comment: Dyslipidaemia and interstitial lung disease are adverse reactions reported for CZP.[1] The higher mean and median KL-6 values in the CZP + MTX group compared with the PBO + MTX group, and the higher proportion of subjects in the CZP + MTX with a

shift from normal total cholesterol value at Baseline to a high value at Week 52 compared with the PBO + MTX group, are, therefore, consistent with the known safety profile for CZP. Blood creatine phosphokinase increased is also a known adverse reaction.[1]

8.4.4. Haematology

8.4.4.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1, the mean and median changes from baseline at the Last/Withdrawal Visit were generally similar in each treatment groups for each of the haematological parameters evaluated. Of note, at the Last/Withdrawal Visit, there was a greater mean decrease from Baseline in neutrophils in the CZP + MTX group (mean (SD) -1.382 (2.130)) compared with the PBO + MTX group (mean (SD) -0.790 (2.264)). The median decrease from Baseline in neutrophils was also larger in the CZP + MTX group but the ranges of changes from Baseline at this visit were similar (PBO + MTX: median -0.970, range -8.24, 13.80; CZP + MTX: median -1.320, range -9.64, 11.35). The mean changes from Baseline in the neutrophils/leukocytes (%) were consistent (PBO + MTX: mean (SD) -1.86 (9.92); CZP + MTX: mean (SD) -9.88 (10.81)).

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. Differences of note, were the proportions of subjects who shifted from normal leukocyte values and normal neutrophil values, respectively, at Baseline, to low values at the end of Period 1 (leukocytes: PBO + MTX: 1.8% (n = 4), CZP + MTX: 4.6% (n = 30); neutrophils: PBO + MTX: 1.4% (n = 3), CZP + MTX: 6.7% (n = 44)). The proportion of subjects in the CZP + MTX group who shifted from normal neutrophils/leukocytes (%) value at Baseline to low at the end of Period 1 was also higher than the PBO + MTX group (PBO + MTX: 1.4% (n = 3), CZP + MTX: 5.8% (n = 38)).

8.4.4.2. Other studies

During the Treatment Period of Study C-OPERA, of note, the mean white blood cell values were lower at the Last/Withdrawal Visit compared with Baseline in both treatment groups with a larger mean change from Baseline value in the CZP + MTX group. The median decreases from Baseline in the white blood cell value at the Last/Withdrawal Visit were, however, the same in both treatment groups.

Also of note was a greater median decrease from Baseline in neutrophil value in the CZP + MTX group compared with the PBO + MTX group at the Last/Withdrawal Visit.

8.4.5. Urinalysis

8.4.5.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1, the sponsor reports that there were no clinically meaningful changes over time in the urinalysis parameters.

Comment: In Period 1 of Study C-EARLY the results for the urinalysis parameters were reported by subject for each measurement time point. The results were not summarised by treatment group.

8.4.5.2. Other studies

In Study C-OPERA, the proportions of subjects in either treatment group who had shifts from a normal value for a given urinalysis parameter at Baseline to an abnormal value during the Treatment Period were generally similar in each treatment group.

8.4.6. Electrocardiograph

8.4.6.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1, three subjects in the CZP + MTX 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 PBO + MTX had 'abnormal, clinically significant' 12-lead ECG reports at either of these measurement time points.

8.4.6.2. Other studies

In Study C-OPERA, the proportions of subjects in the SS with abnormal ECG findings were similar in each treatment group at Screening, Week 24, Week 52 and the Last/Withdrawal Visit as were the proportions of subjects who had a shift from a normal ECG at Screening to an abnormal ECG at Week 24, Week 52 and the Last/Withdrawal Visit, respectively.

8.4.7. Vital signs

8.4.7.1. Pivotal studies

In Period 1 of Study C-EARLY, based on the SS1, the mean and median changes from Baseline at each measurement time point were small for systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and temperature in each treatment group and there were no notable differences between the groups.

8.4.7.2. Other studies

During the Treatment Period of Study C-OPERA, there were no changes in vital sign parameters of note.

8.4.8. Chest X-ray

8.4.8.1. Pivotal studies

Based on SS1, in the CZP + MTX group, two subjects had clinically significant abnormalities on chest X-ray at the Week 52/Withdrawal Visit compared with one subject at the Screening Visit. One of these two subjects had rheumatoid nodules on chest X-ray at the Week 52/Withdrawal Visit. For the second subject, the description of the clinically significant abnormalities on chest X-ray at the Week 52/Withdrawal Visit was not located in the submission. In the PBO + MTX group, the number of subjects who had clinically significant abnormalities on chest X-ray decreased from two at the Screening Visit to one at the Week 52/Withdrawal Visit (MTX-induced pneumonitis). The proportion of subjects in each treatment group for whom the Week 52/Withdrawal Visit chest X-ray was not done was high (PBO + MTX: 41.9% (n = 91), CZP + MTX: 36.0% (n = 237)).

8.4.8.2. Other studies

During the Treatment Period of Study C-OPERA, four subjects in the CZP + MTX group had clinically significant abnormalities on chest X-ray at Last Visit/Withdrawal compared with three subjects in the PBO + MTX group. Of the four subjects in the CZP + MTX group, one subject had predominantly peripheral ground glass opacity over the lungs, two subjects each had infiltration opacity in one lung field and the fourth subject had reticular opacities in the lower lungs.

Comment: The sponsor is requested to comment on whether the four subjects in the CZP + MTX group during the Treatment Period of Study C-OPERA who had clinically significant abnormalities on chest X-ray at Last Visit/Withdrawal were considered to have drug-related interstitial lung disease. Interstitial lung disease is reported as an adverse reaction in the frequency category rare in the PI.[1] If all four subjects in the CZP + MTX group during the Treatment Period of Study C-OPERA who had clinically

significant abnormalities on chest X-ray at Last Visit/Withdrawal are considered to have drug-related interstitial lung disease, the frequency would be 4/159 (2.5%).

8.5. Post-marketing experience

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 CHMP.

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 tuberculosis
- 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.

Comment: The data referred to by the sponsor in relation to the PSUR covering the period 7 March 2013 to 6 March 2014, could not be located in the submission. The CHMP opinion in relation to this PSUR was located on the EMA's website.[13] It appears that, based on their assessment of the PSUR covering the period 7 March 2013 to 6 March 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) recommended changes to the EU SPC and the CHMP was in agreement. The recommended changes to the EU SPC were:

- an update to Section 4.4 (Special warnings and precautions for use) to indicate that there had been cases of TB reported despite patients receiving TB treatment before or concomitantly with CZP treatment
- an update to Section 4.8 (Undesirable effects) to include extrapulmonary TB, and the addition of 'zoster' to the example of herpes in the table of Section 4.8.[13]

The 'Precautions' section for the currently approved Australian PI for Cimzia includes a similar statement in relation to TB as that added to the EU SPC.[1,5] It is noted that the tables 'Adverse drug reactions in RA clinical trials and post-marketing', in the current Australian PI and draft PI, respectively, include 'tuberculosis', and 'viral infections (including herpes, papillomavirus, influenza)' whereas the same table in the EU SPC, includes the adverse drug reactions 'tuberculosis (including miliary, disseminated and extrapulmonary disease)' and 'viral infections (including herpes zoster, papillomavirus, influenza)'. It is noted that the 'Precautions' section and 'Adverse effects' section of the Australian PI provide further detail regarding the sites of reported TB infections and that 'herpes zoster disseminated' is described as an invasive opportunistic infection in the text of the 'Adverse effects' section. However, the sponsor is requested to comment on whether it proposes to make similar changes to the adverse reactions in the Australian PI.

[13] Committee for Medicinal Products for Human Use. Cimzia- Scientific conclusions and grounds recommending the variation to the terms of the marking authorisation. Procedure No.: EMEA/H/C/001037/PSUV/0041. Period covered by the PSUR: 7 March 2013 to 6 March 2014. 23 October 2014. EMA/CHMP/33893/2015. European Medicines Agency, London.

Only the Executive Summary of the PSUR covering the period from 7 March 2014 to 6 March 2015 was reviewed by the clinical evaluator. The Risk Management Plan (RMP) Version 10.1, dated 4 September 2014, was submitted with the PSUR. The summary of ongoing safety concerns in this RMP was reviewed as follows:

A draft RMP is not included in the submission.

The RMP Version 10.1 dated 4 September 2014 was submitted to the TGA with the PSUR covering the period from 7 March 2014 to 6 March 2015. With regard to the safety concerns highlighted in the Executive Summary of the PSUR, it is noted that the summary of ongoing safety concerns in the RMP includes, as one of the hepatobiliary events, hepatitis B reactivation as an important identified risk and immunogenicity, including sarcoidosis, is included as an important identified risk (see Table 10, above).

Based on the information in the Executive Summary of the PSUR for the period 7 March 2014 to 6 March 2015, it is anticipated that changes may have been made to the RMP to reflect the changes to the summary of ongoing safety concerns and to incorporate confirmed and potential new safety signals. The sponsor is requested to clarify if the RMP and Australian Specific Annex have been updated since the versions dated 4 September 2014, and 3 June 2015, respectively.

8.6. Integrated safety results

8.6.1. Overall RA pool

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.

There are two sets of data in the overall RA pool:

- Placebo-Controlled Data: Data from placebo-controlled studies (5 studies) or placebo controlled phases (from 5 studies)
- All Studies Data: Data from all studies and all phases (14 studies)

A summary of TEAEs in the overall RA pool is shown in Table 11, below.

Table 11. Overall RA Pool: Overall summary of TEAEs, Safety population

	PC Data Pool				All Data Pool
	PBO N=1137	CZP 200mg Q2W N=1762	CZP 400mg Q4W N=347	All CZP in PC N=2965	All CZP in All Studies N=4049
Patient-years at risk[a]	372.8	692.7	136.4	1302.1	9277.3
	n (%)				
Any TEAEs	713 (62.7)	1185 (67.3)	255 (73.5)	2048 (69.1)	3561 (87.9)
Intensity[b]					
Mild	530 (46.6)	925 (52.5)	192 (55.3)	1620 (54.6)	3059 (75.5)
Moderate	384 (33.8)	607 (34.4)	159 (45.8)	1120 (37.8)	2546 (62.9)
Severe	93 (8.2)	129 (7.3)	32 (9.2)	256 (8.6)	867 (21.4)
Relationship to study medication[c]					
No/unrelated/none	476 (41.9)	712 (40.4)	197 (56.8)	1294 (43.6)	2673 (66.0)
Unlikely	215 (18.9)	500 (28.4)	45 (13.0)	736 (24.8)	1827 (45.1)
Possible	211 (18.6)	479 (27.2)	39 (11.2)	861 (29.0)	1883 (46.5)
Probable	9 (0.8)	54 (3.1)	7 (2.0)	87 (2.9)	162 (4.0)
Highly probable	5 (0.4)	47 (2.7)	0	47 (1.6)	64 (1.6)
Yes/related/definite	72 (6.3)	36 (2.0)	57 (16.4)	128 (4.3)	259 (6.4)
Related to study medication[d]	283 (24.9)	554 (31.4)	95 (27.4)	1009 (34.0)	2047 (50.6)
SAEs	61 (5.4)	131 (7.4)	34 (9.8)	260 (8.8)	1063 (26.3)
TEAEs leading to death	1 (0.1)	6 (0.3)	0	11 (0.4)	58 (1.4)
TEAEs leading to withdrawal	31 (2.7)	83 (4.7)	14 (4.0)	131 (4.4)	536 (13.2)

CZP=certolizumab pegol; PBO=placebo; PC=placebo-controlled; Q2W=every 2 weeks; Q4W=every 4 weeks; RA=rheumatoid arthritis; SAE=serious adverse event; TEAE=treatment-emergent adverse events
Note: Data are displayed as numbers of subjects (percentage of subjects).

[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.
[b] Events with changing intensity are presented only for the maximum reported intensity.
[c] Events with changing relationship to study medication are presented only for the maximum reported relationship.
[d] Events with at least a possible relationship to study medication are categorized as related.

TEAEs were reported in a higher proportion of subjects in the All CZP in All Studies group (87.9%) compared with the All CZP in PC group (69.1%) but it is reported that the IR per 100 patient years was higher in the latter group (All CZP in All Studies group: IR: 189 per 100 patient years, All CZP in PC group: 336 per 100 patient-years).

The proportion of subjects reported with TEAEs was higher in the CZP group compared with the placebo group (All CZP in PC group: 69.1%, placebo group: 62.7%) and severe TEAEs were reported in similar proportions of subjects in the CZP and placebo groups (All CZP in PC group: 8.6%, placebo group: 8.2%).

Results of note that were highlighted by the sponsor:

- 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.
- 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.
- In the All CZP in PC group, it is reported that the IR of serious infections was 7.12 per 100 patient years, the IR of malignancies was 1.62 per 100 patient years, the IR of autoimmune disorders was 0.23 per 100 patient-years, and the IR of serious bleeding events was 0.31 per 100 patient-years.
- The incidence of serious cardiac events was reported to be higher in the CZP group compared with the placebo group in the overall RA pool but MACE was not specifically investigated. The sponsor indicates that there was a higher incidence of cardiovascular TEAEs with CZP treatment compared with placebo but the risk did not appear to increase with increased exposure. The sponsor highlights that heart failures, including congestive heart failure, were only reported in subjects treated with CZP in the overall RA pool.
- The proportion of subjects in the All CZP in PC group, and the placebo group, respectively, with Baseline/concomitant MTX use who had hepatic events was higher than those with no Baseline/concomitant MTX use (All CZP in PC group: MTX use 6.5%, no MTX use 3.5%, placebo group: MTX use 3.9%, no MTX use 3.0%).
- In the overall RA pool, the incidences of events that possibly represented early hypersensitivity reactions, delayed hypersensitivity reactions, and injection site reactions were reported to be low, with more of such events in the CZP-treated subjects compared with placebo-treated subjects. Events did not increase with exposure to CZP.
- In the PC data pool of the overall RA pool, 9.6% of subjects were reported to be anti-CZP antibody positive.
- In the overall RA pool, it is reported that there were no clinically relevant effects of CZP on markedly abnormal haematology or biochemistry values observed and that there were similar proportions of subjects in the placebo and All CZP in PC groups who had shifts to markedly abnormal haematology or biochemistry values. It is also reported that there were no clinically significant vital sign or physical finding in the studies which comprised the overall RA pool.
- The sponsor reports that there was a higher incidence of severe infections, serious infections and infections leading to withdrawal with CZP treatment compared with placebo but that the incidence did not increase with increasing exposure.
- The sponsor highlights that the IR of malignancies was similar in the CZP in PC group and placebo group and similar between the CZP in PC group and All CZP group suggesting that there was no evidence of an increased risk of malignancies with CZP treatment and that the risk was not increased with longer exposure to CZP.
- Serious blood dyscrasias reported in the overall RA pool were anaemia, pancytopenia, thrombocytopenia and leucopenia.
- The sponsor indicates that there was no indication of increased risk of serious bleeding events and hepatic events with increased exposure to CZP.
- The IR of serious skin disorders was higher in the All CZP in All studies group (0.54 per 100 patient years) compared with the All CZP in PC group (0.21 per 100 patient-years). In the All CZP in all studies group, 3 subjects were reported with SAEs of cutaneous vasculitis, leukocytoclastic vasculitis and vasculitic rash and 4 subjects had SAEs of urticaria.
- It is reported that, in the overall RA pool, there were no notable differences in TEAEs identified between subgroups for the demographic and baseline characteristics analysed

except that the incidences of TEAEs were lower in Central Europe and Eastern Europe compared with the other geographical regions.

Comment: It appears that the safety data from Study C-EARLY and Study C-OPERA would not be included in the integrated data as the cut off for the integrated data for the overall RA pool and early RA subpool, respectively, was 30 November 2011. Study C-OPERA was commenced just before that date and Study C-EARLY had not yet commenced.

The supporting data for the overall RA pool have not been included in the submission. The sponsor is requested to clarify if the data in the overall RA pool have previously been submitted to the TGA and to provide the report, RA ISS, referenced in the Summary of Clinical Safety.

The results in the CZP + MTX 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. It appears that subjects that were included in the All CZP in PC group in the overall RA pool could have received any dose of CZP and may or may not have been on a concomitant study medication. Of note, the proportion of subjects who had AEs that led to discontinuation in the CZP + MTX 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 + MTX 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 + MTX 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. This explanation seems reasonable. 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 CZP is initiated.

8.6.2. Early RA subpool

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. One subject received CZP intravenously and the remainder of the subjects received CZP subcutaneously. For the safety analyses of the integrated data from all studies, 270 subjects were included in the CZP 200mg every 2 weeks (Q2W) group, 347 subjects were included in the CZP Q2W group, which included any dose of CZP given every 2 weeks, and 50 subjects were included in the CZP 400 mg every 4 weeks(Q4W) group. The estimated exposure to CZP treatment was 737.1 patient years. In the PC Data Pool, 305 subjects had been treated with CZP (All CZP in PC). For the safety analyses of the integrated data from the PC data pool, 210 subjects were included in the CZP 200mg Q2W group, 261 subjects were included in the CZP Q2W group and 35 subjects were included in the CZP 400 mg Q4W group. One hundred subjects had been treated with PBO.

The sponsor indicates that the safety results from the early RA subpool were consistent with the safety results in Study C-EARLY and that the incidence and pattern of AEs observed in the early

RA subpool is consistent with the incidence and pattern of AEs observed in the overall RA subpool.

A summary of TEAEs in the early RA subpool is shown in Table 12, below.

Table 12. Early RA Subpool, overall summary of TEAEs, Safety population

	PC Data Pool				All Data Pool
	PBO N=100	CZP 200mg Q2W N=210	CZP 400mg Q4W N=35	All CZP in PC N=305	All CZP in All Studies N=401
Patient-years at risk[a]	33.3	71.3	13.9	116.2	737.1
	n (%)				
Any TEAEs	66 (66.0)	150 (71.4)	24 (68.6)	215 (70.5)	343 (85.5)
Intensity[b]					
Mild	50 (50.0)	115 (54.8)	20 (57.1)	168 (55.1)	295 (73.6)
Moderate	39 (39.0)	65 (31.0)	12 (34.3)	99 (32.5)	222 (55.4)
Severe	8 (8.0)	22 (10.5)	6 (17.1)	36 (11.8)	83 (20.7)
Relationship to study medication[c]					
No/unrelated/none	48 (48.0)	89 (42.4)	22 (62.9)	134 (43.9)	258 (64.3)
Unlikely	23 (23.0)	51 (24.3)	4 (11.4)	69 (22.6)	157 (39.2)
Possible	16 (16.0)	59 (28.1)	3 (8.6)	86 (28.2)	179 (44.6)
Probable	2 (2.0)	7 (3.3)	0	8 (2.6)	19 (4.7)
Highly probable	0	8 (3.8)	0	8 (2.6)	11 (2.7)
Yes/related/definite	3 (3.0)	4 (1.9)	4 (11.4)	10 (3.3)	15 (3.7)
Related to study medication[d]	20 (20.0)	72 (34.3)	7 (20.0)	105 (34.4)	197 (49.1)
SAEs	9 (9.0)	15 (7.1)	3 (8.6)	26 (8.5)	81 (20.2)
TEAEs leading to death	0	1 (0.5)	0	2 (0.7)	9 (2.2)
TEAEs leading to withdrawal	2 (2.0)	16 (7.6)	0	21 (6.9)	53 (13.2)

CZP=certolizumab pegol; PBO=placebo; PC=placebo-controlled; Q2W=every 2 weeks; Q4W=every 4 weeks; RA=rheumatoid arthritis; SAE=serious adverse event; TEAE=treatment-emergent adverse events

Note: Data are displayed as numbers of subjects (percentage of subjects).

[a] Patient years at risk was calculated as the total study medication duration replacing the maintenance dosing interval (14 or 28 days) by 70 days censored by date of last clinical contact.

[b] Events with changing intensity are presented only for the maximum reported intensity.

[c] Events with changing relationship to study medication are presented only for the maximum reported relationship.

[d] Events with at least a possible relationship to study medication are categorized as related.

Of note, from the supporting data in the submission:

- In the All CZP in PC group, the majority of subjects (79.3% (n = 242)) were using MTX at Baseline and approximately half of the subjects (51.8% (n = 158)) were receiving a dose of MTX of at least 15 mg/week. The proportions in the All CZP in All Studies subjects were similar.
- The All CZP in PC and PBO groups were generally similar at Screening with regard to baseline and demographic factors as were the All CZP in PC and All CZP in All Studies groups.

- Total study drug duration was longer in the All CZP in PC group compared with the PBO group (PBO: 31.2 years, All CZP in PC: 109.1 years) and longer in the All CZP in All Studies group compared with the All CZP in PC group (All CZP in All Studies: 687.0 years, All CZP in PC: 109.1 years).
- In the All CZP in All Studies group, 35.4% (n = 142) of subjects had at least 12 months exposure to CZP, 26.2% (n = 105) had at least 24 months exposure to CZP and 14.2% (n = 57) had at least 60 months exposure to CZP.
- Similar proportions of subjects in the All CZP in PC group and PBO group had any TEAE (PBO: 66.0% (n = 66), All CZP in PC: 70.5% (n = 215)). Similar proportions of subjects had TEAEs of mild, moderate and severe intensity, respectively. A higher proportion of subjects in the All CZP in PC group, compared with the PBO group, had TEAEs related to the study medication (PBO: 20.0% (n = 20), All CZP in PC: 34.4% (n = 105)) and TEAEs leading to withdrawal (PBO: 2.0% (n = 2), All CZP in PC: 6.9% (n = 21)) (see Table 12, above).
- In subjects with a baseline MTX dose of ≥ 15 mg/day, similar proportions of subjects in the PBO and All CZP in PC groups had TEAEs related to the study medication (PBO (n = 55): 29.1% (n = 16), All CZP in PC (n = 158) 30.4% (n = 48)).
- Compared with the All CZP in PC group, higher proportions of subjects in the All CZP in All Studies group had any TEAE, TEAEs with intensity severe, SAEs, TEAEs leading to death and TEAEs leading to withdrawal (See Table 12, above).
- Upper respiratory tract infection was the TEAE reported in the highest proportion of subjects in the All CZP in PC group (6.9% (n = 21)), followed by nasopharyngitis (6.6% (n = 20), headache (5.9% (n = 18)), rash (5.6% (n = 17)) and nausea (5.2% (n = 16)).
- Compared with subjects who received CZP 200mg Q2W, higher proportions of subjects who received CZP 400 mg Q4W were reported with certain TEAE PTs including nasopharyngitis, headache and rash but the number of subjects in the CZP 400 mg Q4W group was small (n = 35) and the absolute numbers of subjects reporting these AEs in the CZP 400 mg Q4W group were small.
- Of note, one subject in the CZP 200 mg Q2W group was reported with severe lupus-like syndrome (and was in the All CZP in PC group).
- In the All Data Pool, single subjects who received any dose of CZP Q2W (but not in the All CZP in PC group) were reported with sudden death, sarcoidosis, disseminated TB and renal failure. One subject in the CZP 400mg Q4W was reported with bronchopneumopathy.
- Of note, the IR of any related TEAEs was twice as high in the CZP 200 mg Q2W group compared with the PBO group (PBO: 68.74 per 100 patient years, 95% CI (41.99, 106.16), CZP 200 mg Q2W: 136.23 per 100 patient years, 95% CI (106.59, 171.56)).
- In relation to the treatment-related TEAEs, of note:
  - neutropenia was reported in 2 subjects in the All CZP in PC group and no subjects who had been treated with PBO
  - there were reports of treatment-related cardiac disorders in subjects treated with CZP but not with PBO
  - in the All CZP in PC group, compared with the PBO group, there were notably higher IRs of treatment-related TEAEs falling under the Infections and infestations SOC and Skin and subcutaneous tissue disorders SOC
  - 15 subjects in the All CZP in PC group had treatment-related TEAEs that led to study withdrawal. No subjects in the PBO group withdrew due to treatment-related TEAEs.

- Serious cardiac disorders were reported in no subjects who had received placebo and five subjects in the All CZP in PC group of which three were assessed as related to the study treatment (congestive cardiomyopathy, acute myocardial infarction and myocardial infarction).
- Three TEAEs leading to death (cardiac arrest, pneumonia necrotising, blood glucose increased) were reported in two subjects in the All CZP in PC group compared with no subjects in the placebo group. These subjects had received CZP 200 mg Q2W. In the All CZP in All Studies group, 9 subjects, including the two above-mentioned subjects, had 13 TEAEs leading to death. The TEAEs leading to death reported in the additional 7 subjects were reported in single subjects (myocardial infarction, sudden death, pyrexia, peritoneal infection, disseminated TB, colon cancer, metastases to liver, metastases to lung, lung cancer metastatic, cerebrovascular accident). Of the TEAEs leading to death, pneumonia necrotising, pyrexia, disseminated TB, colon cancer, metastases to liver, and metastases to lung were assessed as having a possible, probable, highly probable or definite relationship to the study medication.
- One subject who had baseline MTX use and who received the CZP 200 mg Q2W was reported with hepatitis toxic. One subject from Eastern Europe who had received CZP 200 mg Q2W was reported with disseminated TB.
- In the PC Data Pool, comparing CZP 200 mg Q2W and placebo, the following TEAE HLT or PT IRs were of particular note:
  - ischaemic coronary artery disorders: PBO: 0, CZP 200 mg Q2W: 4.26 per 100 patient years, 95% CI (0.88, 12.44)
  - abdominal pain upper: PBO: 0, CZP 200 mg Q2W: 4.37 per 100 patient years, 95% CI (1.42, 10.21)
  - nausea: PBO: 9.10 patient years, 95% CI (1.88, 26.58), CZP 200 mg Q2W: 17.36 per 100 patient years, 95% CI (8.97, 30.33)
  - pyrexia: PBO: 0, CZP 200 mg Q2W: 5.64 per 100 patient years, 95% CI (1.54, 14.44)
  - lower respiratory tract and lung infections: PBO: 3.01 patient years, 95% CI (0.08, 16.79), CZP 200 mg Q2W: 15.88 per 100 patient years, 95% CI (7.93, 28.42)
  - urinary tract infection: PBO: 3.03 patient years, 95% CI (0.08, 16.86), CZP 200 mg Q2W: 12.93 per 100 patient years, 95% CI (5.91, 24.54)
  - back pain: PBO: 0, CZP 200 mg Q2W: 14.41 per 100 patient years, 95% CI (6.91, 26.50)
  - muscle spasms: PBO: 0, CZP 200 mg Q2W: 7.20 per 100 patient years, 95% CI (2.34, 16.79).
- The IRs of TEAEs in the All CZP in All Studies group were generally similar to, or lower than, the IRs of TEAEs in subjects in the All CZP in PC group.
- Of note, the IRs of some TEAEs were higher in subjects receiving CZP 400 mg Q4W than in subjects receiving CZP 200 mg Q2W. For example, neutropenia was reported in one subject receiving CZP 400 mg Q4W (IR 7.24 per 100 patient-years (95% CI (0.18, 40.33)) and no subjects receiving CZP 200 mg Q2W.
- The IR of SAEs was higher in the All CZP in PC group than the All CZP in All Studies group (All CZP in PC: IR 23.42, 95% CI (15.30, 34.31), All CZP in All Studies: IR 12.62, 95% CI (10.02, 15.69)) as was the IR of TEAEs leading to withdrawal (All CZP in PC: IR 18.56, 95% CI (11.49, 28.38), All CZP in All Studies: IR 7.28, 95% CI (5.45, 9.52)).

- 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)).
- In the Open Label Data Pool, there were 2 subjects (0.7%) in the CZP Q2W group who had a bilirubin level ≥ 1 x ULN and 3 x ULN elevation of AST or ALT. It is noted that a subject had ALT 349 U/L (normal range 6 to 48), AST 952 U/L (normal range 10 to 45), and bilirubin 392 micromol/L (normal range 3 to 21), 1071 days since first injection in the current period. This case also had markedly abnormal high values of ALP, creatinine, and potassium at this measurement time point.

Comment: The All CZP in PC group (n = 305) included 76% of the subjects who were in the All CZP in All Studies group (n = 401). The number of subjects who received PBO was 100. IRs were based on small absolute numbers of TEAEs.

The safety profile in the early RA subpool seems to be generally consistent the safety findings in Period 1 of Study C-EARLY even though subjects in the early RA pool were not DMARD naïve. From the early RA data subpool no specific new safety issues were identified that are not already identified in the PI.

Of note, subjects in the All Data pool who had RA disease for less than one year and were receiving CZP Q2W had an IR of any hepatic events of 5.61 per 100 patient years whereas in Study C-EARLY the IR in the CZP + MTX group was 15.54 per 100 subject-years. The explanation for the difference between the two groups may be, as commented above for the Overall RA Pool, the initiation of MTX treatment in DMARD-naïve subjects in the CZP + MTX group in Study C-EARLY. These results suggest that the frequencies of certain TEAEs in DMARD-naïve patients may be higher than the frequencies in patients who are not DMARD-naïve. The IR of any hepatic event in the PBO + MTX group in Period 1 of Study C-EARLY was similar to the IR in the CZP + MTX group.

Of note, the IRs of some TEAEs in subjects receiving CZP 400 mg Q4W were higher than the IR in the 200 mg Q2W. Small absolute numbers of subjects were included in the CZP 400 mg Q4W group in all studies (n = 50) and in the PC data pool (n = 35). The currently approved PI indicates, in the 'Dosage and administration' section, that 400 mg every 4 weeks has been shown to be safe and effective.[1] However, this submission does not include any studies that evaluate the efficacy and safety of that dosage regimen in relation to the proposed indication.

The sponsor is requested to clarify if it has been ruled out that the subject with ALT and AST > 3 x ULN and bilirubin > 2 x ULN was a Hy's Law case and also whether the two subjects in the CZP Q2W group in the Open Label Data Pool who each had a bilirubin level ≥ 1 x ULN and 3 x ULN elevation of AST or ALT were Hy's Law cases.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. 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 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 TEAEs in the Hepatobiliary disorders SOC.

Comment: As commented above in section 8.3.1.1 (section: All adverse events, pivotal study), 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%).[1] 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.

8.7.2. 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, ITP and leucopenia in the CZP + MTX group but these were not reported as serious.

Comment: 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.[1] In the 'Adverse effects' section of the Australian PI, 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.[5] The sponsor is requested to confirm this.

8.7.3. 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.

8.7.4. Cardiovascular safety

During Period 1 of Study C-EARLY, based on the SS1, two subjects in the CZP + MTX group had MACE events (acute myocardial infarction (n = 1), myocardial infarction (n = 1)) that were serious AEs 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.

8.7.5. 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 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.

8.7.6. 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 TB and died. A comment regarding this case is made above in Section: 8.3.4.1.

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.

8.7.7. 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.

8.7.8. 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.

8.7.9. 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 PTs 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 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)).

8.7.10. 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.

8.7.11. 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 hematopoietic 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 hematopoietic 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.

Comment: 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.[1] 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.

8.7.12. 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.

Comment: Interstitial lung disease is listed as an adverse reaction in the PI in the frequency category rare.[1] 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.

8.7.13. 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 13, below.

Table 13. 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).

Comment: Based on Table 13 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.

8.8. Evaluator's overall conclusions on clinical 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.[1] 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.[1] 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 a duration of RA of 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.[1] 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.[1]

9. First round benefit-risk assessment

9.1. 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.

9.2. 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.[1] 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.[1] The IR of any hepatic event in the CZP + MTX group in Study C-EARLY group was notably higher than the IR in subjects in the integrated data (All Data pool) who 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.[1] 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.

9.3. 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.

10. 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 following clinical questions in Section 11
- amending the draft PI as recommended or providing justification as to why the recommended changes should not be made.

11. Clinical questions

11.1. Pharmacokinetics

The clinical evaluator had no questions for the sponsor.

11.2. Pharmacodynamics

The clinical evaluator had no questions for the sponsor.

11.3. Efficacy

The sponsor to be asked to:

1. Clarify whether the formulation used in Period 1 of Study C-Early is identical to that marketed in Australia.
2. Clarify the definition of severe, active, progressive RA in the proposed indication.
3. Provide, or clarify the location of the information in the CSR for Study C-EARLY, the number of subjects in each treatment group in Period 1 of Study C-EARLY who were withdrawn from the study because they did not tolerate at least 15 mg MTX/week during the first 8 weeks of the study.
4. Confirm that 15 subjects (1.7%) of the overall randomised subject population in Period 1 of Study C-EARLY were randomised in Sweden.
5. As unblinded study centre personnel performed the ESR measurement and entered the ESR value into the IXRS in Period 1 of Study C-EARLY, and the laboratory staff who recorded the ESR values received from study centres were also not blind to the treatment assignment, this may be a potential source of bias. Please provide comment.
6. With regard to the additional analysis undertaken using the RAD1 in Period 1 of Study C-EARLY, in which the Week 52 mTSS scores of all subjects were estimated by linear extrapolation of the post-Baseline mTSS scores, please clarify if this means that Week 0 mTSS score was used to extrapolate the Week 52 score for each subject.
7. With regard to the additional analysis undertaken using the RAD1 in Period 1 of Study C-EARLY, in which the Week 52 mTSS score of all subjects were estimated by linear extrapolation of the post-Baseline mTSS score, it is not clear to the clinical evaluator how such an extrapolation would be undertaken. Please provide clarification.
8. Clarify if there was a comparison undertaken of the change in mTSS score from Baseline between those subjects in Period 1 of Study C-EARLY who had a change in mTSS score at Week 52 based on a Week 52 radiograph and those subjects for whom the change in mTSS score at Week 52 was estimated, stratified by treatment group. If such a comparison was undertaken, please clarify the location of the results in the CSR.
9. Clarify the proportion of subjects in each treatment group in Period 1 of Study C-EARLY who received the scheduled study treatment up to Week 52 but were not eligible for Period 2.
10. Clarify if the CS1 in Period 1 of Study C-EARLY includes subjects who discontinued and had a Withdrawal Visit in place of the Week 52 visit.
11. With regard to the results for mandatory IXRS withdrawals at key visits in Period 1 of Study C-EARLY, the results in of a table from the amended CSR and another from the table set for Study RA0055 Period 1 CSR Amendment 1 differ. Please clarify why the results are different.
12. The numbers of subjects by discontinuation reason 'adverse event' in Period 1 of Study C-EARLY are not identical in the participant flow diagram in the amended CSR of Study C-EARLY (PBO + MTX n = 17, CZP + MTX n = 51) (See Figure 6 in the Efficacy section above for this study) compared with the relevant table from the amended Period 1 tables for Study C-EARLY (PBO + MTX n = 20, CZP + MTX n = 56). Please clarify why the results are different.

13. With regard to the definition of active disease in the inclusion criteria for Study C-EARLY, the mean and median number of swollen and tender joints at Screening, and the mean and median DAS28 (ESR), CRP and ESR values, respectively, at Screening do not appear to be presented in the submission. Please provide comment on this point.
14. In Period 1 of Study C-EARLY, it is not clear what proportion of subjects in each treatment group had RA that was severe and active and progressive. Please clarify the location of this information in the CSR or provide it.
15. Clarify if subjects were permitted to receive non-pharmacological management of RA in Period 1 of Study C-EARLY and, if so, whether there was a difference in the proportion of subjects in each treatment group receiving such therapy at Baseline.
16. In Period 1 of Study C-EARLY, for a number of the efficacy outcomes that reported changes from Baseline at different time points in the study, not all of the subjects in the analysis set were included in the analysis at each reported measurement time point despite the use of LOCF to deal with missing data, for example, change from Baseline in DAS28 (ESR) by week for the FAS1. Please clarify why this is the case.
17. Clarify if the primary analysis of the primary efficacy outcome in Study C-OPERA was only the analysis in the FAS performed using rank ANCOVA with linear extrapolation for missing data (ANCOVA LINEAR) or if the ANCOVA model undertaken for the measured values, using the treatment group as a factor and Baseline value as a covariate, was also a primary analysis of the primary efficacy outcome.
18. In a specified table in the CSR for Study C-OPERA, it is not clear to the clinical evaluator why one subject in the CZP + MTX group in the FAS did not contribute to the change from Baseline analyses for mTSS, bone erosion and JSN, even though linear extrapolation was used to impute missing data. Please clarify this point.
19. 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 Period 1 of Study C-EARLY.

11.4. Safety

20. Provide an update on the EU regulatory status of Cimzia and advise if there have been any concerns raised by other regulators in countries where a similar application has been submitted.
21. In Period 1 of Study C-EARLY, 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. Please confirm the number of subjects who were exposed to CZP + MTX for at least 365 days.
22. In Study C-OPERA, 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. Please confirm the number of subjects who were exposed to CZP + MTX for at least 365 days.
23. In Study C-OPERA, it seems unusual that the TEAE IR is higher than the TEAE ER in both the PBO + MTX group and the CZP + MTX group. Please clarify why this would be the case.
24. With regard to drug-related TEAEs, from the information in the amended CSR for Study C-EARLY, drug-related TEAEs are related to CZP/PBO and/or MTX in Study C-EARLY. In Study C-OPERA, it appears that the drug-related TEAEs are related to either CZP or PBO as CZP and PBO are described as the study drugs (investigational product and reference

product) in the study protocol (amendment 3). Please confirm whether this interpretation is correct.

25. It is noted that, in the amended Clinical Overview, the sponsor indicates that a case of bone marrow toxicity reported in Period 1 of Study C-EARLY was considered to be related to MTX although it is not reported as related in the relevant amended tables for Period 1 of Study C-EARLY. In the amended Clinical Overview it is also indicated that 5.3% of subjects in the CZP + MTX group (n = 35) and 5.5% of subjects in the PBO + MTX group (n = 12) in Period 1 of Study C-EARLY had adverse events associated with MTX use. Please clarify the location of the supporting data that specifies the study drug to which a TEAE is related.
26. It is noted that the proportions of subjects with drug-related TEAEs falling within certain SOCs were higher in both treatment groups in the Treatment Period of Study C-OPERA compared with Period 1 of Study C-EARLY, for example the Gastrointestinal disorders SOC and the Infections and infestations SOC, even though the mean weekly MTX dose was higher in both treatment groups in Study C-EARLY. These differences may reflect the different study populations in the two studies. Please provide comment.
27. With regard to the fatal case of TB in Period 1 of Study C-EARLY, please provide further comment in relation to this case and in relation to the frequency of periodic evaluation for TB risk factors and testing for latent infection recommended for patients treated with CZP. It is noted that the currently approved Australian PI is silent regarding the frequency of such periodic testing.
28. Comment on whether CZP + MTX is considered to induce or promote the growth of benign or malignant neoplasms.
29. Comment on whether the four subjects in the CZP + MTX group during the Treatment Period of Study C-OPERA who had clinically significant abnormalities on chest X-ray at Last Visit/Withdrawal were considered to have drug-related interstitial lung disease.
30. With regard to the changes to the EU SPC recommended by the Pharmacovigilance Risk Assessment Committee based on the PSUR covering the period 7 March 2013 to 6 March 2014, please comment on whether the sponsor proposes to make similar changes to the adverse reactions 'tuberculosis', and 'viral infections (including herpes, papillomavirus, influenza)' in the table 'Adverse drug reactions in RA clinical trials and post-marketing' in the Australian PI.
31. The supporting data for the overall RA pool have not been included in the submission. Please clarify if the data in the overall RA pool have previously been submitted to the TGA and provide the report, RA ISS, referenced in the Summary of Clinical Safety.
32. With regard to the early RA subpool, please clarify if it has been ruled out that the subject with ALT and AST > 3 x ULN and bilirubin > 2 x ULN was a Hy's Law case and also whether the two subjects in the CZP Q2W group in the Open Label Data Pool who each had a bilirubin level ≥ 1 x ULN and 3 x ULN elevation of AST or ALT were Hy's Law cases.
33. Clarify if the RMP and Australian Specific Annex have been updated since the versions dated 4 September 2014, and 3 June 2015, respectively.

12. Second round evaluation of clinical data submitted in response to questions

12.1. Efficacy

12.1.1. Question 1

- Clarify whether the formulation used in Period 1 of Study C-Early is identical to that marketed in Australia.

12.1.1.1. Sponsor's response

The sponsor confirms that the formulation used in Period 1 of Study C-Early is identical to that marketed in Australia.

12.1.1.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.2. Question 2

- Clarify the definition of severe, active, progressive RA in the proposed indication.

12.1.2.1. Sponsor's response

The sponsor highlights that the proposed indication is based on the study population.

With regard to severe disease, the sponsor indicates that it is not aware of a standard definition of severe disease but clarifies that severe disease is related to disease activity and that disease activity can be evaluated using a composite score, DAS28 (ESR), which takes into account signs and symptoms, based on SJC and TJC, patient global assessment of disease activity and a laboratory marker of inflammation (ESR). The sponsor highlights that there is an established definition for the degree of disease activity based on the DAS28 (ESR) and that an inclusion criterion of Study C-EARLY was that subjects were to have a DAS28 (ESR) > 3.2, indicating at least moderate disease activity. The sponsor highlights that 96.5% of subjects in Study C-EARLY had high disease activity based on a DAS28 (ESR) > 5.1, and that this high disease activity is considered, by the sponsor, to be severe disease. The sponsor also highlights that the study population also had a high level of inflammatory markers, which it considers to be correlated with the severity of disease.

With regard to active disease, the sponsor highlights that this relates to criterion 9 of the inclusion criteria of Study C-EARLY, specifically that subjects have ≥ 4 swollen joints and ≥ 4 tender joints (DAS28) at Screening and Baseline, a DAS28 (ESR) > 3.2 at Screening and Baseline, and CRP ≥ 10 mg/L at Screening and/or ESR ≥ 28 mm/h at Screening and Baseline.

With regard to progressive disease, the sponsor indicates that is not aware of a standard definition of progressive disease. The sponsor highlights the prognostic factors that have been associated with a higher probability of disease progression that were included in Section 3.4.1 of the CSR for Study C-EARLY, specifically, high disease activity, SJC ≥ 3, the presence of ACPA and/or RA factor, especially at high levels, and high CRP (≥ 6 mg/L) and ESR levels. The sponsor highlights that CRP is correlated with radiological progression and has included reference to a supporting publication.

The sponsor also highlights that 77.8% had erosions at Baseline, indicating radiographic progression.

12.1.2.2. Clinical evaluator's comment

The sponsor's response is acceptable. The referenced publication, a review article, was accessed on the internet and is supportive of the sponsor's comments regarding progressive disease.[14]

There do not appear to be standard definitions of severe RA, active RA and progressive RA.

12.1.3. Question 3

- Provide, or clarify the location of the information in the CSR for Study C-EARLY, the number of subjects in each treatment group in Period 1 of Study C-EARLY who were withdrawn from the study because they did not tolerate at least 15 mg MTX/week during the first 8 weeks of the study.

12.1.3.1. Sponsor's response

The sponsor indicates that it is unable to provide the number of subjects in each treatment group in Period 1 of Study C-EARLY who were withdrawn from the study because they did not tolerate at least 15 mg MTX/week during the first 8 weeks of the study as this information was not specifically collected. The sponsor indicates that, of subjects who were discontinued with a total of 60 days or less on study medication, there were 8 subjects (1.2%) in the CZP + MTX group of the RS1 who had drug-related AEs that led to discontinuation that were possibly related to MTX. The sponsor indicates that there are other subjects who had a primary reason for discontinuation other than an AE who had one or more AEs that were suggestive of MTX intolerance.

12.1.3.2. Clinical evaluator's comment

The sponsor's response is acceptable.

The proposed indication does not specify a minimum, or maximum, dose of MTX to be administered in combination with CZP. Therefore, as commented in Section 7.1.1.3. (above), the results of Study C-EARLY may not be generalisable to the target population of the proposed indication if, in clinical practice, the dose of MTX given concomitantly with CZP is less than 15 mg weekly.

12.1.4. Question 4

- Confirm that 15 subjects (1.7%) of the overall randomised subject population in Period 1 of Study C-EARLY were randomised in Sweden.

12.1.4.1. Sponsor's response

The sponsor confirms that 15 subjects (1.7%) of the overall randomised subject population (n = 879) in Period 1 of Study C-EARLY were randomised in Sweden. The sponsor had highlighted the supporting data in the CSR for Study C-EARLY.

12.1.4.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.5. Question 5

- As unblinded study centre personnel performed the ESR measurement and entered the ESR value into the IXRS in Period 1 of Study C-EARLY, and the laboratory staff who recorded the ESR values received from study centres were also not blind to the treatment assignment, this may be a potential source of bias. Please provide comment.

[14] Emery P et al. Clinical identification and treatment of rapidly progressing disease state in patients with rheumatoid arthritis. Rheumatology.2008;47: 392-8.

12.1.5.1. Sponsor's response

The sponsor highlights that in the protocol for Study C-EARLY, and the site blinding plan, specified that blinded staff must not be involved in activities related to study drug administration and determination of the ESR values, and that the protocol specified the investigators were to delegate the measurement of the ESR values, and the reporting of the values to the central laboratory, to unblinded site personnel. The sponsor indicates that the unblinded individuals at the central laboratory had no role in the assessments of study subjects or the analysis of data and reported ESR values to the investigator per protocol, at Screening and Baseline, to enable the investigator to determine if subjects met the inclusion criteria. The blinded personnel did not, therefore, have knowledge of the ESR values that could bias their evaluation of the subjects.

12.1.5.2. Clinical evaluator's comment

The sponsor's response is acceptable. The reason for the use of unblinded staff to administer the study drug, determine ESR values and report the values to the central laboratory, is now clear to the clinical evaluator. The relevant section of the protocol for Study C-EARLY was reviewed by the clinical evaluator and supports the sponsor's response.

12.1.6. Question 6

- With regard to the additional analysis undertaken using the RAD1 in Period 1 of Study C-EARLY, in which the Week 52 mTSS scores of all subjects were estimated by linear extrapolation of the post-Baseline mTSS scores, please clarify if this means that Week 0 mTSS score was used to extrapolate the Week 52 score for each subject.

12.1.6.1. Sponsor's response

The sponsor clarifies that, in the analysis using the RAD1 in which the Week 52 mTSS scores of all subjects were estimated by linear extrapolation of the post-Baseline mTSS scores, the Day 364 mTSS was estimated by linear extrapolation for all subjects in the RAD1.

The sponsor highlights that at least two time points are required for linear extrapolation to any other time point. By definition, subjects in the RAD1 provided valid radiographs at Baseline and at Week 52 or the Withdrawal Visit. The Week 0 (Baseline) mTSS was used in conjunction with either the Early Withdrawal mTSS or the Week 52 mTSS (when this was not exactly Day 364) to estimate the Day 364 mTSS. The sponsor indicates that a post-hoc analysis was undertaken for subjects who did not have either an Early Withdrawal mTSS of a Week 52 mTSS. In this analysis the Week 52 mTSS was imputed for both treatment arms from the slope estimates obtained from the ANCOVA model on the Week 52 mTSS score for PBO + MTX subjects.

12.1.6.2. Clinical evaluator's comment

The sponsor's response is acceptable. The sponsor indicates that the results of the post-hoc analysis for subjects who had no Week 52 or Early Withdrawal radiograph are in a table in Study RA0055 Period 1 CSR Amendment 1. These results could not be located in the submission.

12.1.7. Question 7

- With regard to the additional analysis undertaken using the RAD1 in Period 1 of Study C-EARLY, in which the Week 52 mTSS score of all subjects were estimated by linear extrapolation of the post-Baseline mTSS score, it is not clear to the clinical evaluator how such an extrapolation would be undertaken. Please provide clarification.

12.1.7.1. Sponsor's response

The sponsor clarifies that, by definition, subjects in RAD1 had either:

1. A Baseline radiograph and Week 52 radiograph (considered to be Day 364 for purposes of linear extrapolation); or

2. A Baseline radiograph and an Early Withdrawal radiograph.

The sponsor clarifies that, for subjects who had the first set of radiographs, if the Week 52 score was not exactly at Day 364, then Week 0 and Week 52 scores established the line from which the exact Day 364 score could be estimated. For subjects who had the second set of radiographs, the Week 0 and Early Withdrawal scores established the line from which the exact Day 364 score could be estimated.

12.1.7.2. Clinical evaluator's comment

The sponsor's response is acceptable. The process of extrapolation used in this analysis is now understood by the clinical evaluator.

12.1.8. Question 8

· Clarify if there was a comparison undertaken of the change in mTSS score from Baseline between those subjects in Period 1 of Study C-EARLY who had a change in mTSS score at Week 52 based on a Week 52 radiograph and those subjects for whom the change in mTSS score at Week 52 was estimated, stratified by treatment group. If such a comparison was undertaken, please clarify the location of the results in the CSR.

12.1.8.1. Sponsor's response

The sponsor indicates that such an analysis was not undertaken.

12.1.8.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.9. Question 9

· Clarify the proportion of subjects in each treatment group in Period 1 of Study C-EARLY who received the scheduled study treatment up to Week 52 but were not eligible for Period 2.

12.1.9.1. Sponsor's response

The sponsor clarifies that the proportions of randomised subjects (RS1) in the PBO + MTX and CZP + MTX treatment groups who completed the Week 52 visit (and had received treatment with CZP or PBO through Week 50 and MTX through Week 51) were 65. 3% (n = 143) and 75.8% (n = 500), respectively. The proportions of randomised subjects in the PBO + MTX and CZP + MTX treatment groups who completed the Week 52 visit but were not eligible to enter Period 2 of the study based on lack of sustained LDA at Week 52 were 34.7% (n = 76) and 31.5% (n = 208), respectively.

The sponsor highlights that the information is in a figure contained in the Study RA0055 Period 1 CSR Amendment 1.

12.1.9.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.10. Question 10

· Clarify if the CS1 in Period 1 of Study C-EARLY includes subjects who discontinued and had a Withdrawal Visit in place of the Week 52 visit.

12.1.10.1. Sponsor's response

The sponsor clarifies that the Completer Set 1 only included the subjects who completed to Week 52.

12.1.10.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.11. Question 11

- With regard to the results for mandatory IXRS withdrawals at key visits in Period 1 of Study C-EARLY, the results in of a table from the amended CSR and another from the table set for Study RA0055 Period 1 CSR Amendment 1 differ. Please clarify why the results are different.

12.1.11.1. Sponsor's response

The sponsor clarifies that the information in the two tables are based on different sources of information. The sponsor indicates that the results in the table from amended CSR are based on the information provided by investigators to the IXRS at Weeks 20, 24, 36 (Sweden only) and Week 52 that determined if subjects met protocol-specified mandatory criteria for withdrawal based on improvements in disease activity. The results from the table set for Study RA0055 Period 1 CSR Amendment 1 were based on the electronic Case Report form (eCRF) information which specified a primary reason for discontinuation when a subject withdrew from the study. As there was no option on the eCRF to indicate that the primary reason for discontinuation was that the subject met the mandatory criteria for withdrawal, when subjects were discontinued for this reason at Weeks 20, 24, 36 (Sweden only) or 52, the investigators were instructed to select the primary reason for discontinuation on the eCRF as lack of efficacy at Week 20, 'Other' with specification of 'not enough improvement' at Week 24 and Week 36 (Sweden only), and 'Other' with specification of 'not in sustained LDA' at Week 52. The results in the Amendment 1 table reflect the numbers of subjects who had these reasons listed as the primary reason for discontinuation. The sponsor has highlighted that ideally the results in both tables would be the same. At Week 36, the results were identical. At Week 20, some subjects were withdrawn due to lack of efficacy but did not meet the mandatory criteria for withdrawal, therefore, the number based on the eCRF is higher than the IXRS. At Week 24 and Week 52, some subjects met the mandatory criteria for withdrawal but the primary reason for discontinuation on the eCRF were different so the numbers based on the eCRF are smaller than based on the IXRS.

12.1.11.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.12. Question 12

- The numbers of subjects by discontinuation reason 'adverse event' in Period 1 of Study C-EARLY are not identical in the participant flow diagram in the amended CSR of Study C-EARLY (PBO + MTX n = 17, CZP + MTX n = 51) (See Figure 6 in the Efficacy section above for this study) compared with the relevant table from the amended Period 1 tables for Study C-EARLY (PBO + MTX n = 20, CZP + MTX n = 56). Please clarify why the results are different.

12.1.12.1. Sponsor's response

The sponsor clarifies that the results are different because the numbers of subjects by discontinuation reason 'adverse event' in Period 1 of Study C-EARLY in the participant flow diagram (Study RA0055 Period 1 CSR Amendment 1) includes only subjects who discontinued due to an adverse event prior to Week 52 whereas the table from the amended Period 1 tables for Study C-EARLY includes subjects in the RS1 who discontinued either prior to Week 52 due to an adverse event or at Week 52 due to an adverse event. The sponsor indicates that, based on another Study RA0055 Period 1 CSR Amendment 1 table, 3 subjects in the PBO + MTX group, and 5 subjects in the CZP + MTX group, discontinued at Week 52 due to an adverse event and, therefore, the remainder, 17 subjects in the PBO + MTX group, and 51 subjects in the CZP + MTX group, discontinued prior to Week 52 due to an adverse event.

12.1.12.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.13. Question 13

- With regard to the definition of active disease in the inclusion criteria for Study C-EARLY, the mean and median number of swollen and tender joints at Screening, and the mean and median DAS28 (ESR), CRP and ESR values, respectively, at Screening do not appear to be presented in the submission. Please provide comment on this point.

12.1.13.1. Sponsor's response

The sponsor clarifies that the Screening values for these parameters were not summarised in a table.

12.1.13.2. Clinical evaluator's comment

The sponsor's response is acceptable. To meet the inclusion criterion for active disease subjects were required to have specific results at Screening and Baseline (see section efficacy: inclusion and exclusion criteria for this study above) and it is assumed that subjects met these criteria unless there was a protocol violation in relation to the inclusion criteria (as mentioned in the sponsor's response to Question 14 (concerning efficacy) below). A summary of the characteristics of subjects at Screening is not essential to the evaluation.

12.1.14. Question 14

- In Period 1 of Study C-EARLY, it is not clear what proportion of subjects in each treatment group had RA that was severe and active and progressive. Please clarify the location of this information in the CSR or provide it.

12.1.14.1. Sponsor's response

The sponsor highlights that the subject population for Study C-EARLY represent a severe, active, and progressive RA population based on a combination of factors.

The sponsor clarifies that it did not attempt to quantify the number of subjects who had severe and active and progressive RA. The sponsor highlights that it is not aware of a widely accepted definition of progressive disease. The sponsor highlights that, in Period 1 of Study C-EARLY:

- Most subjects had severe disease

The sponsor highlights that severe disease is generally considered to be synonymous with high disease activity and, based on Study RA0055 Period 1 CSR Amendment 1, 96.5% of subjects had high disease activity (DAS28 (ESR) > 5.1) and the remainder moderate disease activity (DAS28 (ESR) > 3.2 to ≤ 5.1) at Baseline (based on FAS1).

- Most subjects had active disease

Active disease is defined in inclusion criterion 9. Six subjects in the RS1, all in the CZP + MTX group, did not meet the criterion of ≥ 4 swollen joints and ≥ 4 tender joints (DAS28) at Screening and Baseline. All subjects had a DAS28 (ESR) > 3.2 at Screening and Baseline.
6 subjects in the RS1, 5 in the CZP + MTX group and one in the PBO + MTX group, did not meet the criterion of CRP ≥ 10 mg/L at Screening and/or ESR ≥ 28 mm/h at Screening and Baseline.

- Most subjects either had evidence of progression (erosion at Baseline) or met inclusion criteria to select subjects with a high propensity to progress based on known poor prognostic factors

The sponsor highlights that the inclusion criteria selected subjects with factors associated with a higher probability of progression, specifically, high disease activity, SJC ≥ 3, presence of ACPA and/or RF (especially at high levels) and high CRP (≥ 6 mg/L) and ESR levels. The sponsor highlights that CRP is well correlated with radiological progression.

In relation to these prognostic factors, the sponsor reiterates that 96.5% of subjects had high disease activity, all but 5 subjects had SJC ≥ 4 at Screening and Baseline and all but six subjects

met the CRP and ESR criterion. Two subjects did not have a positive ACPA and/or RF result at Screening, both of whom were in the CZP + MTX group. The sponsor highlights that already, at Baseline, 77.8% of subjects had erosions even though 75.9% of subjects had a calculated time since diagnosis of ≤ 4 months.

12.1.14.2. Clinical evaluator's comment

The sponsor's response is acceptable. Based on the sponsor's response, most subjects would have met the sponsor's criteria for severe, active and progressive disease.

12.1.15. Question 15

- Clarify if subjects were permitted to receive non-pharmacological management of RA in Period 1 of Study C-EARLY and, if so, whether there was a difference in the proportion of subjects in each treatment group receiving such therapy at Baseline.

12.1.15.1. Sponsor's response

The sponsor clarifies that the protocol did not prohibit subjects receiving non-pharmacological management of RA in Period 1 of Study C-EARLY. The sponsor indicates that any difference in the proportion of subjects in each treatment group receiving such therapy at Baseline could not be determined as the use of non-pharmacological therapies was not collected and recorded in a systematic way.

12.1.15.2. Clinical evaluator's comment

The sponsor's response is acceptable. It is unlikely that non-pharmacological therapies would have had a major impact on efficacy outcomes in this study population with severe, active, and progressive RA. Therefore, it is anticipated that any difference in the proportion of subjects in each treatment group receiving such therapy during the study is unlikely to have confounded the results to a large extent.

12.1.16. Question 16

- In Period 1 of Study C-EARLY, for a number of the efficacy outcomes that reported changes from Baseline at different time points in the study, not all of the subjects in the analysis set were included in the analysis at each reported measurement time point despite the use of LOCF to deal with missing data, for example, change from Baseline in DAS28 (ESR) by week for the FAS1. Please clarify why this is the case.

12.1.16.1. Sponsor's response

The sponsor clarifies that, based on the SAP for Period 1 of Study C-EARLY, unless otherwise stated, if there were data missing for post-Baseline assessments, only earlier post-Baseline values could be carried forward, not Baseline and pre-Baseline values. The sponsor gives the example that, if a subject had a Baseline value but was missing values at Week 2 and Week 4, these values would remain missing. If the same subject had a value at Week 6 and was missing a value at Week 8, the Week 6 value could be carried forward. The sponsor highlights that this approach is consistent with the criteria for inclusion of subjects in the FAS1, specifically that they were required to have a valid Baseline and post-Baseline DAS28 (ESR). The subject highlights also that the LOCF values for DAS28 (ESR), CDAI and SDAI were based on LOCF for the components of these composite measures.

12.1.16.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.17. Question 17

- Clarify if the primary analysis of the primary efficacy outcome in Study C-OPERA was only the analysis in the FAS performed using rank ANCOVA with linear extrapolation for missing data (ANCOVA LINEAR) or if the ANCOVA model undertaken for the measured values, using

the treatment group as a factor and Baseline value as a covariate, was also a primary analysis of the primary efficacy outcome.

12.1.17.1. Sponsor's response

The sponsor clarifies that the rank ANCOVA with linear extrapolation for missing data (ANCOVA LINEAR) was considered the primary analysis of the primary efficacy outcome in Study C-OPERA. The sponsor highlights that, in a specified table of the interim CSR for Study C-OPERA (Study RA0096 52-week Interim CSR), the ANCOVA on the measured values is referred to as a sensitivity analysis although this point is not clear in the section of the interim CSR in which the primary analysis of the primary efficacy variable is described.

12.1.17.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.18. Question 18

- In a specified table in the CSR for Study C-OPERA, it is not clear to the clinical evaluator why one subject in the CZP + MTX group in the FAS did not contribute to the change from Baseline analyses for mTSS, bone erosion and JSN, even though linear extrapolation was used to impute missing data. Please clarify this point.

12.1.18.1. Sponsor's response

The sponsor clarifies that, based on the SAP, the linear extrapolation method that was used for the analyses of mTSS, erosion score and JSN score used radiographs from Baseline and one other time point. The sponsor highlights that the first study drug administration date was set to Day 1, and, for analysis at Week 52, the measurement value of 365 ± 30 days was used, or, if this was missing, the mTSS was extrapolated using the value before 335 days.

The sponsor clarifies that as one subject had a radiograph at Week 0/Baseline only, linear extrapolation could not be undertaken and the subject was, therefore, not included in the summary statistics for Week 52 and did not contribute to the change from Baseline analyses for mTSS, bone erosion and JSN.

12.1.18.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.1.19. Question 19

- 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 Period 1 of Study C-EARLY.

12.1.19.1. Sponsor's response

The sponsor highlights that, in Period 1 of Study C-EARLY, activities were included to avoid or minimise any effects of potential bias. The sponsor highlights the following points with regard to potential sources of bias identified in Section 7.4: Evaluator's conclusions on clinical efficacy for pivotal study indication in this document:

- There is no indication that protocol violations and discontinued subjects introduced bias as the results of the pre-specified analyses performed on the PPS1 and CS1 confirm the results of the primary analysis.
- The SAP specified the handling of missing data. The results of the pre-specified analyses performed on CS1 confirm similar trends to the results of the primary analysis.
- Site blinding plans minimised the effect of possible sources of bias.

- With regard to local protocol amendments, the sponsor indicates that only 1.7% of the study population were in Sweden and therefore no bias was introduced and, in other countries, the specific protocol amendments were not considered to have influenced the primary efficacy analysis as the amendments related to safety concerns.

The sponsor also highlights that it considers a single phase III pivotal study is adequate to support the proposed indication as the pre-requisites for a one pivotal study application have been addressed. The sponsor asserts that the results of Period 1 of Study C-EARLY meet the prerequisites from the TGA-adopted guideline 'Points to Consider on Application with 1. Meta-analyses: 2. One Pivotal Study. CPMP/EWP/2330/99';[12] specifically:

- The results of Period 1 of Study C-EARLY have internal validity as potential sources of bias have been avoided or minimised in Period 1 of Study C-EARLY.
- The results of Period 1 of Study C-EARLY have external validity.
- The results of Period 1 of Study C-EARLY are clinically relevant.
- The results of Period 1 of Study C-EARLY had an appropriate degree of statistical significance.
- Data quality - blinding of sites was implemented.
- The results of Period 1 of Study C-EARLY showed internal consistency in different pre-specified sub-populations and all important efficacy outcomes showed similar findings.
- The study was conducted across 181 sites and the largest site had 27 randomised subjects, therefore, there was no centre dominating in terms of size or effect.
- The hypothesis tested in biologically plausible. A similar indication has been approved for other anti-TNFs.

12.1.19.2. Clinical evaluator's comment

The sponsor's response is acceptable.

The activities that have been implemented by the sponsor to avoid or minimise potential sources of bias are noted.

12.2. Safety

12.2.1. Question 20

- Provide an update on the EU regulatory status of Cimzia and advise if there have been any concerns raised by other regulators in countries where a similar application has been submitted.

12.2.1.1. Sponsor's response

The sponsor indicates that a dossier to support the extension of the RA indication in DMARD-naïve patients was submitted to the EMA in February 2015 and was approved by the European Commission Decision on 16 December 2015. The sponsor states that no major questions were raised by the EU regulators. The sponsor advises that a similar dossier that was submitted to Swiss Medic is currently under review. The sponsor indicates that, at the end of February, it had received 12 questions from Swiss Medic in relation to this submission, including two major concerns relating to the difference in regional efficacy, and the reasons for this finding, and the mortality in the integrated safety data pool of patients with early RA compared with the RA overall pool. The sponsor indicates that it is assessing the questions raised by Swiss Medic.

12.2.1.2. Clinical evaluator's comment

The sponsor's response is acceptable.

With regard to difference in regional efficacy, this was noted by the clinical evaluator during the first round clinical evaluation. As commented in the first round evaluation, it is difficult to know if the inconsistent finding in the subgroup analysis results for Latin America represents the true picture in the population as the numbers of subjects in each treatment group in the FAS1 from this region were relatively small.

With regard to mortality in the integrated safety pool of patients with early RA compared with the RA overall pool, it is reported in the first round evaluation that 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)). The reason for this difference is unclear. The sponsor is requested to comment on this finding.

12.2.2. Question 21

- In Period 1 of Study C-EARLY, 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. Please confirm the number of subjects who were exposed to CZP + MTX for at least 365 days.

12.2.2.1. Sponsor's response

The sponsor clarifies that the calculation of exposure is different from the calculation of the number of subjects who completed Week 52 of the study. The sponsor explains that exposure is based on actual injection dates with the duration of exposure to CZP/PBO in Period 1 of Study C-EARLY calculated as the date of the last Period 1 injection (not including the Week 52 injection) minus the date of the first Period 1 injection plus 14 days. The sponsor highlights that the planned maximum duration of exposure to CZP + MTX was 52 weeks (364 days with an acceptable window of ± 3 days). The sponsor indicates that, in total, 483 subjects had at least 361 days of exposure to CZP with 361 days being the minimum day window for the Week 52 visit. The sponsor indicates that there are supporting data in a specified table.

12.2.2.2. Clinical evaluator's comment

The sponsor's response is acceptable. The supporting data in the specified table could not be located.

A total of 483 subjects exposed to CZP for at least 361 days would seem adequate evidence of safety in the proposed patient sub-population using the same dosage regimen as was used in Study C-EARLY.

12.2.3. Question 22

- In Study C-OPERA, 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. Please confirm the number of subjects who were exposed to CZP + MTX for at least 365 days.

12.2.3.1. Sponsor's response

The sponsor clarifies that the calculation of exposure is different from the calculation of the number of subjects who completed Week 52 of the study. The sponsor explains that exposure is based on actual injection dates with the duration of exposure to CZP/PBO in the Treatment Period of Study C-OPERA calculated as the date of the last Period 1 injection (not including the Week 52 injection) minus the date of the first Period 1 injection plus 15 days. The sponsor highlights that the planned maximum duration of exposure to CZP + MTX was 52 weeks (365 days with an acceptable window of ± 5 days). The sponsor indicates that, in total, 109

subjects had at least 360 days of exposure to CZP with 360 days being the minimum day window for the Week 52 visit. The sponsor indicates that there are supporting data in a specified table.

12.2.3.2. Clinical evaluator's comment

The sponsor's response is acceptable. The supporting data in the specified table could not be located.

12.2.4. Question 23

- In Study C-OPERA, it seems unusual that the TEAE IR is higher than the TEAE ER in both the PBO + MTX group and the CZP + MTX group. Please clarify why this would be the case.

12.2.4.1. Sponsor's response

The sponsor clarifies that if TEAEs occur early in the study it is possible for the IR of TEAEs to be higher than the ER. The sponsor highlights that, in the case of Study C-OPERA, 71% of TEAEs in the PBO + MTX group and 63% of TEAEs reported in the CZP + MTX group had occurred by Week 24 based on the supporting data in Study RA0096 52-week interim CSR, and that approximately 63% of subjects in each treatment group reported at least one TEAE within the first 8 weeks of treatment.

12.2.4.2. Clinical evaluator's comment

The sponsor's response is acceptable. The description of the calculation of the IR in the analysis of adverse events in the CSR for Study C-OPERA was re-reviewed.

12.2.5. Question 24

- With regard to drug-related TEAEs, from the information in the amended CSR for Study C-EARLY, drug-related TEAEs are related to CZP/PBO and/or MTX in Study C-EARLY. In Study C-OPERA, it appears that the drug-related TEAEs are related to either CZP or PBO as CZP and PBO are described as the study drugs (investigational product and reference product) in the study protocol (amendment 3). Please confirm whether this interpretation is correct.

12.2.5.1. Sponsor's response

The sponsor confirms that the first round clinical evaluator's interpretation of the relationship of the TEAEs to the study medication in Study C-OPERA is correct. The sponsor also confirms that the procedures used to assess the relationship of TEAEs were different in Study C-EARLY and Study C-OPERA. The sponsor clarifies that in both studies the relationship of TEAEs to the study medication, PBO + MTX or CZP + MTX, as either not related or related, was determined by the investigator. The sponsor clarifies that, in Study C-EARLY, the study medication was designated as CZP/PBO and MTX but there was no differentiation made between the medications and the investigator was to consider if the TEAE was related, or not related, to CZP/PBO and MTX without indicating a specific study medication. The sponsor highlights that, in Study C-OPERA, CZP and PBO were considered study medication and MTX was considered to be an essential concomitant medication. The sponsor confirms that, in Study C-OPERA, the investigator was to consider whether the TEAE was related to CZP or PBO only. The sponsor concludes that comparison of drug-related TEAEs between the studies should be avoided as the different procedures used to assess the relationship of TEAEs makes comparison of drug-related TEAEs difficult to interpret.

12.2.5.2. Clinical evaluator's comment

The sponsor's response is acceptable.

As the proposed indication relates to the use of CZP in combination with MTX knowing specifically whether a TEAE considered drug-related in Study C-EARLY was considered related to CZP or MTX or both is not essential.

12.2.6. Question 25

- It is noted that, in the amended Clinical Overview, the sponsor indicates that a case of bone marrow toxicity reported in Period 1 of Study C-EARLY was considered to be related to MTX although it is not reported as related in the relevant amended table for Period 1 of Study C-EARLY. In the amended Clinical Overview it is also indicated that 5.3% of subjects in the CZP + MTX group (n = 35) and 5.5% of subjects in the PBO + MTX group (n = 12) in Period 1 of Study C-EARLY had adverse events associated with MTX use. Please clarify the location of the supporting data that specifies the study drug to which a TEAE is related.

12.2.6.1. Sponsor's response

The sponsor clarifies that the data in the relevant amended table for Period 1 of Study C-EARLY were generated from the AE form that was completed by the investigator and the investigator determined the relationship of the TEAE bone marrow toxicity as not related to the study medication. The sponsor clarifies that the case of bone marrow toxicity met the criterion of seriousness and during the safety follow-up of this case the investigator subsequently reported that the bone marrow toxicity was related to MTX. The sponsor clarifies that this information was included in the narrative for the subject and the narrative was the source of the statement in the Clinical Overview. The sponsor highlights the process for assessment of the relationship of TEAEs to study medication in Study C-EARLY described in response to this question.

The sponsor indicates that a manual search of the Study RA0055 Period 1 CSR listing for AE terms which included MTX use was performed to establish the incidence of AEs associated with MTX use in subjects in Study C-EARLY. The sponsor indicates that this was the source of the information in the amended Clinical Overview that 5.3% of subjects in the CZP + MTX group (n = 35) and 5.5% of subjects in the PBO + MTX group (n = 12) in Period 1 of Study C-EARLY had adverse events associated with MTX.

12.2.6.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.2.7. Question 26

- It is noted that the proportions of subjects with drug-related TEAEs falling within certain SOCs were higher in both treatment groups in the Treatment Period of Study C-OPERA compared with Period 1 of Study C-EARLY, for example the Gastrointestinal disorders SOC and the Infections and infestations SOC, even though the mean weekly MTX dose was higher in both treatment groups in Study C-EARLY. These differences may reflect the different study populations in the two studies. Please provide comment.

12.2.7.1. Sponsor's response

The sponsor acknowledges the higher proportions of subjects in both treatment groups with drug-related TEAEs in the Treatment Period of Study C-OPERA compared with Period 1 of Study C-EARLY in the example SOCs highlighted in the question (Gastrointestinal disorders SOC and the Infections and infestations SOC). The sponsor comments that the comparison of drug-related TEAEs in the CZP + MTX group between Study C-OPERA and Study C-EARLY is difficult to interpret due to both the difference in the study populations and the differences regarding the definitions of study medication (CZP/PBO in Study C-OPERA and CZP/PBO + MTX in Study C-EARLY). The sponsor provides the following data, in Table 14.

Table 14. Sponsor provided table for the incidence of drug-related TEAEs in selected SOCs

Incidence of drug-related TEAEs in selected SOCs

SOC	C-EARLY Period 1		C-OPERA	
	PBO+MTX N=217	CZP+MTX N=659	PBO+MTX N=157	CZP+MTX N=159
Gastrointestinal disorders, n (%)	24 (11.1)	94 (14.3)	30 (19.1)	32 (20.1)
Infections and infestations, n (%)	23 (10.6)	112 (17.0)	68 (43.3)	67 (42.1)

CZP=certolizumab pegol; MTX=methotrexate; PBO=placebo; SOC=system organ class; TEAE=treatment-emergent adverse event

12.2.7.2. Clinical evaluator's comment

The sponsor's response is acceptable.

It is interesting to note that in Period 1 of Study C-EARLY, the proportions of subjects with TEAEs related to CZP/PBO + MTX in these two SOCs were lower in both treatment groups compared with the proportions in the Treatment Period of Study C-OPERA even though, in Study C-OPERA, the investigator was to consider whether the TEAE was related to CZP or PBO only.

12.2.8. Question 27

- With regard to the fatal case of TB in Period 1 of Study C-EARLY, please provide further comment in relation to this case and in relation to the frequency of periodic evaluation for TB risk factors and testing for latent infection recommended for patients treated with CZP. It is noted that the currently approved Australian PI is silent regarding the frequency of such periodic testing.

12.2.8.1. Sponsor's response

The sponsor highlights that at Screening the subject had no evidence of active TB based on clinical signs and symptoms and chest X-ray, and had a negative QuantiFERON-TB Gold test and did not report close contact with an individual with active TB or who had recently been treated for TB. The sponsor offers the following possible explanations for why the TB screening tests were negative for this subject:

- The subject did not have TB
- The subject became infected and developed active TB after Screening but did not have latent or active TB at Screening
- The subject had latent TB at Screening and had a false negative QuantiFERON-TB Gold test result

The sponsor provides further detail with regard to the case, specifically that the diagnosis of TB was based on the presence of transmural granulomas in the jejunum and a positive acid-fast bacillus stain and a positive acid-fast bacillus stain of the sputum. The sponsor clarifies that these findings indicate a probable mycobacterium infection in the jejunum and a possible pulmonary mycobacterium infection but these findings were not confirmed by performing tests to confirm Mycobacterium tuberculosis infection. The sponsor highlights that the subject may have had a mycobacterium infection other than Mycobacterium tuberculosis and that this is unlikely to have been detected by the QuantiFERON-TB Gold test.

The sponsor highlights that the subject denied having been exposed to an individual infected with TB or who had recently been treated for TB according to the TB questionnaire administered at Screening and 18 days before the diagnosis of enteric TB at Week 12 of the study.

The sponsor highlights that false negative QuantiFERON-TB Gold test results can occur based on the package insert for the test. The sponsor also highlights that the PIs for Humira, Simponi and Actemra remind prescribers of the possibility of false negative screening tests for latent TB infection and that the Actemra PI specifically mentions interferon-gamma release assays such as the QuantiFERON-TB Gold test. The sponsor highlights that the Australian Rheumatology Association Guidelines caution against false negative tests too.

The sponsor indicates that it considers that the current wording in the Australian PI for Cimzia is appropriate in relation to screening for TB infection. The sponsor highlights that the PIs for the anti-TNFα drugs Enbrel and Humira state that active TB has developed in patients being treated with these drugs who tested negative for latent TB infection (LTBI) prior to initiation of treatment, but the type of test for latent TB is not specified. The sponsor highlights that the PIs for Enbrel, Humira and Simponi, all anti-TNFα drugs, do not include recommendations regarding the frequency of evaluation of TB risk factors and testing for LTBI and that the Australian Rheumatology Association Guidelines do not include such frequencies. The sponsor explains that physicians treating patients with CZP should monitor changes in risk for exposure, which may in turn lead to further evaluation. The sponsor highlights such monitoring and evaluation would be based on the individual patient's circumstances as it does not seem possible to specify an evidence-based frequency of testing for LTBI applicable to all patients on CZP.

12.2.8.2. Clinical evaluator's comment

The sponsor's response is acceptable.

The current wording in the Australian PI for Cimzia in relation to screening for TB infection is adequate at this point in time.[1]

12.2.9. Question 28

- Comment on whether CZP + MTX is considered to induce or promote the growth of benign or malignant neoplasms.

12.2.9.1. Sponsor's response

The sponsor indicates that data from subjects exposed to CZP, specifically the ISS RA, suggest that there is no increased risk of malignant tumours, or begin or malignant neoplasms, with treatment with CZP compared with PBO, and that there is no evidence of an increased risk of these events with longer exposure to CZP. The sponsor provides Table 15, below giving of the incidences and incidence rates of malignancies and neoplasms in Study C-EARLY, Study C-OPERA and the ISS RA in response to this question.

Table 15. Incidence and incidence rates of any malignancies and neoplasms in Study C-EARLY, Study C-OPERA and ISS RA

	C-EARLY		C-OPERA		ISS RA		
	PBO+MTX N=217	CZP+MTX N=659	PBO+MTX N=157	CZP+MTX N=159	PBO N=1137	All CZP in PC N=2965	All CZP in All Studies N=4049
Pt-yrs at risk (per 100 pt-yrs)	1.93	6.05	1.16	1.36	3.73	13.02	92.77
	n (%) Incidence rate (per 100 pt-yrs)						
Any malignancies (including unspecified)	2 (0.9) 1.04	8 (1.2) 1.33	0	1 (0.6) 0.74	7 (0.6) 1.88	21 (0.7) 1.62	129 (3.2) 1.41
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.4) 1.57	12 (1.8) 1.99	2 (1.3) 1.74	8 (5.0) 6.03	14 (1.2) 3.78	35 (1.2) 2.71	223 (5.5) 2.48

CZP=certolizumab pegol; incl=including; ISS=Integrated Summary of Safety; MTX=methotrexate; PBO=placebo; PC=placebo-controlled; pt-yrs=patient-years; RA=rheumatoid arthritis; SMQ=Standardized MedDRA Query
Note: For RA0055 and RA0096, malignancies were defined using the SMQ="Malignant or unspecified tumours." For the ISS RA, malignancies were determined by a manual review performed by the UCB medical reviewer.

The sponsor highlights that in both Study C-EARLY and Study C-OPERA the majority of neoplasms were benign, and that although, in each of the studies, the proportions of subjects with malignant tumours and benign and malignant neoplasms were higher in the CZP + MTX group compared with the PBO + MTX group over the 52 weeks of treatment, these proportions are based on small absolute numbers making it difficult to interpret the results.

The sponsor also highlights that in the Australian PI, specific benign and malignant neoplasms are already included as adverse drug reactions in RA studies and post-marketing in the Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC and that neoplasms are considered to be a class effect with anti-TNFα therapies.

The sponsor clarifies that, based on the available data, it is not known if CZP + MTX promotes the growth of benign or malignant neoplasms.

12.2.9.2. Clinical evaluator's comment

The sponsor's response is acceptable.

It is noted that in the ISS RA the incidence rates of any malignancies (including unspecified), and Neoplasms benign, malignant and unspecified (including cysts and polyps), respectively, were similar in the PBO, All CZP in PC and All CZP in All Studies group. In the PBO group, the number of patient years at risk was much lower than the patient-years at risk in the other two analysis groups.

12.2.10. Question 29

- Comment on whether the four subjects in the CZP + MTX group during the Treatment Period of Study C-OPERA who had clinically significant abnormalities on chest X-ray at Last Visit/Withdrawal were considered to have drug-related interstitial lung disease.

12.2.10.1. Sponsor's response

The sponsor clarifies that three of the four subjects in the CZP + MTX group during the Treatment Period of Study C-OPERA who had clinically significant abnormalities on chest X-ray at Last Visit/Withdrawal had AEs that coded to the preferred term interstitial lung disease. In two of these subjects the interstitial lung disease was considered by the investigator to be related to the study medication. Of the three subjects with interstitial lung disease, the sponsor

highlights that one subject had a history of interstitial lung disease and that MTX may have induced or aggravated the interstitial lung disease in all three subjects.

12.2.10.2. Clinical evaluator's comment

The sponsor's response is acceptable.

Based on the sponsor's response to Question 24, that in Study C-OPERA, CZP and PBO were considered study medication and MTX was considered to be an essential concomitant medication, the interstitial lung disease reported in two subjects that were considered to be related to the study medication must have been considered to have been related to CZP even though it is indicated that the non-study medication, MTX, may have induced or aggravated the interstitial lung disease in these subjects.

12.2.11. Question 30

- With regard to the changes to the EU SPC recommended by the Pharmacovigilance Risk Assessment Committee based on the PSUR covering the period 7 March 2013 to 6 March 2014, please comment on whether the sponsor proposes to make similar changes to the adverse reactions 'tuberculosis', and 'viral infections (including herpes, papillomavirus, influenza)' in the table 'Adverse drug reactions in RA clinical trials and post-marketing' in the Australian PI.

12.2.11.1. Sponsor's response

The sponsor indicates that it agrees to make changes to the adverse reactions 'tuberculosis', and 'viral infections (including herpes, papillomavirus, influenza)' in the table 'Adverse drug reactions in RA clinical trials and post-marketing' in the Australian PI to be consistent with the changes to the EU SPC recommended by the Pharmacovigilance Risk Assessment Committee based on the PSUR covering the period 7 March 2013 to 6 March 2014.

12.2.11.2. Clinical evaluator's comment

The sponsor's response is acceptable.

On further consideration, the addition of 'zoster' after herpes is resulting in the removal of safety information as 'herpes', as currently included in the PI, indicates herpes simplex virus type I and herpes simplex virus type 2 infections.' 'Herpes zoster' on the other hand indicates infection with the varicella zoster virus. It is therefore recommended that the ADR 'herpes' is also retained.

12.2.12. Question 31

- The supporting data for the overall RA pool have not been included in the submission. Please clarify if the data in the overall RA pool have previously been submitted to the TGA and provide the report, RA ISS, referenced in the Summary of Clinical Safety.

12.2.12.1. Sponsor's response

The sponsor clarifies that the supporting data for the overall RA pool have been previously submitted to the TGA with the application for the active psoriatic arthritis and ankylosing spondylitis indications in adults and, for this reason, were not included in this current submission. The sponsor highlights that the previous submission was made in April 2013 and approved on 1 May 2014. The sponsor has re-submitted the data for the overall RA pool as part of the response.

12.2.12.2. Clinical evaluator's comment

The sponsor's response is acceptable.

As the sponsor has clarified that the RA ISS has previously been submitted to the TGA, it has not been re-evaluated. The sections of the 'Integrated Summary of Rheumatoid Arthritis Safety Data

(Data cut off: 30 November 2011)' referenced in the amended Summary of Clinical Safety of this current submission were briefly reviewed. It is noted that the studies that were included in the RA ISS had different dosage regimens and the routes of administration were SC, except in one study in which the route of administration was IV, and that for the PC data pool, the treatment groups summarised were CZP 200 mg Q2W following a 400 mg loading dose regimen, CZP Q2W any dose, CZP 400 mg Q4W and all CZP doses. It appears that most subjects in the overall RA pool, if not all, were not DMARD-naïve. Study medication was defined as CZP or PBO for the presentation of the safety data.

It is noted that based on the overall RA pool, the IR of any SAE in placebo controlled studies was higher in the CZP 400 mg Q4W group (26.07 per 100 patient-years) compared with the CZP 200 mg Q2W group (19.77 per 100 patient years). The sponsor indicates that this difference may be related to differences in the studies, group size and exposure. This explanation seems reasonable.

12.2.13. Question 32

- With regard to the early RA subpool, please clarify if it has been ruled out that the subject with ALT and AST > 3 x ULN and bilirubin > 2 x ULN was a Hy's Law case and also whether the two subjects in the CZP Q2W group in the Open Label Data Pool who each had a bilirubin level ≥ 1 x ULN and 3 x ULN elevation of AST or ALT were Hy's Law cases.

12.2.13.1. Sponsor's response

The sponsor clarifies that of the two subjects in the CZP Q2W group in the Open Label Data Pool who each had a bilirubin level ≥ 1 x ULN and ≥ 3 x ULN elevation of AST or ALT, one of these subjects was the subject with ALT and AST > x ULN and bilirubin > 2 x ULN. The sponsor confirms that neither of these two subjects met the criteria of Hy's Law, which the sponsor defines in the response. One subject did not meet the criteria for Hy's Law as the maximum total bilirubin level was not > 2 x ULN. In addition, ALT, AST, bilirubin and ALP values were already decreasing when CZP was discontinued. In the other subject, there was evidence of cholestasis, specifically an ALP value of 816 (ULN = 145), at the same time as the ALT and AST > 3 x ULN and bilirubin > 2 x ULN. The subject had been diagnosed with cancer with metastases in the month before the elevations in ALT, AST, bilirubin and ALP values.

12.2.13.2. Clinical evaluator's comment

The sponsor's response is acceptable.

12.2.14. Question 33

- Clarify if the RMP and Australian Specific Annex have been updated since the versions dated 4 September 2014, and 3 June 2015, respectively.

12.2.14.1. Sponsor's response

The sponsor clarifies that the RMP and Australian Specific Annex dated 4 September 2014, and 3 June 2015, respectively, have not been updated and confirms that these versions are the current versions of these documents.

12.2.14.2. Clinical evaluator's comment

The sponsor's response is acceptable.

In the Executive Summary of the PSUR covering the period from 7 March 2014 to 6 March 2015, it is indicated that Crohn's disease is being evaluated as a new safety signal. Crohn's disease does not appear to be included in the summary of ongoing safety concerns in the RMP Version 10.1, dated 4 September 2014.

13. Second round benefit-risk assessment

13.1. 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.

13.2. 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.[1]

13.3. 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' to support the submission of this single pivotal study.[12] 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.[1] 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.[1] 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.[15] 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 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

[15] 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.

described in the PI, may reflect the different safety data on which the safety profile described in the PI is based.[1] 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.

14. 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' above);
- 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.

15. References

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