Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Certolizumab pegol (rbe)

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

First round CER: 14 May 2014

Second Round CER: 19 September 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <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 of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine aminotransferase
ANA	anti-nuclear antibodies
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
COX	cyclooxygenase
CRO	contract research organisation
CRP	c-reactive protein
CV	coefficient of variation
CZP	certolizumab pegol
DAS28(ESR)	disease activity score for 28 joints using the ESR
DBP	diastolic blood pressure
DMARD	disease modifying anti-rheumatic drug
ECG	electrocardiogram
EQ-5D	EuroQol-5D
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GI	gastro-intestinal
HAQ-DI	health assessment questionnaire disability index
HIV	human immunodeficiency virus

Abbreviation	Meaning
HRQoL	health related quality of life
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IVRS	interactive voice response system
LDH	lactate dehydrogenase
LOCF	last observation carried forward
MedDRA	Medical dictionary for Drug Regulatory Affairs
mTSS	modified total Sharp score
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PAAP	Patient's Assessment of Arthritis Pain
PEG	polyethylene glycol
PhGADA	Physician's Global Assessment of Disease Activity
PK	pharmacokinetic(s)
PT	preferred term
PtGADA	Patient's Global Assessment of Disease activity
RA	rheumatoid arthritis
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous(ly)
SD	standard deviation

Abbreviation	Meaning
SF-36	short form 36
SJC	swollen joint count
SOC	system organ class
TB	tuberculosis
TJC	tender/painful joint count
TNF	tumour necrosis factor
VAS	visual analogue scale
WBC	white blood cell
WHO	World Health Organisation

1. Background

1.1. Submission type

This is a Category 1 submission to extend the indications of Cimzia in rheumatoid arthritis.

1.2. Drug class and therapeutic indication

Certolizumab pegol is a recombinant, humanised antibody inhibitor of TNFα. It is indicated for the treatment of moderate to severe rheumatoid arthritis in adults.

The approved indication is:

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

The proposed additional indication is:

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

2. Clinical rationale

Cimzia is one of the class of antibody TNFα inhibitors which have been shown to reduce inflammation, reduce symptoms and improve physical function in adult patients with moderate to severe RA who have not responded adequately to DMARDs. Joint damage and deformity contribute to progressive disability and impairment of quality of life. One year radiographic data presented in the initial Cimzia submission showed that clinical improvement was associated with inhibition of progression of structural damage. However, the TGA advised as a condition of approval that 2 year data be assessed to ensure that prevention of structural damage is sustained long term.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

Two pivotal and one supporting study have been submitted.

- Studies C87028 and C87051 are long term safety studies which extend the pivotal efficacy studies C87027 and C87050 approved in the previous application. Both extension studies provide 2 year radiographic data to support the new indication for prevention of structural damage.
- The supporting study C87015 provides long term safety data but no radiographic endpoints to support the new indication.

Clinical overview and literature references.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

All studies were conducted according to the principles of ICH GCP.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

No new PK data have been submitted.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

No new PD data have been submitted.

6. Dosage selection for the pivotal studies

Not applicable.

7. Clinical efficacy

Additional indication: to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

7.1. Pivotal efficacy studies

7.1.1. Study C87028

7.1.1.1. Study design, objectives, locations and dates

This study was conducted at 121 centres in 22 countries in Europe, N. America, S. America, Australia and New Zealand. The first patient was enrolled in June 2005 and the last patient completed in February 2012. It was a Phase III, open label, follow up study to assess the efficacy and safety of CZP + MTX in the treatment of patients with active RA who had participated in the controlled, pivotal Phase III study C87027 (RAPID-1).

There were two populations eligible to enrol in C87028. 'Withdrawers' were patients who failed to achieve ACR20 at Week 12 of the feeder study (confirmed at Week 14) and 'Completers' who were patients who completed Week 52 of the feeder study. The study Baseline was baseline of the feeder study C87027. The study Entry visit was Week 16 of the feeder study for Withdrawers, and Week 52 of the feeder study for Completers.

On treatment efficacy was assessed every 12 weeks until the last visit (completion or withdrawal) with a safety follow up visit 24 weeks after the last dose of study medication. Follow up visits were maintained for up to 6.2 years in patients who continued in the study. The primary endpoint was safety. The secondary efficacy objectives included the effects of CZP in treating the signs and symptoms of RA, the effects on physical function and health outcomes. To

support the proposed new indication, an interim analysis was performed at the Week 96 cut off point to assess the effects of CZP + MTX in preventing structural damage in patients with active RA after 2 years.

Radiographic assessments (digitised with centralised reading) of the hands and feet were obtained at entry. The Entry assessment was the C87027 Week 52 assessment for the Completers population, and the C87027 Week 16 assessment for the Withdrawers population. Further radiographic assessments were performed at Weeks 24, 48, 72, and 96 or at the early withdrawal visit if it occurred before Week 96. All patients had safety follow up visits at 12 and 24 weeks after the last dose of study medication. Radiographic assessments were made by a central reader although the readers were different for the C87027 and C87028 studies. The degree of joint damage was assessed using the mTSS, which combines scores for joint erosion and joint space narrowing (JSN). The joint erosion score is a summary of erosion severity using a six point scale (0 to 5) in 32 joints of the hands and 12 joints in the feet for a maximal score of 280. The JSN score summarises the severity of JSN in 30 joints of the hands and 12 joints of the feet using a seven point scale (0 to 6) for a maximal score of 168. The mTSS is the most widely used scoring system for assessing structural damage in clinical trials. It ranges from 0 to 448 points and the smallest detectable difference (and minimum clinically important difference) that can be reliably discriminated from the measurement error of the method is 5.0 points.

7.1.1.1.1. Inclusion and exclusion criteria

The main inclusion criteria were:

- patients who failed to achieve an ACR20 response at Weeks 12 and 14 in C87027, or who completed the entire Week 52 assessment of C87027.
- patients with a normal chest X-ray at entry.

The main exclusion criteria were: a diagnosis of any other inflammatory disease; a secondary non-inflammatory arthritis such as osteoarthritis; a history of infected joint prosthesis at any time with the prosthesis still in situ; concomitant biological therapy or other experimental therapy; serious or life-threatening infection including TB; patients at high risk of infection; hepatitis B or C; HIV infection; lymphoproliferative disorders; a history of blood dyscrasias; active malignancy of any type; severe, progressive and/or other diseases; and demyelinating disease.

7.1.1.1.2. Study treatments

A dose of CZP 400 mg SC every 2 weeks was originally chosen. However, this was changed by protocol amendment to CZP 200 mg SC every 2 weeks after a minimum of 6 months of treatment. This reduction was based on the safety and efficacy results of C87027 and C87050 which demonstrated no significant dose effect of CZP. Certolizumab pegol was provided as a lyophilised powder at a strength of 200 mg/vial, for single use in a 5 mL vial, reconstituted with water for injection. CZP 400 mg was given every 2 weeks as two 1 mL injections, while CZP 200 mg was given every 2 weeks as a single 1 mL injection. All CZP SC injections were given by site personnel into the upper arm, lateral abdominal wall, or upper outer thigh.

7.1.1.1.3. Efficacy variables and outcomes

The main efficacy variables were:

- mTSS with erosion and joint space narrowing score based on X-rays of the hands and feet
- ACR20, ACR50 and ACR70
- Physical function scores
- Patient and physician global assessment scores
- CRP and ESR

- Anti-CZP antibodies

There was no formal primary efficacy objective for the study. The main objective was to demonstrate the prevention of structural damage in patients with active RA.

A range of secondary efficacy outcomes employed validated methods and metrics widely used in published studies and accepted by regulatory authorities. The main outcomes included;

- Percentage of patients achieving ACR20, ACR50 and ACR50 responses
- Change in DAS28 score from baseline using ESR
- Change from baseline in TJC and SJC counts
- Change from baseline in CRP and ESR
- Change from baseline in HAQ-DI, PtGADA-VAS, PhGADA-VAS and PtAAP-VAS scores
- Percentage of patients with anti-CZP antibodies

7.1.1.1.4. Randomisation and blinding methods

This was an open label, single arm extension study.

7.1.1.1.5. Analysis populations

All enrolled patients who received at least one dose of study medication were included in the Safety Set (SS).

7.1.1.1.6. Sample size

There was no formal calculation of sample size but it was estimated that 800 patients would be enrolled. A total of 846 patients from C87027 enrolled in the study.

7.1.1.1.7. Statistical methods

No formal hypotheses were tested. All efficacy and safety analyses were performed on the SS using SAS version 9.1.3. Summaries were reported for the Withdrawer and Completer sub populations separately, as well as combined, grouping by treatment in C87027 as well as the total population. Efficacy results were analysed using observed case analysis. No missing data were imputed and partial or missing dates were listed as such. There were no adjustments for multiplicity because there was no formal hypothesis testing. Descriptive statistics of the actual and percentage values, and changes from baseline were provided with 95% CIs. Time to withdrawal from Entry was summarised using Kaplan-Meier plots. At the request of regulatory authorities to support the proposed indication, further interim analyses of the radiographic data at 2 years were performed. Linear imputation (a combination of extrapolation and interpolation) was used for missing data. The data were also analysed using both a last observation carried forward (LOCF) imputation method and observed data.

7.1.1.1.8. Participant flow

A total of 845 patients were enrolled in the feeder study and received at least one dose of CZP. A total of 349 (41.3%) patients withdrew from the study most commonly due to withdrawal of consent in 142 patients (16.8%) and AEs in 137 patients (16.2%). A higher percentage of Withdrawers withdrew from the study (51.0%) compared with Completers (35.9%). In Withdrawers, withdrawal of consent and lack of efficacy (21.5% and 5.7%, respectively) were higher compared with Completers (14.2% and 1.6%, respectively). Additional details are shown in Table 1.

Table 1: C87028 Summary of subject accountability (SS).

Category	Withdrawers N=298 n (%)	Completers N=548 n (%)	All subjects N=846 n (%)
Received any open-label treatment	298 (100)	548 (100)	846 (100)
Withdrawn from the study	152 (51.0)	197 (35.9)	349 (41.3)
Reason for withdrawal from the study			
Adverse event	55 (18.5)	82 (15.0)	137 (16.2)
Subject decision	64 (21.5)	78 (14.2)	142 (16.8)
Lost to follow-up	3 (1.0)	6 (1.1)	9 (1.1)
Lack of efficacy	17 (5.7)	9 (1.6)	26 (3.1)
Protocol noncompliance	8 (2.7)	7 (1.3)	15 (1.8)
Other	5 (1.7)	17 (3.1)	22 (2.6)

SS=Safety Set
Note: "Withdrawers" and "Completers" refer to the status at the end of the feeder study (C87027).
Note: Subjects could have had more than 1 reason for withdrawal.

7.1.1.1.9. Major protocol violations/deviations

A total of 147 patients (17.4%) had at least one important protocol deviation, mostly related to study conduct. The percentage of patients with important deviations was similar in the Withdrawer and Completer groups and most related to not having an annual chest X-ray performed. Eight patients did not meet the entry criteria but were enrolled and treated. Only one patient missed three or more CZP doses.

7.1.1.1.10. Baseline data

A summary of the baseline demographics (of the feeder study C87027) was provided. Overall, the majority of patients were female (82.9%) and White (90.5%) with a mean age of 51.5 years. Mean weight was 73.69 kg and mean BMI was 27.31 kg/m^2. The demographics for Withdrawers and Completers were similar. Baseline RA characteristics were provided. Overall, the mean TJC and SJC were 30.9 and 21.8, respectively. The mean PtGADA-VAS, PhGADA-VAS, and PtAAP-VAS values were 63.5, 63.7, and 63.0, respectively. The mean HAQ-DI score was 1.7 and the mean DAS28 (ESR) was 6.9. The geometric mean ESR was 45.5 mm/hour and the geometric mean CRP was 14.6 mg/L. The RA characteristics were similar in the Withdrawer and Completer groups. The history of RA at baseline of the feeder study is shown in Table 2. The mean disease duration was 6.16 years and the majority had a disease duration > 3 years. Overall, 22.5% of patients had a history of nodules. A summary of RA medications taken at baseline of the feeder study is shown in Table 3. The mean MTX dose was 13.48 mg/week and the majority of patients (55.4%) were taking an MTX dose in the range of ≥ 10 to < 15 mg/week. Only one patient received MTX < 10 mg/week. The mean number of previous DMARDs used was 1.2. At baseline, the majority of patients used steroids (57.7%) and folic acid (71.3%). The majority of patients (94.2%) did not use anti-TNFα medications or other biologics. The history of medication use at baseline was similar in Withdrawers and Completers.

Table 2: C87028 Summary of history of RA at Baseline of feeder study (SS).

History	Withdrawers N=298	Completers N=548	All subjects N=846
Disease duration [a] (years)			
n	298	548	846
Mean (SD)	6.25 (4.50)	6.10 (4.17)	6.16 (4.29)
Median	5.53	5.44	5.46
Min, max	0.5, 29.6	0.3, 25.6	0.3, 29.6
Disease duration class [a] (years), n (%)			
≤3	97 (32.6)	164 (29.9)	261 (30.9)
>3	201 (67.4)	384 (70.1)	585 (69.1)
Extra-articular features (any history), n (%)			
Nodules	70 (23.5)	120 (21.9)	190 (22.5)
Vasculitis	13 (4.4)	8 (1.5)	21 (2.5)
Neuropathy	14 (4.7)	16 (2.9)	30 (3.5)
Other location/site	34 (11.4)	81 (14.8)	115 (13.6)
Extra-articular features (at C87027 screening), n (%)			
Nodules	55 (18.5)	96 (17.5)	151 (17.8)
Vasculitis	4 (1.3)	7 (1.3)	11 (1.3)
Neuropathy	11 (3.7)	10 (1.8)	21 (2.5)
Other location/site	27 (9.1)	64 (11.7)	91 (10.8)

max=maximum; min=minimum; RA=rheumatoid arthritis; SD=standard deviation; SS=Safety Set
Note: "Withdrawers" and "Completers" refer to the status at the end of the feeder study (C87027).
[a] Disease duration was based on date of first RA diagnosis and date of the Screening Visit in the feeder study.

Table 3: C87028 Summary of history of RA medication at Baseline of feeder study (SS).

History	Withdrawers N=298	Completers N=548	All subjects N=846
Concomitant methotrexate dose (mg/week)			
n	296	543	839
Mean (SD)	13.20 (4.15)	13.63 (4.05)	13.48 (4.09)
Median	11.25	12.50	12.50
Min, max	10.0, 30.0	5.0, 25.0	5.0, 30.0
Concomitant methotrexate dose class (mg/week), n (%)			
<10	0	1 (0.2)	1 (0.1)
≥10 to <15	182 (61.1)	287 (52.4)	469 (55.4)
≥15 to <25	104 (34.9)	240 (43.8)	344 (40.7)
≥25	10 (3.4)	15 (2.7)	25 (3.0)
Number of previous DMARDs [a]			
n	298	548	846
Mean (SD)	1.3 (1.3)	1.2 (1.2)	1.2 (1.3)
Median	1.0	1.0	1.0
Min, max	0, 7	0, 8	0, 8
Number of previous DMARDs class [a], n (%)			
0	104 (34.9)	183 (33.4)	287 (33.9)
1	96 (32.2)	183 (33.4)	279 (33.0)
2	46 (15.4)	100 (18.2)	146 (17.3)
3	32 (10.7)	52 (9.5)	84 (9.9)
>3	20 (6.7)	30 (5.5)	50 (5.9)
Baseline steroid use, n (%)			
Yes	167 (56.0)	321 (58.6)	488 (57.7)
No	131 (44.0)	227 (41.4)	358 (42.3)
Baseline folic acid use, n (%)			
Yes	201 (67.4)	402 (73.4)	603 (71.3)
No	97 (32.6)	146 (26.6)	243 (28.7)
Previous anti-TNFα use [b], n (%)			
Yes	17 (5.7)	32 (5.8)	49 (5.8)
No	281 (94.3)	516 (94.2)	797 (94.2)

DMARD=disease-modifying antirheumatic drug; max=maximum; min=minimum; RA=rheumatoid arthritis; SD=standard deviation; SS=Safety Set; TNFα=tumor necrosis factor alpha
Note: "Withdrawers" and "Completers" refer to the status at the end of the feeder study (C87027).
[a] Does not include methotrexate.
[b] Anti-TNFα and other biologic treatments were included.

7.1.1.1.11. Results for the primary efficacy outcome

Changes in mTSS, JSN score and erosion score from Baseline of the feeder study are shown in Table 4. The last assessment was performed at Week 96 unless the patient had withdrawn before this visit. The Week 96 time point corresponds to CZP exposure of up to 2 years for Withdrawers, and up to 3 years for Completers. The mean change in mTSS from Baseline of the feeder study was 0.53 at Entry into C87028. Patients who had received placebo during the feeder study had a mean change from Baseline in mTSS of 1.48 at Entry into C87028, compared with 0.27 for patients who had received CZP during the feeder study. At Week 96, the mean change from Baseline in mTSS for the 661 patients with evaluable data was 0.95 (SD 4.79). The

mean change from Baseline of the feeder study for all patients at last visit (study completion or withdrawal) was 0.87 (SD 4.72).The median change from baseline of the feeder study in mTSS was 0.00 at all time-points, indicating that at least 50% of patients had no change from baseline in mTSS. Throughout the study, Withdrawers tended to have smaller increases from baseline in mTSS compared with Completers. Similar trends were seen in JSN scores. The mean change in JSN score from Baseline in the feeder study was 0.41 at Entry into C87028 and 0.81 at Week 96. Similar trends were also seen in erosion scores which increased little over time. The mean change from Baseline of the feeder study was 0.11 at Entry into C87028 and 0.14 at Week 96. The median change in JSN score and erosion scores from Baseline was 0.00 at all time-points indicating that at least 50% of patients had no change from baseline in JSN or erosion scores.

Table 4: Summary of mTSS, JSN Score and erosion score- change from Baseline of feeder study (SS).

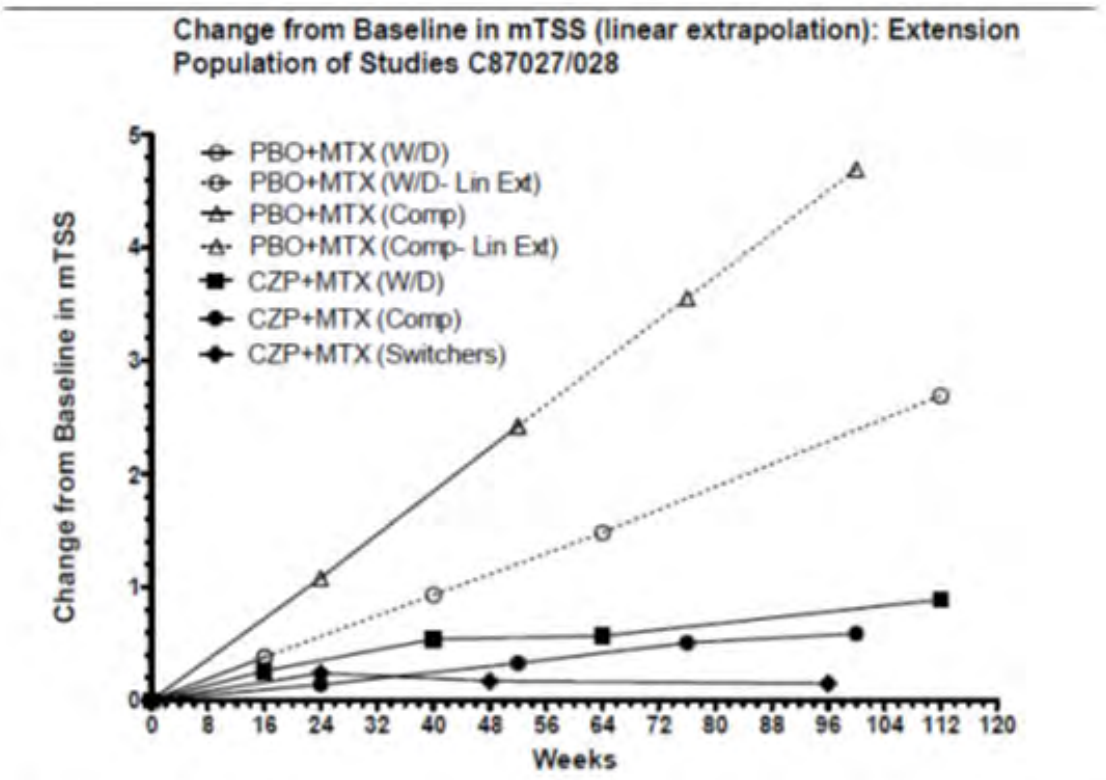
Disposition	mTSS			JSN			Erosion score		
	Withdrawers N=298 n (%)	Completers N=548 n (%)	All subjects N=846 n (%)	Withdrawers N=298 n (%)	Completers N=548 n (%)	All subjects N=846 n (%)	Withdrawers N=298 n (%)	Completers N=548 n (%)	All subjects N=846 n (%)
Entry into C87028[a]									
n	298	547	845	298	547	845	298	547	845
Baseline mean (SD)	49.86 (61.49)	45.77 (53.92)	47.21 (56.70)	26.60 (30.47)	23.98 (26.31)	24.90 (27.86)	23.26 (32.57)	21.79 (29.18)	22.31 (30.41)
Mean change (SD)	0.44 (2.23)	0.57 (3.66)	0.53 (3.23)	0.31 (1.53)	0.47 (2.10)	0.41 (1.92)	0.13 (1.07)	0.10 (2.21)	0.11 (1.89)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	-0.50, 1.00	-0.50, 1.00	-0.50, 1.00	0.00, 0.50	0.00, 0.50	0.00, 0.50	0.00, 0.50	-0.50, 0.50	-0.50, 0.50
Min, max	-7.0, 20.5	-16.0, 19.5	-16.0, 20.5	-4.5, 15.5	-8.5, 14.0	-8.5, 15.5	-3.0, 10.5	-10.0, 16.0	-10.0, 16.0
Week 24									
n	259	522	781	259	522	781	259	522	781
Baseline mean (SD)	50.92 (62.13)	45.72 (53.87)	47.44 (56.75)	27.13 (30.83)	23.97 (26.29)	25.02 (27.90)	23.79 (32.89)	21.75 (29.16)	22.43 (30.44)
Mean change (SD)	0.64 (2.72)	0.90 (4.29)	0.81 (3.84)	0.50 (1.83)	0.72 (2.63)	0.65 (2.39)	0.14 (1.37)	0.18 (2.39)	0.17 (2.11)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	-0.50, 1.00	-0.50, 1.50	-0.50, 1.00	0.00, 0.50	0.00, 1.00	0.00, 1.00	0.00, 0.50	-0.50, 0.50	-0.50, 0.50
Min, max	-10.0, 15.0	-13.5, 26.0	-13.5, 26.0	-4.5, 15.0	-7.0, 20.5	-7.0, 20.5	-5.5, 7.5	-10.0, 19.5	-10.0, 19.5
Week 48									
n	233	492	725	233	492	725	233	492	725
Baseline mean (SD)	53.06 (62.48)	45.28 (54.22)	47.78 (57.08)	28.08 (30.82)	23.63 (26.35)	25.06 (27.92)	24.98 (33.20)	21.66 (29.39)	22.72 (30.68)
Mean change (SD)	0.74 (3.22)	0.77 (4.64)	0.76 (4.23)	0.65 (2.21)	0.66 (2.54)	0.65 (2.43)	0.08 (1.55)	0.11 (2.78)	0.10 (2.45)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	-0.50, 1.50	-0.50, 1.50	-0.50, 1.50	0.00, 1.00	0.00, 1.00	0.00, 1.00	-0.50, 0.50	-0.50, 0.50	-0.50, 0.50
Min, max	-12.0, 18.0	-30.5, 28.5	-30.5, 28.5	-6.5, 17.5	-11.5, 23.0	-11.5, 23.0	-7.0, 7.5	-19.0, 19.5	-19.0, 19.5
Week 72									
n	219	463	682	219	463	682	219	463	682
Baseline mean (SD)	52.83 (61.07)	45.15 (54.56)	47.62 (56.80)	28.13 (30.39)	23.67 (26.73)	25.10 (28.01)	24.70 (32.27)	21.48 (29.38)	22.51 (30.35)
Mean change (SD)	0.29 (5.37)	0.91 (5.08)	0.71 (5.18)	0.42 (3.46)	0.76 (2.99)	0.65 (3.15)	-0.13 (2.57)	0.16 (2.85)	0.07 (2.76)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	-0.50, 1.00	-0.50, 1.50	-0.50, 1.50	0.00, 1.00	0.00, 1.00	0.00, 1.00	-0.50, 0.50	-0.50, 0.50	-0.50, 0.50
Min, max	-47.5, 18.5	-31.0, 33.0	-47.5, 33.0	-32.5, 18.0	-11.5, 27.5	-32.5, 27.5	-20.0, 9.5	-19.5, 20.0	-20.0, 20.0
Week 96									
n	209	452	661	209	452	661	209	452	661
Baseline mean (SD)	53.63 (61.15)	45.72 (54.87)	48.22 (57.00)	28.62 (30.42)	23.88 (26.82)	25.38 (28.08)	25.01 (32.39)	21.84 (29.58)	22.84 (30.51)
Mean change (SD)	0.83 (4.19)	1.01 (5.05)	0.95 (4.79)	0.79 (2.85)	0.82 (3.09)	0.81 (3.01)	0.04 (2.00)	0.18 (2.83)	0.14 (2.59)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	-0.50, 1.00	-0.50, 1.50	-0.50, 1.50	0.00, 1.00	0.00, 1.00	0.00, 1.00	-0.50, 0.50	-0.50, 0.50	-0.50, 0.50
Min, max	-14.5, 23.5	-29.5, 36.0	-29.5, 36.0	-7.0, 23.0	-11.0, 31.5	-11.0, 31.5	-9.0, 9.5	-18.5, 20.0	-18.5, 20.0
Completion/Withdrawal[b]									
n	275	541	816	275	541	816	275	541	816
Baseline mean (SD)	50.34 (61.05)	45.87 (54.05)	47.38 (56.51)	26.84 (30.23)	24.03 (26.39)	24.98 (27.76)	23.50 (32.44)	21.84 (29.24)	22.40 (30.35)
Mean change (SD)	0.78 (3.75)	0.92 (5.14)	0.87 (4.72)	0.70 (2.55)	0.80 (3.13)	0.77 (2.95)	0.08 (1.81)	0.12 (2.85)	0.10 (2.55)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	-0.50, 1.00	-0.50, 1.50	-0.50, 1.50	0.00, 1.00	0.00, 1.00	0.00, 1.00	-0.50, 0.50	-0.50, 0.50	-0.50, 0.50
Min, max	-14.5, 23.5	-29.5, 36.0	-29.5, 36.0	-7.0, 23.0	-11.0, 31.5	-11.0, 31.5	-9.0, 9.5	-18.5, 20.0	-18.5, 20.0

JSN=joint space narrowing; max=maximum; min=minimum; mTSS=modified total Sharp score; Q1=25% quartile; Q3=75% quartile; SD=standard deviation; SS=Safety Set
Note: "Withdrawers" and "Completers" refer to the status at the end of the feeder study (C87027).
Note: Baseline was the Baseline from the feeder study (C87027).
[a] Entry Visit coincided with either the withdrawal assessment (Week 16) of C87027 for Withdrawers or the Week 52 assessment of C87027 for Completers.
[b] Completion/Withdrawal included last nonmissing value for subjects without a labeled Last Visit (Completion/Withdrawal), except for those subjects who only had data at Entry into C87028.

Changes from Baseline in mTSS at Year 1 and Year 2 using linear extrapolation with non imputed Baseline for missing data are shown in Figure 1. Of the 508 patients who completed 52 weeks of CZP + MTX treatment, 446 patients had evaluable radiographic data at Year 1 and 447 patients at Year 2 (as shown in Table 5). In this Completer subgroup, the mean change in mTSS from Baseline was 0.3 (SD 2.6) at Year 1 and 0.6 (SD 3.4) at Year 2. These differences from baseline are small and not clinically significant. Of the 41 patients who completed 52 weeks of

treatment with placebo + MTX, 40 patients had evaluable data at Year 1 and 41 patients at Year 2. In the Completer group, the mean change in mTSS from Baseline was 2.4 (SD 4.1) at Year 1 and 4.7 (SD 8.1) at Year 2 (extrapolated data at Year 2). The mean changes from Baseline in ES and JSN are shown in Table 5. In general, the inhibition of structural damage at Year 2 was more pronounced for the erosion scores compared with JSN scores. The percentages of patients with no progression in mTSS (≤ 0) was provided. In Completers, Withdrawers, and Switchers (patients who switched from PBO + MTX to CZP + MTX), no progression at Year 1 was shown in 61.9%, 64.5% and 66% of patients, respectively. From the end of Year 1 to the end of Year 2, no progression was shown in 67.3%, 74.6% and 75.0% of patients, respectively.

Figure 1: Change from Baseline in mTSS (linear extrapolation): Extension Population of Studies C87027/028.



Comp=Completers; CZP=certolizumab pegol; Lin Ext= linear extrapolation only (based on Week 0 to Week 16 or Week 0 to Week 52 data); mTSS=modified total Sharp score; MTX=methotrexate; PBO=placebo; W/D=Withdrawers

Table 5: Change from Baseline in ES and JSN scores at 2 years (linear extrapolation): Extension population of Studies C87027/028.

	PBO+MTX		All CZP+MTX		
	Withdrawers (N=136)	Completers (N=41)	PBO+MTX/ CZP+MTX Switchers (N=176)	Withdrawers (N=162)	Completers (N=508)
ES					
n	134	41	146	137	447
Baseline mean (SD)	24.1 (29.4)	24.2 (30.8)	24.7 (29.0)	25.1 (35.5)	24.3 (31.1)
Mean change (SD)	0.6 (6.3)	2.6 (4.8)	-0.2 (1.8)	0.1 (1.7)	0.0 (1.9)
Median change (Q1/Q3)	0.0 (0.0/0.0)	0.0 (0.0/4.6)	0.0 (-0.5/0.0)	0.0 (0.0/0.0)	0.0 (-0.5/0.5)
JSN scores					
n	134	41	146	137	447
Baseline mean (SD)	29.3 (29.4)	27.5 (29.8)	29.8 (29.3)	29.3 (35.2)	26.4 (27.5)
Mean change (SD)	2.2 (8.7)	2.1 (4.2)	0.3 (2.1)	0.8 (2.8)	0.6 (2.3)
Median change (Q1/Q3)	0.0 (0.0/3.5)	0.0 (0.0/2.7)	0.0 (0.0/0.5)	0.0 (0.0/0.5)	0.0 (0.0/0.5)

CZP=certolizumab pegol; ES=erosion score; JSN=joint space narrowing; MTX=methotrexate; PBO=placebo; SD=standard deviation; Q1=lower quartile; Q3=upper quartile

7.1.1.1.12. Results for other efficacy outcomes

The percentage of patients achieving ACR20, ACR50 and ACR70 responses relative to the Baseline of the feeder study were provided. There was an increase in the percentage of ACR20 responders from Entry into C87028 (62.5% of patients) through Week 36 (87.5%) and the response rates were sustained through Week 300. The percentage of ACR20 responders at Entry into C87028 was lower in Withdrawers (10.7%) than in Completers (90.7%). However, by Week 192 and later, the response rates were similar. The trends for ACR50 responders were similar to ACR20 response rates. The overall ACR50 at entry was 43.1%, 55.8% at Week 24, and the response rates were sustained through Week 300. ACR50 response rates were consistently lower in Withdrawers compared with Completers. The results for ACR70 responders were similar to ACR20 and ACR50 responders. Overall, the ACR70 rate was 24.6% at Entry into C97028, 33.6% at Week 24, and similar at all visits through Week 300. Response rates in Withdrawers were consistently lower than in Completers. The majority of patients were anti-CZP antibody negative at Entry into C87028 (88.4%). In general, there were more ACR20 responders throughout the study in patients who were anti-CZP negative compared with those who were anti-CZP antibody positive. Similar trends were observed in patients achieving ACR50 and ACR70. In general, ACR20, ACR50 and ACR70 response rates were lower in Withdrawers than in Completers throughout the study.

A summary of DAS28(ESR) remissions (defined as a score of < 2.6) was provided. A total of 16.1% of patients met the criterion for remission at Entry into C87028, increasing to 22.0% at Week 24 and remaining relatively constant for the remainder of the study. At the last visit, the mean change from Baseline was -2.668 for Withdrawers and -3.516 for Completers.

A summary of TJC remissions (defined as TJC = 0) was provided. At Entry into C87028, 14.1% of patients achieved TJC remission, increasing to 22.3% at Week 48 and remaining stable thereafter. At the last visit, 28.6% of patients had achieved remission.

A summary of SJC remission (defined as SJC = 0) was provided. At Entry into C87028, 22.3% of patients achieved remission, increasing to 39.2% at Week 48 and remaining stable thereafter. At the last visit, 47.3% of patients had achieved remission. Overall, Withdrawers had fewer TJC and SJC remissions than Completers.

A summary of mean change from Baseline of the feeder study for PtAAP-VAS scores (0 = no pain, 100 = most severe pain) was provided. At Entry into C87028, the mean change from the feeder study was -27.4, decreasing further to -34.6 at Week 12 and remaining stable thereafter. At the last visit, the score was -25.6 for Withdrawers and -38.8 for Completers. A summary of mean changes from Baseline in the feeder study for PtGADA-VAS was provided. At Entry into C87028, the mean change from Baseline of the feeder study was -27.8, decreasing further to -34.9 at Week 12 and remaining stable thereafter. At the last visit, the mean change from Baseline was -33.8. A summary of mean changes from Baseline in the feeder study for PhGADA-VAS was provided. At Entry into C87028, the mean change from Baseline of the feeder study was -33.0, decreasing further to -41.9 at Week 12 and remaining stable thereafter. At the last visit, the mean change from Baseline was -42.7. Improvements in PtGADA-VAS and PhGADA-VAS scores were higher for Completers compared with Withdrawers.

A summary of changes from Baseline of the feeder study in CRP and ESR were provided. At Entry into C87028, the geometric mean CRP ratio to Baseline of the feeder study was 0.479, improving further to 0.350 at Week 24 and remaining stable thereafter. The ratio at last visit was 0.443 for Withdrawers and 0.331 for Completers. At Entry into C87028, the geometric mean ESR ratio to Baseline of the feeder was 0.536, improving further to 0.449 at Week 12 and remaining stable thereafter. The ratio at last visit was 0.560 for Withdrawers and 0.486 for Completers. A summary of mean changes from Baseline of the feeder study for HAQ-DI scores (range 0 to 3) were provided. At Entry into C87028, the mean change from Baseline of the feeder study was -0.540, improving further to -0.720 at Week 24 and remaining stable thereafter. At the last visit, the mean change in HAQ-DI from Baseline at Entry into C87028 was -0.499 for Withdrawers and -0.776 for Completers.

From Entry into C87028, 163 (19.3%) patients withdrew from the study due to lack of efficacy or AEs was provided. There were a higher percentage of withdrawals in Withdrawers (24.2%) than in Completers (16.6%).

Comments: C87028 was an open label, extension study which assessed multiple efficacy metrics for a period of 96 weeks from baseline of the feeder study C87027, with long term safety follow up for up to 6.2 years. At Week 96 in C87027/C87028, the early clinical improvements were largely sustained for all efficacy outcomes including signs and symptoms of RA measured by ACR20, CRP, DAS28 and health outcome measures. The development of CZP antibodies reduced ACR20 rates significantly (82.9% versus 69.4% in Ab - and Ab + patients, respectively, at the Completion/Withdrawal visit). Over 20% of patients withdrew during the 96 week period but this was due to lack of efficacy in < 3% of patients. Significant benefits were observed in Withdrawers although, as expected, response rates were higher in Completers. However, only a small number of patients were exposed to placebo beyond Week 12 in the feeder study C87027, making interpretation of the overall benefit uncertain.

There was no radiographic progression of structural damage measured by mTSS in 69% of the CZP + MTX group (that is Completers) compared with 52% in the placebo + MTX group after 52 weeks of treatment. The percentage difference in favour of CZP was statistically significant ($p < 0.001$) and clinically meaningful. Following regulatory guidance, an analysis of radiographic data at the 2 year time point was conducted to confirm that the benefits observed after 52 weeks were sustained long term. At Week 96 in C87028, the mean change from baseline of the feeder study for mTSS was 0.95 in the 661 patients on open label treatment who

completed the study, and 0.87 in 816 patients at the Completion/Withdrawal visit. These differences are not clinically meaningful and suggest there was no significant progression of structural damage in the overall group. This is supported by the mTSS median change from baseline of 0.0 for both groups, indicating that at least 50% of patients had no progression. However, it should be noted that different central radiographic readers were employed for the C87027 and C87028 studies. Of the 508 patients who completed 52 weeks of CZP + MTX and entered C87028, sustained inhibition of progression of structural damage was demonstrated in a subset of 447 of these patients who completed at least 2 years of treatment with CZP with evaluable radiological data at Year 2. Linear extrapolation of the placebo data suggested a higher rate of progression of structural damage compared with the minimal progression observed in the active treatment group.

The study outcomes appear internally consistent with sustained improvements in signs and symptoms matched by inhibition of progression of structural damage, although published studies have shown a poor correlation between clinical status and the degree of structural damage. The degree of benefit in favour of CZP should be interpreted with caution but, overall, the results suggest that the initial benefit compared with placebo observed in the feeder study was sustained long term.

7.1.1.2. Study C87051

7.1.1.2.1. Study design, objectives, locations and dates

This study was conducted at 68 centres in 13 countries in Europe and the USA. The first patient was enrolled in November 2005 and the last patient completed in February 2012. It was Phase III, open label, extension study to assess the efficacy and safety of CZP plus MTX in the treatment of the signs and symptoms of RA, and in the prevention of structural damage in patients with active RA who participated in the 24 week study C87050. There were two populations eligible for enrolment in C87051. Withdrawers were patients who failed to achieve ACR20 response at Week 12 of the feeder study, confirmed at Week 14; and Completers who completed Week 24 of the feeder study. The Entry visit to C87051 corresponded to Week 16 of the feeder study for Withdrawers; and Week 24 of the feeder study for Completers. Following the entry visit into C87051, patients were assessed at Weeks 12, 24, 40 and 52, and then every 12 weeks until the last visit. Safety visits occurred at 12 and 24 weeks after the last dose of study medication. Radiographic assessments (digitised with central reading) of the hands and feet were obtained at entry, Weeks 24, 76 and 104 or at early withdrawal if it occurred before Week 104.

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

7.1.1.2.2. Inclusion and exclusion criteria

The key inclusion criteria were:

- patients who failed to achieve an ACR20 response at Week 12 in C87050, or completed the entire C87050 study
- patients who complied with the C87050 protocol
- a clear chest X-ray at study entry
- MTX therapy continued throughout the study.

The key exclusion criteria were: patients with a diagnosis of any other inflammatory disease; a secondary non inflammatory arthritis such as osteoarthritis; a history of infected joint prosthesis at any time with the prosthesis still in situ; concomitant biological therapy or other experimental therapy; patients with congestive cardiac failure; serious or life threatening infection including TB; patients at high risk of infection; hepatitis B or C; HIV infection; lymphoproliferative disorders; a history of blood dyscrasias; active malignancy of any type; severe, progressive and/or other diseases; and demyelinating disease.

7.1.1.2.3. Study treatments

A dose of CZP 400 mg SC was given every 2 weeks as two 1 mL injections of CZP. However, this was changed by protocol amendment to CZP 200 mg SC every 2 weeks after a minimum of 6 months of treatment. This reduction was based on the safety and efficacy results of C87027 and C87050 which demonstrated no significant dose effect for CZP. Certolizumab pegol was provided as a lyophilised powder at a strength of 200 mg/vial, for single use in a 3 mL vial, reconstituted with water for injection. In addition, CZP for injection was supplied in prefilled, individually packed 1 mL syringes containing an injectable volume of 1 mL for single use at a strength of 200 mg/mL. CZP 400 mg was given every 2 weeks as two 1 mL injections while CZP 200 mg was given every 2 weeks as a single 1 mL injection. CZP SC injections were given by site personnel in the upper arm, lateral abdominal wall, or upper outer thigh. After suitable training, patients were also permitted to self-administer injections.

7.1.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- mTSS with erosion and joint space narrowing score based on X-rays of the hands and feet
- ACR20, ACR50 and ACR70
- Physical function scores
- Patient and physician global assessment scores
- CRP and ESR

The primary study objective was safety and there was no formal primary efficacy objective for the study. For the purpose of this submission, the main secondary efficacy objective was to demonstrate the prevention of structural damage in patients with active RA.

The main secondary efficacy outcomes included:

- Percentage of patients achieving ACR20, ACR50 and ACR50 responses
- Change in DAS28 score from baseline using ESR
- Change from baseline in TJC and SJC counts
- Change from baseline in CRP and ESR
- Change from baseline in HAQ-DI, PtGADA-VAS, PhGADA-VAS and PtAAP-VAS scores

7.1.1.2.5. Randomisation and blinding methods

This was an open label, single arm extension study.

7.1.1.2.6. Analysis populations

All enrolled patients who received study medication were included in the Safety Set (SS).

7.1.1.2.7. Sample size

There was no formal calculation of sample size but it was estimated that 450 patients would be enrolled into C87051. A total of 582 patients from C87027 enrolled in the study.

7.1.1.2.8. Statistical methods

No formal hypotheses were tested. All efficacy and safety analyses were performed on the SS using SAS version 9.1.3. Summaries were reported for the Withdrawer and Completer sub-populations separately, as well as combined, grouping by treatment in C87050 as well as the total population. Efficacy results were analysed using observed case analysis. No missing data were imputed. There were no adjustments for multiplicity because there was no formal hypothesis testing. Descriptive statistics of the actual and percentage values, and changes from baseline were provided with 95% CIs. Time to withdrawal from entry was summarised using Kaplan-Meier plots.

7.1.1.2.9. Participant flow

A total of 567 patients were enrolled in the study and received at least one dose of CZP. A total of 221 (39.0%) patients withdrew from the study most commonly due to withdrawal of consent in 87 patients (15.3%) and AEs in 102 patients (18.0%). Additional details are shown in Table 6. A similar percentage of Withdrawers (39.9%) and Completers (38.3%) withdrew from C87051. A lower percentage of Withdrawers (15.9%) withdrew due to AEs compared with Completers (19.2%), and a higher percentage of Withdrawers withdrew due to withdrawal of consent and lack of efficacy (17.8% and 4.3%, respectively), compared with Completers (13.9% and 0.8%, respectively).

Table 6: C87051, Summary of subject accountability (SS).

Category	Withdrawers N=208 n (%)	Completers N=359 n (%)	All subjects N=567 n (%)
Received any open-label treatment	208 (100)	359 (100)	567 (100)
Withdrawn from the study	83 (39.9)	131 (38.3)	221 (39.0)
Reason for withdrawal from the study			
Adverse event[a]	33 (15.9)	69 (19.2)	102 (18.0)
Subject decision	37 (17.8)	50 (13.9)	87 (15.3)
Lost to follow-up	2 (1.0)	6 (1.7)	8 (1.4)
Lack of efficacy	9 (4.3)	3 (0.8)	12 (2.1)
Protocol noncompliance	0	3 (0.8)	3 (0.5)
Other	2 (1.0)	7 (1.9)	9 (1.6)

AE=adverse event; CRF=case report form; SS=Safety Set
Note: "Withdrawers" and "Completers" refer to the status at the end of the feeder study (C87050).
[a] Per the Disposition CRF page, 102 subjects "Withdrew due to an AE"; however, per the AE page of the CRF, 100 subjects had "Drug withdrawn" as the AE action taken. This discrepancy is due to 5 subjects who had "Withdrew due to an AE" on the Disposition CRF page, but did not have "Drug withdrawn" on the AE page; and 3 subjects who did not have "Withdrew due to an AE" on the Disposition CRF page, but had "Drug withdrawn"on the AE page. This difference of 2 subjects is the explanation for the discrepancy.

7.1.1.2.10. Major protocol violations/deviations

The majority of patients (98.4%) did not have important protocol deviations. A total of 9 patients (1.6%) had at least one important deviation. The most frequently reported important deviations were related to concomitant medications and study medication compliance.

7.1.1.2.11. Baseline data

The demographics at Baseline in the feeder were provided. Most patients were female (85.7%) and White (98.6%) with a mean age of 51.6 years. The mean weight was 72.37 kg and the mean BMI was 26.48 kg/m^2. There were no meaningful demographic differences between Withdrawers and Completers. Baseline RA characteristics were provided. Overall, the mean TJC and SJC were 30.2 and 20.9, respectively. The mean PtGADA-VAS, PhGADA-VAS, and PtAAP-VAS

values were 60.8, 63.6, and 60.4, respectively. The mean HAQ-DI score was 1.6 and the mean DAS28(ESR) was 6.8. The geometric mean ESR was 41.3 mm/hour and the geometric mean CRP was 13.2 mg/L. The RA characteristics were similar in the Withdrawer and Completer groups. The history of RA at Baseline of the feeder study was provided. The mean disease duration was 6.2 years and the majority (69.7%) had a disease duration > 3 years. Overall, 16.2% of patients had a history of nodules. A summary of RA medications taken at Baseline of the feeder study was provided. The mean MTX dose was 13.15 mg/week and the majority of patients (66.1%) were taking an MTX dose in the range of ≥ 10 to < 15 mg/week. The mean number of previous DMARDs used was 1.2. At Baseline, the majority of patients used steroids (54.0%) and folic acid (64.0%). The majority of patients (96.1%) did not use anti-TNFα medications or other biologics. The history of medication use at Baseline was similar in Withdrawers and Completers.

7.1.1.2.12. Results for the primary efficacy outcome

Changes in mTSS, JSN score and erosion score from Baseline of the feeder study (C87050) are shown in Table 7. The last assessment was performed at Week 104 unless the patient had withdrawn before this visit. Withdrawers had a higher mean mTSS score at Baseline of the feeder study, compared with Completers (40.26 and 33.1, respectively). The mean change in mTSS from baseline of the feeder study was 0.42 (4.86) at Entry into C87051. At Week 104, the mean change from Baseline in mTSS for all patients was 0.99 (4.99) and 0.90 (4.70) at the last visit (Completion/Withdrawal). The median change from Baseline of the feeder study in mTSS was 0.00 at all time-points, indicating that at least 50% of patients had no change from Baseline in mTSS.

Table 7: C87051, Summary of mTSS, JSN score and erosion score- change from Baseline of feeder study (SS).

Disposition	mTSS			JSN			Erosion score		
	Withdrawers N=208 n (%)	Completers N=359 n (%)	All subjects N=567 n (%)	Withdrawers N=208 n (%)	Completers N=359 n (%)	All subjects N=567 n (%)	Withdrawers N=208 n (%)	Completers N=359 n (%)	All subjects N=567 n (%)
Entry into C87051 [a]									
n	208	357	565	208	357	565	208	357	565
Baseline mean (SD)	40.26 (57.22)	33.51 (42.65)	35.99 (48.58)	20.77 (28.39)	18.28 (23.25)	19.20 (25.27)	19.49 (29.98)	15.23 (20.94)	16.80 (24.72)
Mean change (SD)	0.33 (4.25)	0.47 (5.19)	0.42 (4.86)	0.09 (3.23)	0.26 (3.33)	0.20 (3.29)	0.25 (1.36)	0.21 (2.01)	0.22 (1.79)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 0.50	0.00, 0.50	0.00, 0.50	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00	0.00, 0.00
Min, max	-35.5, 29.0	-11.0, 73.5	-35.5, 73.5	-29.0, 17.5	-9.5, 49.0	-29.0, 49.0	-6.5, 11.5	-5.5, 24.5	-6.5, 24.5
Week 24									
n	189	338	527	189	338	527	189	338	527
Baseline mean (SD)	40.41 (58.05)	32.99 (42.43)	35.65 (48.69)	20.66 (28.44)	17.96 (23.09)	18.93 (25.15)	19.76 (30.70)	15.02 (20.91)	16.72 (24.94)
Mean change (SD)	0.80 (4.26)	0.58 (5.53)	0.66 (5.11)	0.44 (3.05)	0.36 (3.54)	0.39 (3.37)	0.35 (1.65)	0.23 (2.20)	0.27 (2.01)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 1.00	0.00, 0.50	0.00, 0.50	0.00, 0.50	0.00, 0.00	0.00, 0.00	0.00, 0.50	0.00, 0.00	0.00, 0.00
Min, max	-18.0, 29.0	-11.0, 73.5	-18.0, 73.5	-15.0, 22.5	-9.5, 49.0	-15.0, 49.0	-3.0, 11.5	-8.0, 24.5	-8.0, 24.5
Week 76									
n	168	301	469	168	301	469	168	301	469
Baseline mean (SD)	39.47 (57.08)	31.98 (40.40)	34.66 (47.14)	20.26 (28.01)	17.35 (22.14)	18.39 (24.41)	19.21 (30.27)	14.63 (19.72)	16.27 (24.11)
Mean change (SD)	1.52 (6.01)	0.23 (2.83)	0.69 (4.29)	1.00 (3.87)	0.30 (1.89)	0.55 (2.78)	0.52 (2.72)	-0.07 (1.35)	0.14 (1.97)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 1.50	0.00, 0.50	0.00, 1.00	0.00, 1.00	0.00, 0.00	0.00, 0.50	0.00, 0.50	0.00, 0.00	0.00, 0.00
Min, max	-8.0, 60.0	-25.5, 20.5	-25.5, 60.0	-4.5, 34.5	-11.0, 15.5	-11.0, 34.5	-6.0, 25.5	-14.5, 5.0	-14.5, 25.5
Week 104									
n	154	269	423	154	269	423	154	269	423
Baseline mean (SD)	37.76 (55.27)	32.40 (39.98)	34.35 (46.15)	19.16 (27.22)	17.70 (22.22)	18.23 (24.14)	18.60 (29.14)	14.70 (19.38)	16.12 (23.45
Mean change (SD)	1.89 (7.35)	0.48 (2.77)	0.99 (4.99)	1.20 (4.64)	0.42 (1.82)	0.70 (3.17)	0.69 (3.23)	0.06 (1.37)	0.29 (2.25)(
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 1.50	0.00, 1.00	0.00, 1.00	0.00, 1.00	0.00, 0.50	0.00, 0.50	0.00, 0.50	0.00, 0.00	0.00, 0.50
Min, max	-4.5, 75.5	-10.0, 21.0	-10.0, 75.5	-2.0, 42.5	-6.5, 15.5	-6.5, 42.5	-4.0, 33.0	-8.0, 11.0	-8.0, 33.0
Last Visit (Completion/Withdrawal) [b]									
n	195	345	540	195	345	540	195	345	540
Baseline mean (SD)	40.31 (57.84)	33.68 (42.38)	36.07 (48.59)	20.57 (28.40)	18.35 (23.16)	19.15 (25.17)	19.73 (30.51)	15.33 (20.81)	16.92 (24.82
Mean change (SD)	1.68 (6.74)	0.46 (2.89)	0.90 (4.70)	1.02 (4.20)	0.41 (1.99)	0.63 (2.99)	0.66 (3.04)	0.04 (1.39)	0.27 (2.16)(
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 1.50	0.00, 1.00	0.00, 1.00	0.00, 1.00	0.00, 0.50	0.00, 0.50	0.00, 0.50	0.00, 0.00	0.00, 0.00
Min, max	-12.5, 75.5	-11.5, 21.0	-12.5, 75.5	-6.5, 42.5	-9.5, 15.5	-9.5, 42.5	-6.0, 33.0	-8.0, 11.0	-8.0, 33.0

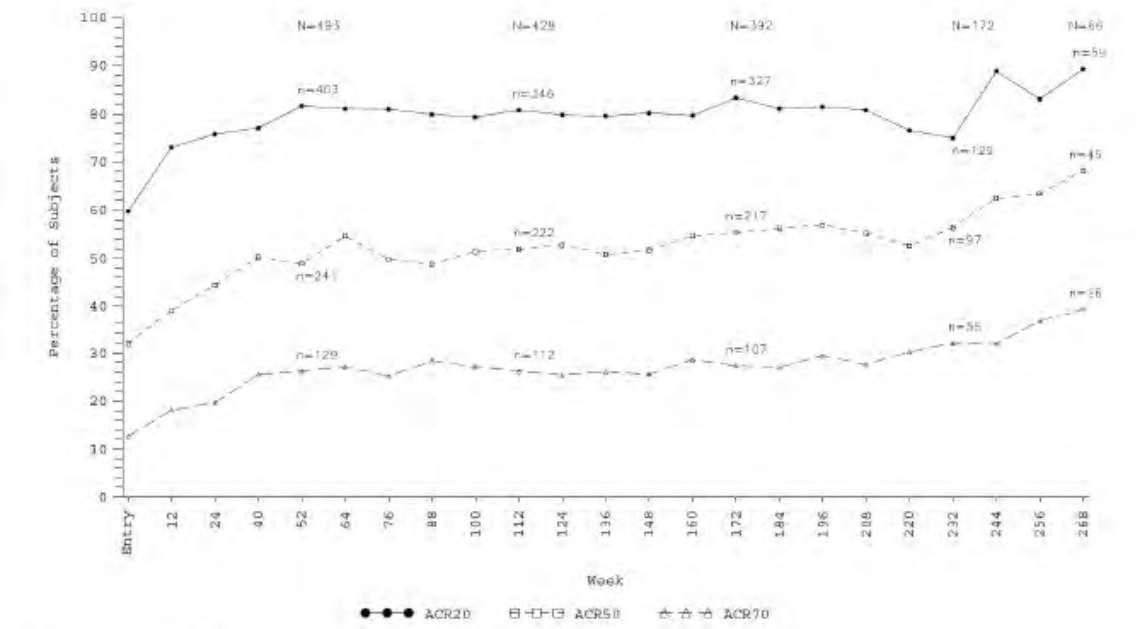
JSN=joint space narrowing; max=maximum; min=minimum; mTSS=modified total Sharp score; Q1=25% quartile; Q3=75% quartile; SD=standard deviation; SS=Safety Set
Note: "Withdrawers" and "Completers" refer to the status at the end of the feeder study (C87050).
Note: Baseline was the Baseline from the feeder study (C87050).
[a] Entry Visit coincided with either the withdrawal assessment (Week 16) of C87050 for Withdrawers or the Week 24 assessment of C87050 for Completers.
[b] Last Visit (Completion/Withdrawal) included last nonmissing value for subjects without a labeled Last Visit (Completion/Withdrawal), except for those subjects who only had data at Entry into C87051.

Similar trends were seen in JSN scores. The mean change in JSN score from Baseline in the feeder study was 0.20 (3.29) at entry into C87051. At Week 104, the mean change from Baseline in baseline JSN scores was 0.70 (3.17) and 0.63 (2.99) at the last visit (Completion/Withdrawal). Similar trends were seen in in erosion scores with little increase over time. The mean change from Baseline of the feeder study was 0.22 (1.79) at Entry into C87051. The mean change was 0.29 (2.25) at Week 104 and 0.27 (2.16) at the last visit (Completion/Withdrawal). The median change in JN score and erosion scores from baseline was 0.00 at all time-points indicating that at least 50% of patients had no change from baseline in JSN or erosion scores.

7.1.1.2.13. Results for other efficacy outcomes

The percentage of patients achieving ACR20, ACR50 and ACR70 responses relative to the Baseline of the feeder study (C87050) are shown in Figure 2. There was an increase in the percentage of ACR20 responders from entry into C87051 (59.8% of patients) through Week 40 (77.1%) and the response rates were sustained for the rest of the study. The percentage of ACR20 responders at Entry into C87051 was lower in Withdrawers (14.9%) than in Completers (85.8%). At last visit, 62.3% of Withdrawers and 81% of Completers had achieved ACR20. The trends for ACR50 responders were similar to ACR20 response rates. The overall ACR50 at Entry was 31.9%, 50.2% at Week 40, and the response rates were sustained until last visit (47.4%). ACR50 response rates were consistently lower in Withdrawers compared with Completers. The results for ACR70 responders were similar to ACR20 and ACR50 responders. Overall, the ACR70 rates were 12.7% at entry into C97051, 25.5% at Week 40, and similar at all visits until last visit (25.5%). Response rates in Withdrawers were consistently lower than in Completers. The majority of patients were ant-CZP antibody negative at Entry into C87028 (88.4%). In general, there were more ACR20 responders throughout the study in patients who were anti-CZP negative compared with those who were anti-CZP antibody positive. Similar trends were observed in patients achieving ACR50 and ACR70. In general, ACR20, ACR50 and ACR70 response rates were lower in Withdrawers than in Completers throughout the study.

Figure 2: C87051 Percentage of subjects achieving ACR20, ACR50 and ACR70 criteria (compared to Baseline of the feeder study) by visit (SS).



ACR=American College of Rheumatology; SS=Safety Set
Note: n's are the number of responders at corresponding visit in an observed analysis.
Note: N's are the total number of subjects at corresponding visit in an observed analysis

A summary of DAS28 (ESR) remissions (defined as a score of < 2.6) was provided. A total of 7.9% of patients met the criterion for remission at entry into C87051, increasing to 15.4% at Week 24 and remaining relatively constant for the remainder of the study. At the last visit, the mean change from baseline was - 2.693 for Withdrawers and - 3.161 for Completers. A summary of TJC remissions (defined as TJC = 0) was provided. At Entry into C87051, 6.0% of patients achieved TJC remission, increasing to 15.9% at Week 52 and remaining stable thereafter. At the last visit, 21.8% of patients had achieved remission. A summary of SJC remission (defined as SJC = 0) was provided. At Entry into C87051, 12.0% of patients achieved remission, increasing to 35.8% at Week 52 and remaining stable thereafter. At the last visit, 42.4% of patients had achieved remission. Overall, Withdrawers had fewer TJC and SJC

remissions than Completers. A summary of mean change from baseline of the feeder study for PtAAP-VAS scores (0 = no pain, 100 = most severe pain) was provided. At Entry into C87051, the mean change from the feeder study was -20.7, decreasing further to -27.8 at Week 24 and remaining stable thereafter. At the last visit, the score was -20.7 for Withdrawers and -29.9 for Completers. A summary of mean changes from Baseline in the feeder study for PtGADA-VAS was provided. At Entry into C87051, the mean change from baseline of the feeder study was -22.1, decreasing further to -27.8 at Week 12 and remaining stable thereafter. At the last visit, the mean change from Baseline was --26.2. A summary of mean changes from baseline in the feeder study for PhGADA-VAS was provided. At Entry into C87051, the mean change from baseline of the feeder study was -29.6, decreasing further to -40.0 at Week 24 and remaining stable thereafter. At the last visit, the mean change from Baseline was -41.9. Improvements in PtGADA-VAS and PhGADA-VAS scores were higher for Completers compared with Withdrawers.

A summary of changes from Baseline of the feeder study in CRP and ESR was provided. At entry into C87051, the geometric mean CRP ratio to Baseline of the feeder study was 0.413, improving further to 0.313 at Week 24 and remaining stable thereafter. The ratio at last visit was 0.416 for Withdrawers and 0.335 for Completers. At Entry into C87051, the geometric mean ESR ratio to baseline of the feeder was 0.539, improving further to 0.45 at Week 24 and remaining stable thereafter. The ratio at last visit was 0.560 for Withdrawers and 0.486 for Completers. A summary of mean changes from Baseline of the feeder study for HAQ-DI scores (range 0 to 3) were provided. At Entry into C87051, the mean change from Baseline of the feeder study was -0.464, improving further to -0.630 at Week 64 and remaining stable thereafter. At the last visit, the mean change in HAQ-DI from Baseline at Entry into C87051 was -0.397 for Withdrawers and -0.664 for Completers. From Entry into C87051, 97 (17.13%) patients withdrew from the study due to lack of efficacy or AEs was provided. The percentage of withdrawals was similar in Withdrawers (18.3%) compared with Completers (16.4%).

Comments: C87051 was an open label, long term follow up study which assessed multiple efficacy metrics over a 2 year period although safety data were collected for up to 6.2 years. The efficacy results were internally consistent throughout the study with sustained improvements in all outcomes including signs and symptoms of RA measured by ACR20, CRP ratio, and health outcome measures. Approximately 25% of patients had withdrawn by Week 104 but only 2% of patients withdrew due to lack of efficacy. Significant benefits were observed in Withdrawers although, as expected, response rates were higher in Completers. As in C87028, ACR20 response rates were significantly lower in patients with anti-CZP antibodies (64.1% versus 82% in Ab + and Ab - patients, respectively, at Week 100). The results suggest that the initial clinical benefit observed in the feeder study appeared to be sustained long term, although the number of patients (n = 41) who completed the placebo period is too small for accurate interpretation. The mean change in mTSS from baseline of the feeder study was 0.42 (4.86) at Entry into C87051. At Week 104, the mean change from Baseline in mTSS for all patients was 0.99 (4.99) and 0.90 (4.70) at the last visit (Completion/Withdrawal). The median change from Baseline of the feeder study in mTSS was 0.00 at all time-points, indicating that at least 50% of patients had no change from Baseline in mTSS. The changes in mTSS over the 2 year observation period are small and not clinically meaningful. The degree of benefit in favour of CZP should be interpreted with caution but, overall, the results suggest that the initial benefit compared with placebo observed in the feeder study was sustained long term.

In C87027, there was no radiographic progression of structural damage (mTSS) in 69% of the CZP + MTX group (that is Completers) compared with 52% in the placebo + MTX group after 52 weeks of treatment. The benefit in favour of CZP was statistically significant ($p < 0.001$) and clinically meaningful. There does not appear to be a corresponding analysis after 24 weeks treatment in C87051.

Moreover, there does not appear to be an analysis of progression of structural damage in the subset of patients who completed at least 2 years of treatment with CZP, and who had evaluable radiographs at completion. This analysis should also be provided.

7.1.2. Other efficacy studies

7.1.2.1. Study 87015

C87015 was a multicentre, open label, long term extension, safety and efficacy study of CZP 400 mg every 4 weeks, with or without concomitant MTX or other DMARDs, in patients with active RA. Eligible patients had participated in C87011 or C87014 during which they had received double blind treatment placebo or CZP for at least 12 weeks in the feeder studies. It was conducted at 71 centres in 7 countries, starting in 2003 and completing in 2011. A total of 402 patients (186 patients from C87011 and 216 patients from C87014) were enrolled into the study; 192 patients had previously received placebo and 210 patients had previously received CZP 400 mg. Withdrawers were patients who withdrew from the feeder study (with the exception of withdrawals due to AEs or non-compliance) and Completers were patients who completed Week 24 of the feeder study. Treatment was continued until marketing approval or at the investigator's decision.

The primary objective was safety. There was no primary efficacy endpoint but efficacy criteria included ACR20/50/70 response rates, DAS28 (CRP), TJC, SJC, PtGADA, PhGADA, and HAQ-DI. Of the 402 patients who enrolled in the study, 56.7% previously treated with CZP withdrew compared with 60.4% previously treated with placebo. The most common reasons for withdrawal were AEs (24.1%) and withdrawal of consent (13.4%). However, withdrawals due to lack of efficacy or AEs of worsening of RA occurred in only 8.0% of the overall population. There was an improvement in ACR20 responder rates from 36.6% at entry to 54.0% at Week 1, and 62.5% at Week 12. At Year 3, 64% of Withdrawers and 70% of Completers achieved an ACR20 response.

The improvement was maintained for up to 6.5 years of treatment in patients who remained in the study. The response rate at 6.5 years in the 62/402 patients who remained in the study was 67.7% (95% CI: 56.1, 79.4). The response rate in the overall 402 enrolled patient population was 57.2% (95% CI: 52.4, 62.1%) assessed at study completion or the time of withdrawal. Similar results were observed for ACR50 and ACR70 response rates although patient numbers achieving ACR70 were small. DAS28 (CRP) values improved from baseline and the improvement was maintained for up to 6.5 years in patients who continued in the study (-2.812 for Withdrawers and -3.180 for Completers). There were also sustained improvements in TJC, SJC and HAQ-DI scores from Week 1. There were sustained improvements in PAAP-VAS, PtGADA and PhGADA for up to 6.5 years and these were similar in Withdrawers and Completers.

The cumulative rate of immunogenicity was 28.1%. Geometric mean CZP plasma levels were typically lower in patients who were anti-CZP positive compared with those who remained antibody negative. There was no analysis of efficacy response rates in anti-CZP positive and negative sub-groups.

Comments: This was primarily a long term, extension safety study although numerous measures of efficacy were monitored. In patients who remained in the study, there was an improvement in all objective indices in disease activity from Week 1 and this was maintained throughout the study period. Approximately 60% of patients withdrew during the 6.5 year study period but only 8% withdrew due to stated lack of efficacy. Completers had somewhat better response rates than Withdrawers suggesting that early response may partially predict long term efficacy. Although there is no control group for comparison, the study supports the long term efficacy of CZP in a significant percentage of RA patients. No X-ray data

were collected so the study does not directly support the claim for prevention of structural damage.

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

None submitted.

7.1.4. Evaluator's conclusions on clinical efficacy for the indication: to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX.

The feeder study designs, methodologies and reporting methods were in line with the Outcome Measures in Rheumatology Clinical Trials consensus (www.omeract.org). The scoring system used for assessing radiological change was the modified total Sharp score (mTSS). This validated X-ray method is a composite of erosion and joint narrowing scores in 32 joints of the hands and 12 joints of the feet. The Sharp score was first proposed in 1971 and the modified Sharp score has been the most widely used scoring system for assessing structural damage in clinical trials for many years. The score ranges from 0 to 448 points and the smallest detectable and minimum clinically important difference is considered to be 5.0 points. In line with consensus guidelines, the changes from baseline in mTSS have been reported as mean, median and inter quartiles as radiographic damage at baseline in RA patients is not normally distributed. However, bias may have been introduced because different radiological reporters were used in the feeder and follow on studies (the 2 year assessment of structural damage was not a pre-determined endpoint).There are various methods for handling missing or incomplete data but there is no single agreed method. However, the sponsor has reported the study results using LOCF imputation, linear extrapolation with non-imputed baseline for missing data, and non extrapolated data to reduce the risk of bias. The lack of placebo control data beyond 52 weeks in C87027 and 24 weeks in C87028 is a significant weakness in the analyses. Moreover, there was a high rate of early withdrawals in the placebo groups so the numbers completing each study were small.

CZP + MTX was superior to MTX + placebo in C87027 after 52 weeks with no radiological progression in 69% and 52% of patients, respectively. This difference was statistically significant ($p < 0.001$) and clinically meaningful. The results in C87050 after 24 weeks are quoted as being similar to those of C87027 but the data are not shown in the Clinical Overview. Control data are not available in C87028 and C87051 so the evidence for continued inhibition of radiological damage over 2 years is necessarily indirect. However, the overall data support the claim for radiological inhibition of structural damage. In the 2 pivotal studies (C87027/8 and C87050/1), overall progression over 2 years in mean mTSS scores was < 1.0 points in both studies, with a median score of 0.0. These radiological findings are similar to published data from studies of other anti-TNFα biologics such as etanercept and infliximab. In contrast, in the placebo + MTX group of C87027, radiographic progression at Week 52 was 2.5 (SD 4.2, n = 38) mTSS points, and 1.6 (SD3.9, n = 15) points in C87050 at Week 24. These data are in line with radiological progression 0.9 to 7.0 in control groups identified in other studies and in a literature review by Strand and Sharp (References 1 to 5). Sensitivity analyses using linear extrapolation were broadly comparable, with less radiological progression than placebo (extrapolated from Year 1 to Year 2) noted in patients who received active treatment. In addition, more than 60% of Completers, Withdrawers and Switchers had no progression (mTSS ≤ 0) over the 2 year treatment period.

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

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data: C87028, C87051 and C87015.

8.1.1. Pivotal efficacy studies

In the pivotal safety studies, the following safety data were collected:

- General adverse events (AEs) were assessed by event duration, relationship to study medication, outcome and seriousness, and classified by primary SOC and PT (MedDRA)
- AEs of particular interest included injection site reactions, hypersensitivity reactions, all infections and malignancies, cardiac and vascular AEs, autoimmune AEs, neurological AEs (potential slow virus diseases), serious bleeding events, bone marrow aplasia and serious skin reactions
- Routine laboratory tests were performed at a central laboratory.

8.1.2. Dose-response and non-pivotal efficacy studies

No dose response studies were submitted. C87015 provided non-pivotal safety data. Data from the full safety set are presented irrespective of whether the patients received CZP or placebo in the feeder studies.

8.1.3. Clinical pharmacology studies

None submitted.

8.2. Pivotal studies that assessed safety as a primary outcome

C87028 and C87051 assessed safety as a primary outcome but the radiological efficacy endpoint of prevention of structural damage in both studies is pivotal for the proposed indication extension.

8.3. Patient exposure

In C87028, the mean duration of exposure to CZP was 1,518 days (4.2 years) and the maximum duration of exposure was 2,268 days (6.2 years).

In C87051, the mean duration of exposure to CZP was 1,423 days (3.9 years) and the maximum duration of exposure per patient was 2,085 days (5.7 years).

In C87015, mean duration of exposure to CZP was a minimum of 1,554 days (4.3 years) and a maximum of 2,737 days (7.5 years).

8.4. Adverse events

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

8.4.1.1. Pivotal studies

8.4.1.1.1. Study C87028

A total of 803 patients (94.9%) reported at least one AE during CZP treatment (including the feeder study) with an event rate of 286/100 patient years. Severe AEs were reported in 210 patients (24.8%) (Table 8). A summary of the most frequently reported AEs (PTs reported in ≥ 10% of patients) are shown in Table 9. The most commonly reported AEs were infections and infestations in 78.6% of patients, musculoskeletal and connective tissue disorders (46.6%),

hypertension 18.9%, nasopharyngitis (18.7%), urinary tract infections (18.1%), rheumatoid arthritis (17.8%), and upper respiratory tract infections (16.3%). A total of 85.6% of patients reported AEs of mild intensity, 76.6% reported AEs of moderate intensity, and 24.8% reported AEs of severe intensity. The most frequently reported severe AEs were rheumatoid arthritis in 1.7% of patients and pneumonia (1.4%).

Table 8:C87028 Summary of AEs (SS).

Category	Total N=846 n (%)
Subjects with at least 1 AE	803 (94.9)
Intensity[a]	
Mild	724 (85.6)
Moderate	648 (76.6)
Severe	210 (24.8)
Relationship to study medication[b]	
Unrelated	645 (76.2)
Unlikely	521 (61.6)
Possible	452 (53.4)
Probable	192 (22.7)
Definite	71 (8.4)
Related to study medication[c]	528 (62.4)
Serious AEs[d]	352 (41.6)
AEs leading to death	16 (1.9)
AEs leading to withdrawal	137 (16.2)

AE=adverse event; SS=Safety Set

Note: Where a subject experienced more than 1 AE in a category, the subject was counted only once in that category.

[a] Adverse events with missing intensities were counted as severe. Adverse events with changing intensity over the course of the study were included only for the maximum reported intensity.

[b] Adverse events with missing relationship to study medication were counted as related. Adverse events with changing relationship to study medication over the course of the study were included only for the maximum reported relationship.

[c] Adverse events with a possible, probable, or definite relationship to study medication.

[d] Adverse events with a missing serious flag were counted as serious.

Table 9: C87028 Summary of AEs reported in at least 10% of subjects (SS).

MedDRA system organ class Preferred term	Total N=846 n (%) [Event rate]
Subjects with at least 1 AE	803 (94.9) [285.56]
Infections and infestations	**665 (78.6) [83.08]**
Nasopharyngitis	158 (18.7) [7.38]
Urinary tract infection	153 (18.1) [7.79]
Upper respiratory tract infection	138 (16.3) [7.29]
Bronchitis acute	103 (12.2) [3.82]
Pharyngitis	88 (10.4) [3.69]
Influenza	87 (10.3) [3.14]
Musculoskeletal and connective tissue disorders	**394 (46.6) [36.17]**
Rheumatoid arthritis[a]	151 (17.8) [7.19]
Back pain	105 (12.4) [4.18]
Vascular disorders	**256 (30.3) [11.97]**
Hypertension	160 (18.9) [6.67]
Nervous system disorders	**219 (25.9) [11.34]**
Headache	93 (11.0) [3.88]

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; pt-yrs=patient years; SS=Safety Set
Note: Preferred terms reported in ≥10% of subjects are included.
Note: Data are displayed as number and percentage of subjects, and event rate per 100 pt-yrs, where 100 pt-yrs was the total summation of individual pt-yrs at risk, divided by 100.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
[a] The preferred term of rheumatoid arthritis indicates worsening rheumatoid arthritis.

8.4.1.1.2. Study C87051

A total of 505 patients (89.1%) reported at least one AE during CZP treatment (including the feeder study) with an event rate of 159/100 patient years. Severe AEs were reported in 130 patients (22.9%). A summary of the most frequently reported AEs (PTs reported in ≥ 10% of patients) are shown in Table 10. The most commonly reported AEs were infections and infestations in 69.7% of patients, musculoskeletal and connective tissue disorders (34.2%), hypertension 113.6%, nasopharyngitis (11.5%), urinary tract infections (10.9%), rheumatoid arthritis (15.2%), and upper respiratory tract infections (16.0%). A total of 76.7% of patients reported AEs of mild intensity, 65.8% reported AEs of moderate intensity, and 22.9% reported AEs of severe intensity. The most frequently reported severe AEs were rheumatoid arthritis in 1.6% of patients and pulmonary TB (1.1%).

Table 10: C87051 AEs reported in at least 10% of subjects (SS).

MedDRA system organ class Preferred term	Total N=567 n (%) [Event rate]
Subjects with at least 1 AE	505 (89.1) [159.40]
Infections and infestations	**395 (69.7) [52.85]**
Upper respiratory tract infection	91 (16.0) [6.54]
Nasopharyngitis	65 (11.5) [4.29]
Urinary tract infection	62 (10.9) [3.99]
Musculoskeletal and connective tissue disorders	**194 (34.2) [19.93]**
Rheumatoid arthritis[a]	86 (15.2) [7.28]
Vascular disorders	**107 (18.9) [6.15]**
Hypertension	77 (13.6) [3.68]
Investigations	**174 (30.7) [17.24]**
Activated partial thromboplastin time prolonged[b]	65 (11.5) [4.59]

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; pt-yrs=patient years; SS=Safety Set
Note: Preferred terms reported in ≥10% of subjects are included.
Note: Data are displayed as number and percentage of subjects, and event rate per 100 pt-yrs, where 100 pt-yrs was the total summation of individual pt-yrs at risk, divided by 100.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
[a] The preferred term of rheumatoid arthritis indicates worsening rheumatoid arthritis.
[b] Prolongation of activated partial thromboplastin time may have been an artifact of the assay used (HemosIL APTT-SP liquid test).

8.4.1.2. Other studies

8.4.1.2.1. Study C87015

A total of 93.5% of patients reported at least one AE during CZP treatment with an event rate of 416/100 patient years. Severe AEs were reported in 43.8%. A summary of the most frequently reported AEs (PTs reported in ≥ 10% of patients) was provided. The most commonly reported AEs were infections and infestations in 69.7% of patients, musculoskeletal and connective tissue disorders (34.2%), hypertension 113.6%, nasopharyngitis (11.5%), urinary tract infections (10.9%), rheumatoid arthritis (15.2%), and upper respiratory tract infections (16.0%). A total of 85.1% of patients reported AEs of mild intensity, 83.3% reported AEs of moderate intensity, and 43.8% reported AEs of severe intensity. The most frequently reported severe AEs were rheumatoid arthritis in 1.6% of patients and pulmonary TB (1.1%).

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

8.4.2.1. Pivotal studies

8.4.2.1.1. Study C87028

A total of 528 patients (62.4%) reported at least one AE considered by the investigator to be related to study medication (Table 11). The most frequently reported related AEs were infections (42.2% of patients) and abnormal investigations (16.8%).

Table 11: C87028 Related AEs reported in at least 2% of subjects (SS).

MedDRA system organ class Preferred term	Total N=846 n (%)
Subjects with at least 1 related AE	528 (62.4)
Infections and infestations	**357 (42.2)**
Urinary tract infection	80 (9.5)
Upper respiratory tract infection	44 (5.2)
Nasopharyngitis	41 (4.8)
Herpes simplex	39 (4.6)
Pharyngitis	39 (4.6)
Bronchitis acute	35 (4.1)
Sinusitis	34 (4.0)
Bronchitis	30 (3.5)
Herpes zoster	24 (2.8)
Pneumonia	22 (2.6)
Cellulitis	17 (2.0)
Investigations	**142 (16.8)**
Antinuclear antibody positive	21 (2.5)
ALT increased	18 (2.1)
General disorders and administration site conditions	**124 (14.7)**
Fatigue	21 (2.5)
Injection site discolouration	17 (2.0)
Pyrexia	17 (2.0)
Skin and subcutaneous disorders	**95 (11.2)**
Rash	31 (3.7)
Blood and lymphatic system disorders	**69 (8.2)**
Eosinophilia	21 (2.5)
Neutropenia	18 (2.1)
Eye disorders	**34 (4.0)**
Conjunctivitis	18 (2.1)
Musculoskeletal and connective tissue disorders	**58 (6.9)**
Rheumatoid arthritis[a]	25 (3.0)
Nervous system disorders	**47 (5.6)**
Headache	19 (2.2)
Vascular disorders	**31 (3.7)**
Hypertension	17 (2.0)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SS=Safety Set
Note: Preferred terms reported in ≥2% of subjects are included.
Note: Related AEs are events that were considered related to study medication by the Investigator.
Note: Adverse events with missing relationship to study medication were counted as related.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
[a] The preferred term of rheumatoid arthritis indicates worsening rheumatoid arthritis.

8.4.2.1.2. Study C87051

A total of 267 patients (47.1%) reported at least one AE considered by the investigator to be related to study medication (Table 12). The most frequently reported related AEs were infections (28.7% of patients) and abnormal investigations (15.9%).

Table 12: C87051 Related AEs reported in at least 2% of subjects (SS).

MedDRA system organ class Preferred term	Total N=567 n (%)
Subjects with at least 1 related AE	267 (47.1)
Infections and infestations	**163 (28.7)**
Bronchitis acute	17 (3.0)
Urinary tract infection	17 (3.0)
Bacteriuria	14 (2.5)
Upper respiratory tract infection	14 (2.5)
Herpes simplex	12 (2.1)
Investigations	**90 (15.9)**
Activated partial thromboplastin time prolonged[a]	48 (8.5)
Alanine aminotransferase increased	15 (2.6)
Aspartate aminotransferase increased	13 (2.3)
Antinuclear antibody increased	12 (2.1)
Musculoskeletal and connective tissue disorders	**36 (6.3)**
Rheumatoid arthritis[b]	18 (3.2)
Renal and urinary disorders	**21 (3.7)**
Haematuria	13 (2.3)

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SS=Safety Set
Note: Preferred terms reported in ≥2% of subjects are included.
Note: Related AEs are events that were considered related to study medication by the Investigator.
Note: Adverse events with a possible, probable, definite, or missing relationship to study medication were counted as related.
Note: Adverse events with missing relationship to study medication were counted as related.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
[a] Prolongation of activated partial thromboplastin time may have been an artifact of the assay used (HemosIL APTT-SP liquid test).
[b] The preferred term of rheumatoid arthritis indicates worsening rheumatoid arthritis.

8.4.2.2. Other studies

8.4.2.2.1. Study C87015

A total of 240 (59.7%) patients reported at least one AE considered by the investigator to be related to study medication. The most frequently reported AEs were infections, most commonly nasopharyngitis (7.7%), upper respiratory tract infections (7.5%), and urinary tract infections (6.7%).

8.4.3. Deaths and other serious adverse events

8.4.3.1. Pivotal studies

8.4.3.1.1. Study C87028

A total of 352 patients (41.6%) reported SAEs, and AEs leading to death were reported in 16 patients (1.6%). A total of 16.4% of patients reported SAEs related to infection, 4% to rheumatoid arthritis, and 3.4% to pneumonia (Table 13). Five of the 16 deaths were considered related to study medication by the investigator (pneumonia, malignant neoplasm, gastric cancer, disseminated TB, and colon cancer).

Table 13: C87028 SAEs reported in at least 1% of subjects (SS).

MedDRA system organ class Preferred term	Total N=846 n (%) [Event rate]
Subjects with at least 1 SAE	352 (41.6) [18.36]
Infections and infestations	**139 (16.4) [5.35]**
Pneumonia	29 (3.4) [0.85]
Cellulitis	11 (1.3) [0.33]
Pulmonary tuberculosis	9 (1.1) [0.25]
Musculoskeletal and connective tissue disorders	**74 (8.7) [2.51]**
Rheumatoid arthritis[a]	34 (4.0) [1.04]
Hepatobiliary disorders	**16 (1.9) [0.44]**
Cholelithiasis	10 (1.2) [0.27]

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred terms; pt-yrs=patient-years; SAE=serious adverse event; SS=Safety Set
Note: Preferred terms reported in ≥1% of subjects are included.
Note: Data are displayed as number and percentage of subjects, and event rate per 100 pt-yrs, where 100 pt-yrs was the total summation of individual pt-yrs at risk, divided by 100.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
Note: Adverse events with a missing serious flag were counted as serious.
Note: Serious AEs of knee arthroplasty (Subject [redacted]), joint arthroplasty (Subject [redacted]), and ileus and megacolon surgeries (Subject [redacted]) were included in the clinical database. During the study, it was determined that these events did not meet the reporting requirements for an SAE as they were preplanned; no CIOMS are available.

8.4.3.1.2. Study C87051

A total of 200 patients (35.3%) reported SAEs, and AEs leading to death were reported in 17 patients (3.0%). A total of 13.8% of patients reported SAEs related to infection, 3.4% to rheumatoid arthritis, and 4.8% to neoplasms (Table 14). A total of six of the 17 deaths were considered related to study medication by the investigator (colon cancer, gastric cancer, metastatic GI cancer, hepatic cirrhosis, streptococcal toxic shock syndrome, and CNS TB).

Table 14: C87051 SAEs reported in at least 1% of subjects (SS).

MedDRA system organ class Preferred term	Total N=567 n (%) [Event rate]
Subjects with at least 1 SAE	200 (35.3) [14.68]
Infections and infestations	**78 (13.8) [3.99]**
Pneumonia	9 (1.6) [0.39]
Pulmonary tuberculosis	9 (1.6) [0.39]
Musculoskeletal and connective tissue disorders	**46 (8.1) [2.73]**
Rheumatoid arthritis[a]	19 (3.4) [0.95]
Osteoarthritis	10 (1.8) [0.48]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**27 (4.8) [1.26]**
Uterine leiomyoma	6 (1.1) [0.26]
Nervous system disorders	**14 (2.5) [0.78]**
Transient ischaemic attack	7 (1.2) [0.39]

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; pt-yrs=patient years; SAE=serious adverse event; SS=Safety Set
Note: Preferred terms reported in ≥1% of subjects are included.
Note: Data are displayed as number and percentage of subjects, and event rate per 100 pt-yrs, where 100 pt-yrs was the total summation of individual pt-yrs at risk, divided by 100.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
Note: Adverse events with a missing serious flag were counted as serious.
Note: Serious AEs of knee arthroplasty (Subject [redacted]) and hip arthroplasty (Subject [redacted] and Subject [redacted]) were included in the clinical database. During the study, it was determined that these events did not meet the reporting requirements for SAEs; no CIOMS are available.
[a] The preferred term of rheumatoid arthritis indicates worsening rheumatoid arthritis.

8.4.3.2. Other studies

8.4.3.2.1. Study C87015

A total of 184 patients (45.8%) reported SAEs, and AEs leading to death were reported in 11 patients (2.7%). A total of 14.4% of patients reported SAEs related to musculoskeletal and connective tissue disorders, 13.7% to infections and 7.2% to cardiac disorders. There were 11 deaths all of which were considered unrelated to study medication by the investigator (mainly cardiac and pneumonia).

8.4.4. Discontinuation due to adverse events

8.4.4.1. Pivotal studies

8.4.4.1.1. Study C87028

A total of 137 patients (16.2%) reported AEs leading to withdrawal.

8.4.4.1.2. Study C87051

A total of 100 patients (17.6%) reported AEs leading to withdrawal.

8.4.4.2. Other studies

8.4.4.2.1. Study C87015

A total of 100 patients (24.9%) reported AEs leading to withdrawal.

8.5. Laboratory tests

8.5.1. Liver function

8.5.1.1. Pivotal studies

8.5.1.1.1. Study C87028

AEs related to liver function were provided. AEs related to increases in hepatic enzymes, ALT and AST were reported in 5.3%, 6.1% and 4.0% of patients, respectively.

8.5.1.1.2. Study C87051

AEs related to liver function were provided. AEs related to increases in hepatic enzymes, ALT and AST were reported in 2.5%, 5.1% and 4.8% of patients, respectively.

8.5.1.2. Other studies

8.5.1.2.1. Study C87015

The most common AE related to abnormal biochemistry values was increased ALT in 6.7% of patients.

8.5.2. Kidney function

8.5.2.1. Pivotal studies

8.5.2.1.1. Study C87028

AEs related to kidney function were provided. AEs related to elevated blood creatinine were reported in 0.7% of patients.

8.5.2.1.2. Study C87051

AEs related to kidney function were provided. AEs related to elevated blood creatinine were reported in 0.9% of patients.

8.5.2.2. Other studies

8.5.2.2.1. Study C87015

AEs related to kidney function are not reported in the CSR.

8.5.3. Other clinical chemistry

8.5.3.1. Pivotal studies

8.5.3.1.1. Study C87028

On average, mean changes in biochemical parameters over time were small and not considered clinically significant.

8.5.3.1.2. Study C87051

On average, mean changes in biochemical parameters over time were small and not considered clinically significant.

8.5.3.2. Other studies

8.5.3.2.1. Study C87015

On average, mean changes in biochemical parameters over time were small and not considered clinically significant.

8.5.4. Haematology

8.5.4.1. Pivotal studies

8.5.4.1.1. Study C87028

AEs related to haematology laboratory results were provided. The most frequently reported AEs were anaemia (6.9% of patients), eosinophilia (3.9%), leucopaenia (2.6%), and neutropaenia (2.6%). All other events were reported in < 2.0% of patients.

8.5.4.1.2. Study C87051

AEs related to haematology laboratory results were provided. The most frequently reported AEs were prolonged aPTT (11.5% of patients) and anaemia (3.9%). All other events were reported in < 2.0% of patients.

8.5.4.2. Other studies

8.5.4.2.1. Study C87015

AEs related to abnormal haematology results were not reported in the CSR. In general there were no clinically meaningful changes over time in mean haematology values.

8.5.5. Electrocardiograph

8.5.5.1. Pivotal studies

8.5.5.1.1. Study C87028

ECGs were not a protocol requirement.

8.5.5.1.2. Study C87051

ECGs were not a protocol requirement. AEs related to cardiac disorders are reported under AEs of special interest.

8.5.5.2. Other studies

8.5.5.2.1. Study C87015

At Entry into the study, 70 (17.4%) patients had abnormal findings and 1% had clinically relevant abnormalities. At the Completion/Withdrawal visit (21.6%) had abnormal findings (1.2%). AEs related to ECG findings were reported in only three patients.

8.5.6. Vital signs

8.5.6.1. Pivotal studies

8.5.6.1.1. Study C87028

A summary of vital signs reported as AEs was provided. The most common events were hypertension (18.9% of patients) and pyrexia (7.2%). Most cases of hypertension were considered mild and not related to study medication. Concomitant medications such as prednisolone and NSAIDs were potential exacerbating factors.

8.5.6.1.2. Study C87051

A summary of vital signs reported as AEs was provided. The most common events were hypertension (13.6% of patients) and pyrexia (3.9%). Most cases of hypertension were considered mild and not related to study medication. Concomitant medications such as prednisolone and NSAIDs were potential exacerbating factors.

8.5.6.2. Other studies

8.5.6.2.1. Study C87015

The most frequent AE related to vital signs was hypertension in 19.7% of patients. However, there were no clinically meaningful changes or trends over time in SBP, DBP, HR or temperature.

8.5.7. AEs of interest

8.5.7.1. Pivotal studies

8.5.7.1.1. Injection site reactions

In C87028, a total of 9.9% of patients reported at least one AE related to injection site reactions, most commonly pain, erythema and skin discolouration. None of the reactions was considered serious. In C87051, 3% of patients reported reactions, most commonly erythema.

8.5.7.1.2. Systemic hypersensitivity reactions

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

8.5.7.1.3. All infections

In C87028, 665 patients (78.6%) had at least one event in the infection and infestation SOC. SAEs were reported by 16.4% of patients; there were three deaths (0.4%); and 49 patients (5.8%) had AEs leading to withdrawal. The majority of AEs were mild to moderate in severity and 7.2% were severe. SAEs in the infections and infestations SOC reported in at least 0.5% of patients are shown in Table 15. Tuberculous infections were each reported in 19 (2.2%) patients. In C87051, 395 patients (69.7%) had at least one event in the infection and infestation SOC. SAEs were reported by 13.8% of patients; there were two deaths (0.4%); and 36 patients (6.3%) had AEs leading to withdrawal. The majority of AEs were mild to moderate in severity and 7.9% were severe. SAEs in the infections and infestations SOC reported in at least 0.5% of patients. Tuberculous infections reported in 17 (3.0%) patients.

Table 15: C807028 SAEs in the infections and infestations SOC reported in at least 0.5% of subjects (SS).

MedDRA preferred term	Total N=846 n (%) [Event rate]
Subjects with at least 1 SAE in the Infections and infestations SOC	**139 (16.4) [0.25]**
Pneumonia	29 (3.4) [0.85]
Cellulitis	11 (1.3) [0.33]
Pulmonary tuberculosis	9 (1.1) [0.25]
Arthritis bacterial	6 (0.7) [0.16]
Erysipelas	6 (0.7) [0.16]
Bronchitis acute	5 (0.6) [0.16]
Herpes zoster	5 (0.6) [0.14]
Subcutaneous abscess	5 (0.6) [0.14]
Urinary tract infection	5 (0.6) [0.14]
Bronchitis	4 (0.5) [0.11]
Disseminated tuberculosis	4 (0.5) [0.11]
Pyelonephritis acute	4 (0.5) [0.14]
Sepsis	4 (0.5) [0.11]
Tonsillitis	4 (0.5) [0.14]

AE=adverse event; pt-yrs=patient years; SAE=serious adverse event; SOC=System Organ Class; SS=Safety Set
Note: Preferred terms reported in ≥0.5% of subjects are included.
Note: Data are displayed as number and percentage of subjects and event rate per 100 pt-yrs, where 100 pt-yrs was the total summation of individual pt-yrs at risk, divided by 100.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category for the per subject numbers.
Note: Adverse events with a missing serious flag were counted as serious.

8.5.7.1.4. Malignancies

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

8.5.7.1.5. Cardiac and vascular AEs

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

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

8.5.7.1.6. Autoimmune AEs

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

8.5.7.1.7. Neurological AEs

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

8.5.7.1.8. Serious bleeding events

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

8.5.7.1.9. Bone marrow aplasia

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

8.5.7.1.10. Serious skin reactions

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

8.5.7.2. Other studies

8.5.7.2.1. Study C87015

Injection site reactions were reported in 7.7% of patients, most commonly pain and bruising. AEs related to systemic hypersensitivity reactions were reported in 20.6% of patients, most commonly cough, rash, and peripheral oedema. There were 12 SAEs related to systemic hypersensitivity reactions, most commonly syncope (3), and pyrexia (3). A total of 81.8% of patients reported at least one AE related to infections and infestations and 40.8% were considered drug related. Most were mild to moderate, and 14.2% were severe. SAEs were reported in 13.7% of patients, most commonly pneumonia (2.2%). Tuberculous infections were reported in two patients (0.2%). The most common malignancies were thyroid (0.7%) and breast (0.7%) cancers. Cardiac AEs were reported in 14.4% of patients, most commonly coronary artery disease (4.0%). Vascular AES were reported in 31.1% of patients, most commonly hypertension (19.7%). Only two patients reported autoimmune AEs and there were no cases suggestive of demyelinating disorders. There were five SAEs relating to bleeding and one SAE of thrombocytopenia. There were SAEs relating to skin reactions in four patients, subcutaneous abscesses, skin ulceration, and erythema (2 cases).

8.6. Post-marketing experience

Not submitted.

8.7. Safety issues with the potential for major regulatory impact

8.7.1. Liver toxicity

No unexpected toxicities were identified.

8.7.2. Haematological toxicity

No unexpected toxicities were identified.

8.7.3. Serious skin reactions

No unexpected events were identified.

8.7.4. Cardiovascular safety

No unexpected toxicities were identified.

8.7.5. Unwanted immunological events

No unexpected events were identified.

8.8. Other safety issues

8.8.1. Safety in special populations

Not assessed. The great majority of patients were White females aged < 65 years.

8.8.2. Safety related to drug-drug interactions and other interactions

Not applicable.

8.8.3. Safety related to anti-CZP antibody status

8.8.3.1. Study C87028

A total of 98/846 patients (11.6%) had detectable anti-CZP antibodies (Ab +). A summary of AEs by anti-CZP antibody status is shown in Table 16. Overall, the incidence of AEs was similar in the Ab + and Ab - patient groups. However, there was a higher incidence in Ab + patients compared to Ab - patients in AEs related to rheumatoid arthritis (28.6% versus 16.4%); pyrexia (13.3% versus 6.4%); rhinitis (13.3% versus 5.7%); conjunctivitis (12.2% versus 5.7%); diarrhoea (11.2% versus 7.4%); dyspepsia (11.2%); cough (10.2% versus 6.4%); ALT increased (10.2% versus 5.6%); and rash (10.2% versus 7.1%). AEs occurring within 2 hours of CZP injection (possibly indicative of hypersensitivity reactions) were recorded in 16.3% and 9.9% of Ab + and Ab - patients, respectively. The incidence of SAEs was higher in Ab + than Ab - patients (51.0% versus 40.4%). There was a higher incidence of SAEs in Ab + patients compared to Ab - patients in SAEs related to infections (26.5% versus 15.1%); pneumonia (7.1% versus 2.9%); and cardiac disorders (6.1% versus 3.5%).

Table 16: C87028 Overall summary of AEs by anti-CZP antibody status (SS).

Category	Ab- N=748 n (%)	Ab+ N=98 n (%)
Subjects with at least 1 AE	711 (95.1)	92 (93.9)
Intensity[a]		
Mild	644 (86.1)	80 (81.6)
Moderate	574 (76.7)	74 (75.5)
Severe	177 (23.7)	33 (33.7)
Relationship to study medication[b]		
Unrelated	527 (76.5)	73 (74.5)
Unlikely	459 (61.4)	62 (63.3)
Possible	398 (53.2)	54 (55.1)
Probable	160 (21.4)	32 (32.7)
Definite	59 (7.9)	12 (12.2)
Related to study medication[c]	462 (61.8)	66 (67.3)
Serious AEs[d]	302 (40.4)	50 (51.0)
AEs leading to death	15 (2.0)	1 (1.0)
AEs leading to withdrawal	116 (15.5)	21 (21.4)

Ab-=anti-CZP antibody negative; Ab+=anti-CZP antibody positive; AE=adverse event; CZP=certolizumab pegol; SS=Safety Set

Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category.

Note: Anti-CZP antibody positive (Ab+) was defined as having a value >2.4units/mL at any on-treatment study visit (not including the Safety Follow-Up Visits). Anti-CZP antibody negative (Ab-) was defined as having no values >2.4units/mL at any on-treatment study visit (not including Safety Follow-Up Visits).

[a] Adverse events with missing intensities were counted as severe. Adverse events with changing intensity over the course of the study were included only for the maximum reported intensity.

[b] Adverse events with missing relationship to study medication were counted as related. Adverse events with changing relationship to study medication over the course of the study were included only for the maximum reported relationship.

[c] Adverse events with a possible, probable, or definite relationship to study medication.

[d] Adverse events with a missing serious flag were counted as serious.

8.8.3.2. Study C87051

A total of 86/567 patients (15.2%) had detectable anti-CZP antibodies. A summary of AEs by anti-CZP antibody status is shown in Table 17. Overall, the incidence of AEs was similar in the Ab+ and Ab- patient groups. However, there was a higher incidence in Ab+ patients compared to Ab- patients in AEs related to rheumatoid arthritis (26.7% versus 13.1%); musculoskeletal and connective tissue disorders (53.5% versus 30.8%); pyrexia (9.3% versus 2.9%); and renal and urinary disorders (16.3% versus 8.7%). AEs occurring within 2 hours of CZP injection were recorded in 2.3% and 1.9% of Ab+ and Ab- patients, respectively. The incidence of SAEs was higher in Ab+ than Ab- patients (43.0% versus 33.9%). There was a higher incidence of SAEs in Ab+ patients compared to Ab- patients in SAEs related to infections (19.9% versus 12.7%).

Table 17: C87051 AEs reported in at least 10% of subjects in either anti-CZP antibody status group by PTs (SS).

MedDRA preferred term	Ab- N=481 n (%)	Ab+ N=86 n (%)
Subjects with at least 1 AE	**422 (87.7)**	**83 (96.5)**
Rheumatoid arthritis[a]	63 (13.1)	23 (26.7)
Upper respiratory tract infection	79 (16.4)	12 (14.0)
Hypertension	65 (13.5)	12 (14.0)
Activated partial thromboplastin time prolonged[b]	55 (11.4)	10 (11.6)
Urinary tract infection	52 (10.8)	10 (11.6)
Bronchitis acute	44 (9.1)	10 (11.6)
Nasopharyngitis	56 (11.6)	9 (10.5)
Back pain	38 (7.9)	9 (10.5)

Ab-=anti-CZP antibody negative; Ab+=anti-CZP antibody positive; AE=adverse event; CZP=certolizumab pegol; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SS=Safety Set
Note: Preferred terms reported by ≥10% of subjects in either antibody group are included.
Note: Where a subject reported more than 1 AE in a category, the subject was counted only once in that category.
Note: Anti-CZP antibody positive (Ab+) was defined as having a value >2.4units/mL at any on-treatment study visit (not including the Safety Follow-Up Visits). Anti-CZP antibody negative (Ab-) was defined as having no values >2.4units/mL at any on-treatment study visit (not including the Safety Follow-Up Visits).
Note: Columns are sorted by descending percentage of subjects in the following order of anti-CZP antibody status: Ab+, Ab-.
[a] The preferred term of rheumatoid arthritis indicates worsening rheumatoid arthritis.
[b] Prolongation of activated partial thromboplastin time may have been an artifact of the assay used (HemosIL APTT-SP liquid test).

8.8.3.3. Study C87015

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

8.9. Evaluator's overall conclusions on clinical safety

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

AEs of interest (injection and hypersensitivity reactions, infections, malignancies, cardiac, vascular, autoimmune and neurological) were identified based on earlier studies and the known effects of biologic anti-TNFα inhibitors. Most AEs of interest were mild or moderate in intensity. There was a high incidence of hypertension, possibly exacerbated by concomitant medications,

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

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of CIMZIA in the proposed usage are:

- Increased ACR20, ACR50 and ACR70 response rates
- Reduced markers of inflammation including CRP and ESR
- Improved symptom scores
- Improved health related quality of life
- Inhibition of radiological progression of structural damage.

9.2. First round assessment of risks

The risks of CIMZIA in the proposed usage are:

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

9.3. First round assessment of benefit-risk balance

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

10. First round recommendation regarding authorisation

Authorisation is recommended for the proposed additional indication: '*Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX*'. However, approval is subject to incorporation of suggested changes to the proposed PI and adequate response to questions in Section 11 of this report.

[1] Correction of a typographical error. This should read 'There were no new safety signals'

11. Clinical questions

11.1. Pharmacokinetics

Not applicable.

11.2. Pharmacodynamics

Not applicable.

11.3. Efficacy

11.3.1. Question 1:

The Clinical Overview reports several post hoc sensitivity analyses to support to the proposed indication. These included linear extrapolation of placebo data, and an analysis of progression of structural damage in the subset of patients who completed at least 2 years of treatment with CZP, and who had evaluable radiographs at completion. These analyses have been reported for C87027/28 but not for C87050/51. The sponsor is requested to provide these analyses and to identify any significant differences between the outcomes of the two trials.

11.3.2. Question 2:

Different central radiographic readers were used to evaluate Year 1 and Year 2 data as the second year analyses were not pre-determined for C87027/28 and C87050/51. The sponsor is requested to provide an estimate of what degree of bias might have been introduced due to observer error.

11.4. Safety

No questions.

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

Question 1

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

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

Question 2

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

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

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

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

13.2. Second round assessment of risks

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

13.3. Second round assessment of benefit-risk balance

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

14. Second round recommendation regarding authorisation

Authorisation is recommended for the proposed additional indication: '*Cimzia has been shown to reduce the rate of progression of joint damage as measured by X-ray, when given in combination with MTX*'. However, approval is subject to incorporation of suggested changes to the proposed PI.

15. References

1. Sharp JT, et al. Treatment with leflunomide slows radiographic progression of rheumatoid arthritis: results from three randomised controlled trials of leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 2000; 43:495 - 505.
2. Lipsky PE, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; 343:1594 - 1602.
3. Jiang Y, et al. A multicentre, double-blind, dose-ranging, randomised, placebo-controlled study of recombinant human interleukin-1 receptor antagonist in patients with rheumatoid arthritis: radiographic progression and correlation of Genant and Larsen scores. *Arthritis Rheum* 2000; 43:1001 - 1009.
4. Breedveld FC, et al. A multicentre, randomised, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate therapy. *Arthritis Rheum* 2006; 54:26 - 37.
5. Strand V and Sharp JT. Radiographic data from recent randomised controlled trials in rheumatoid arthritis. *Arthritis Rheum* 2003; 48:21 - 34.

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