Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for certolizumab pegol

Proprietary Product Name: Cimzia

Sponsor: UCB Australia Pty Ltd

Date of CER: 30 August 2013

Date of CER: 13 December 2013

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.
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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 <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
AE	Adverse Event
AS	Ankylosing Spondylitis
ASAS	Assessment of Spondyloarthritis International Society
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
BMI	Body Mass Index
BSA	Body Surface Area
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
CRP	C-Reactive Protein
CS	Corticosteroids
CV	Coefficient of Variation
CZP	Certolizumab Pegol
DMARD	Disease Modifying Anti-Rheumatic Drug
ES	Erosion Score
ESR	Erythrocyte Sedimentation Ratio
FAS	Full Analysis Set
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire – Disability Index
HCQ	Hydroxychloroquine
JSN	Joint Space Narrowing
LEF	Leflunomide

Abbreviation	Meaning
LS	Least Square
MCID	Minimal Clinically Important Difference
mTSS	modified Total Sharp Score
MTX	Methotrexate
NRS	Numerical Rating Scale
nr-SpA	non-radiographic axial Spondyloarthritis
NSAID	Non-Steroidal Anti-Inflammatory Drug
PASI	Psoriasis Area Severity Index
PD	Pharmacodynamic
PGA	Psoriasis Global Assessment
PhGADA	Physician Global Assessment of Disease Activity
PK	Pharmacokinetic
PPS	Per Protocol Set
PsA	Psoriatic Arthritis
PtGADA	Patient Global Assessment of Disease Activity
PY	Patient-Years
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RS	Randomized Set
SAE	Serious adverse event
SD	Standard Deviation
SOC	System Organ Class
SpA	Spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	Sulfasalazine

Abbreviation	Meaning
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal

1. Introduction

CZP is a member of the Tumour Necrosis Factor alpha (TNFα) inhibitor drug class (ATC code: L04AB05). It is a recombinant humanised antibody, which binds with high affinity to human TNFα, thereby neutralising its effect. It does not neutralise lymphotoxin, or TNFβ. The Fab' (fragment antigen binding) fragment is conjugated with a polyethylene glycol chain. CZP does not contain a fragment crystallizable (Fc) region, which is normally present in the complete antibody. The pegylation of the Fab' fragment increases its half-life and may also decrease its immunogenicity, without affecting the affinity and specificity of the antibody in binding to human TNFα in vivo.

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 an inadequate response or intolerance to previous therapy with one or more disease-modifying antirheumatic drugs (DMARDs) or*
>
> – *as monotherapy in case of a contraindication or intolerance to MTX (see Dosage and Administration).*

The proposed additional indication is:

> *Psoriatic arthritis: Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis. Cimzia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function.*
>
> *Axial spondyloarthritis: Cimzia is indicated for the treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis and patients with non-radiographic axial spondyloarthritis.*

2. Clinical rationale

PsA is a chronic inflammatory arthropathy that occurs in up to 30% of patients with skin psoriasis (prevalence 1-3% of general population). The arthritis is usually diagnosed years after the skin disease appears, but sometimes onset is before (15%) or simultaneous (20%) with the skin disease. It affects men and women equally. The arthritis usually starts between the ages of 30 and 50 years. PsA has a heterogeneous disease course, but more than 50% of affected individuals experience a progressive, erosive arthritis that is accompanied by pain, functional impairment and reduced quality of life. Peripheral joint involvement may be polyarticular or oligoarticular. The typical pattern of joint disease is an asymmetrical distribution with distal interphalangeal involvement and dactylitis (swollen digits). Spondylitis is present in approximately one third of all patients with PsA, and for 5% of affected individuals is the predominant clinical manifestation. Radiologically, PsA is characterized by juxta-articular new bone formation, absence of peri-articular osteopenia and relative preservation of the joint space until late in the disease course. As PsA and RA share a similar immunopathologic etiology, therapeutic options for PsA are similar to that utilised in RA treatment.

TNF is a pro-inflammatory cytokine, which is present in significantly elevated serum and synovial concentrations in patients with PsA. It affects a variety of pathophysiological processes including activation of T-cells, induction of acute phase proteins, and stimulation of haemopoietic precursor cell growth and differentiation. CZP is a recombinant, humanized TNF antibody, which binds with high affinity to human TNFα. Current approved treatment options in Australia for moderately to severely active PsA include NSAIDs, corticosteroids (CS), non-biological DMARDs (mainly MTX, Sulfasalazine [SSZ] and Leflunomide [LEF]). In addition, 4 anti-TNF drugs (infliximab, etanercept, adalimumab and golimumab) are currently registered in Australia, Europe and the USA for the treatment of PsA in terms of improving the signs and symptoms of peripheral arthritis, and the accompanying psoriatic skin disease. In addition, they have all shown in clinical studies to improve physical functioning and health related quality of life. Golimumab is also approved in Europe for reducing the progression of joint damage, and the other 3 anti-TNF drugs have demonstrated to varying degrees attenuation of the progression of radiographic joint damage. The sponsor states that the registration of additional anti-TNF drug in patients with PsA meets a need for patients who don't obtain or maintain sufficient efficacy benefit (that is primary or secondary efficacy failure), or who are intolerant to the currently available anti-TNF agents.

Axial SpA is a chronic inflammatory arthritis of the axial skeleton, which encompasses Ankylosing Spondylitis (AS), as well as a subgroup characterized by little or no changes evident on plain X-rays. This latter subgroup is referred to as non-radiographic axial SpA (nrSpA). The most frequently investigated subset of patients with axial SpA is those with AS, as classification criteria allowing for early diagnosis of axial SpA have only recently been developed as medical technology has advanced (mainly, the widespread use of Magnetic Resonance Imaging [MRI]). The modified New York (NY) criteria were developed nearly 30 years ago, and have been widely accepted in clinical practice and trials (van der Linden et al, 1984). The modified NY criteria work well in established disease, but have limited value in detecting early disease. A prospective study indicated that the sensitivity of the modified NY criteria increased with disease duration having zero sensitivity for a disease duration of 2 years versus 60.2% sensitivity for a disease duration of > 10 years (Rudwaleit et al, 2004). The modified NY criteria require clear evidence of sacroiliitis on conventional plain X-rays, but MRI has the ability to reliably detect the early stages of axial SpA before established X-ray destruction has become apparent. There is published evidence to support the concept that the occurrence of radiographic sacroiliitis in subjects with axial SpA is mainly a function of time and disease severity. Patients with axial SpA, including AS and nr-SpA, can now be diagnosed using the Assessment of Spondyloarthritis International Society (ASAS) classification criteria (Rudwaleit et al, 2009), which allow the diagnosis and classification of axial SpA in the absence of definitive radiographic evidence of sacroiliitis.

The main clinical symptom of axial SpA is inflammatory back pain, typically starting in the sacroiliac joints (buttock area) and lumbar spine. However, patients may develop musculoskeletal symptoms away from the spine (peripheral joint arthritis and enthesitis), as well as extra-articular manifestations (colitis, uveitis, skin psoriasis). Between 30-60% of AS patients have significant functional loss. Early in the disease, disability is determined mainly by inflammatory activity, whereas in long-standing established disease, both inflammation and bony ankylosis contribute to disability.

The main treatment options available for axial SpA are NSAIDs and physiotherapy. Non-biologic DMARDs such as MTX, SSZ and CS may be tried, but the supporting evidence of efficacy is very limited to non-existent. Four anti-TNF drugs (infliximab, etanercept, adalimumab and golimumab) are currently registered in Australia, Europe and the USA for the treatment of AS in terms of improving the signs and symptoms of spinal and peripheral arthritis, physical functioning and health related quality of life. Based on the similarities between AS and nr-SpA as they are likely to represent a disease spectrum continuum, it is anticipated that anti-TNF drugs may be effective in patients with nr-SpA. Initial small MRI studies of the nr-SpA subset using

anti-TNF therapies (for example adalimumab) have shown efficacy (Sieper et al, 2011), but currently no anti-TNF treatment is registered for the nr-SpA indication as the original licensing studies restricted patient entry to those with confirmed AS. Hence, there is an unmet need for effective and safe therapies in patients with active nr-SpA.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- All 4 of the efficacy/safety studies collected pharmacokinetic data.
- No population pharmacokinetic analyses.
- 2 pivotal efficacy/safety studies – Study PsA001 for the proposed PsA indication; and Study AS001 for the proposed SpA indication.
- No dose-finding studies.
- 2 other efficacy/safety studies – Studies C87040 and C87044 were conducted in patients with moderate to severe plaque psoriasis as supportive evidence in the PsA indication.
- No pooled analysis, or meta-analysis was provided.
- The sponsor's Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.

3.2. Paediatric data

The submission did not include paediatric data.

3.3. Good clinical practice

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

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

All 4 clinical studies collected a limited quantity of Pharmacokinetic (PK) data in the target populations of PsA, axial SpA and skin psoriasis.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional PK studies in humans. The following information is derived from the sponsor's summaries, as well as the currently approved product information.

CZP is slowly absorbed from the site of SC injection, reaching maximum serum concentration 2-7 days after administration. Absolute bioavailability is approximately 80% (range: 76-88%), and the apparent volume of distribution at steady state in adults with RA is 8.0 L. The half-life of CZP is approximately 14 days for all tested doses. The presence of anti-CZP antibodies results in

approximately a 3-fold increase in plasma clearance. The key PK variables observed in patients with RA are consistent with those seen in healthy subjects. No specific studies have been performed to assess the effect of renal or hepatic impairment on the PK of CZP, or its pegylated fraction. Age and gender do not appear to be significant factors in determining the PK characteristics of CZP in patients with RA.

4.3. Physicochemical characteristics of the active substance

CZP is a genetically engineered, humanised antibody Fab' fragment, conjugated with polyethylene glycol (PEG), which has an approximate molecular weight of 90 kD. It does not contain an Fc region, which is normally present in the complete antibody. It binds with high affinity to TNFα, and blocks its interaction with cell surface TNF receptors found on a variety of cells in the body. The sponsor does not propose any change to the physiochemical structure or manufacturing process with this application for extension of indication.

4.4. Pharmacokinetics in the target population

All 4 clinical studies included in this submission collected a limited quantity of PK data in the target populations of PsA and axial SpA and skin psoriasis.

4.4.1. Study PsA001

Trough serum samples for CZP concentration were collected at baseline; and weeks 2, 4, 12, 16 and 24 in Study PsA001. The geometric mean plasma concentrations of CZP were highest (and similar) at weeks 2 and 4 for both dose regimens of CZP, as all subjects randomized to CZP received a loading dose regimen of 400 mg at weeks 0, 2 and 4. After completion of the loading dose phase, trough CZP concentrations at weeks 12, 16 and 24 were lower than at weeks 2 and 4, but remained steady over time. At weeks 12, 16 and 24, trough CZP concentrations were lower in the CZP 400 mg Q4W group compared to the CZP 200 mg Q2W arm, which is consistent with the difference in dosing interval.

In subjects who tested positive for anti-CZP antibodies, the geometric mean plasma concentration of CZP was considerably lower (by approximately 70-80%) at weeks 12, 16 and 24 than those observed in subjects who were persistently negative for anti-drug antibodies. For example, at Week 16 the geometric mean plasma concentration of CZP in the anti-CZP antibody positive subjects was 3.821 µg/mL in the 200 mg group (n = 15) and 2.087 µg/mL in the 400 mg group (n = 16); versus 18.926 µg/mL in the 200 mg group (n = 113) and 12.087 µg/mL in the 400 mg group (n = 108) in the anti-drug antibody negative subjects. This result is consistent with significantly increased plasma clearance of CZP in the presence of anti-CZP antibody formation.

4.4.1.1. Study AS001

Trough serum samples for CZP concentration were collected at baseline; and weeks 2, 4, 12, 16 and 24 in Study AS001. The geometric mean plasma concentrations of CZP were highest (and similar) at weeks 2 and 4 for both dose regimens of CZP, as all subjects randomized to CZP received a loading dose regimen of 400 mg at weeks 0, 2 and 4. After completion of the loading dose phase, trough CZP concentrations at weeks 12, 16 and 24 were lower than at weeks 2 and 4, but remained steady over time. At weeks 12, 16 and 24, trough CZP concentrations were lower in the CZP 400 mg Q4W group compared to the CZP 200 mg Q2W arm, which is consistent with the difference in dosing interval.

In subjects who tested positive for anti-CZP antibodies, the geometric mean plasma concentration of CZP was considerably lower (by approximately 70-80%) at weeks 12, 16 and 24 than those observed in subjects who were persistently negative for anti-drug antibodies. For example, at Week 16 the geometric mean plasma concentration of CZP in the anti-CZP antibody

positive subjects was 4.53 µg/mL in the 200 mg group (n = 4) and 3.28 µg/mL in the 400 mg group (n = 5); versus 21.42 µg/mL in the 200 mg group (n = 74) and 13.07 µg/mL in the 400 mg group (n = 71) in the anti-drug antibody negative subjects. This result is consistent with significantly increased plasma clearance of CZP in the presence of anti-CZP antibody formation.

4.4.1.2. Studies C87040 and C87044

In both skin psoriasis trials, trough serum samples for CZP were taken at screening and every 4 weeks during the 12-week active treatment phase, as well as the safety follow-up phase. In Study C87040, the geometric mean values (CV%) for plasma concentrations in the CZP 200 mg treatment arm (n = 50-54) were as follows: 25.05 µg/mL (42.6%) at Week 4, 21.22 µg/mL (40.6%) at Week 12, and 3.21 µg/mL (75.5%) at Week 16 (Week 4 of the follow-up period). In the CZP 400 mg treatment group (n = 53-55), geometric mean values (CV%) for plasma concentrations were higher at all scheduled time assessments indicating an increased drug exposure: 39.98 µg/mL (41.9%) at Week 4, 39.98 µg/mL (47.0%) at Week 12, and 7.49 µg/mL (110.3%) at Week 16 (Week 4 of the follow-up period). Additionally, in Study C98040, 10 patients were identified as developing neutralizing anti-CZP antibodies, and for 8 of those subjects trough serum CZP concentrations were below the lower limit of quantification suggesting increased plasma clearance of CZP in the presence of neutralizing anti-CZP antibody formation.

At Week 12 in the re-treatment Study C98044, the geometric mean plasma concentrations in the CZP 200 mg arm were 16.12 µg/mL versus 22.84 µg/mL at Week 12 in the first treatment period. In the CZP 400 mg treatment group, the geometric mean plasma concentrations at Week 12 were also higher in the first treatment phase at 43.79 µg/mL versus 34.01 µg/mL at Week 12 in the re-treatment period. Plasma levels were similar during the first and re-treatment periods for those subjects who tested negative for anti-CZP antibodies. However, in the patients who were positive for anti-CZP antibodies trough plasma CZP concentrations were markedly reduced in the presence of anti-CZP antibodies upon re-treatment.

4.5. Evaluator's overall conclusions on pharmacokinetics

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

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

- Plasma trough CZP concentrations were highest at weeks 2 and 4 of both pivotal studies when subjects received a loading regimen of CZP 400 mg at weeks 0, 2 and 4;
- Trough CZP concentrations at weeks 12, 16 and 24 (maintenance phase) were lower in subjects treated with CZP 400 mg Q4W versus CZP 200 mg Q2W, which is consistent with the extended dosing interval approach;
- Subjects who developed anti-CZP antibodies had significantly lower trough CZP concentrations indicating increased plasma clearance of CZP; and
- Plasma levels of CZP are similar during the first and re-treatment periods for those subjects who remain persistently negative for anti-CZP antibodies.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

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

5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans. The following information is derived from the sponsor's summaries, as well as the currently approved product information.

5.3. Mechanism of action

CZP is a recombinant humanised antibody, which binds with high affinity to human TNFα, thereby neutralising its effect. It has been shown to neutralise both membrane associated and soluble TNFα in a dose dependent manner. TNFα is a key pro-inflammatory cytokine in the pathogenesis of inflammatory conditions. CZP does not contain a fragment crystallizable (Fc) region, which is normally present in the complete antibody, and therefore does not fix complement or cause antibody-dependent, cell mediated cytotoxicity in vitro. It does not induce apoptosis in vitro in human peripheral blood monocytes or lymphocytes.

5.4. Pharmacodynamic effects

No new information has been provided in this submission.

5.5. Evaluator's overall conclusions on pharmacodynamics

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

5.6. Dosage selection for the pivotal studies

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

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

6. Clinical efficacy

6.1. Indication 1

Indication 1:

Cimzia is indicated for the treatment of adult patients with active psoriatic arthritis. Cimzia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function.

6.1.1. Pivotal efficacy study

6.1.1.1. Study PsA001

6.1.1.1.1. Study design, objectives, locations and dates

Study PsA001 was a Phase III randomized, double-blind, parallel-group, placebo-controlled trial which evaluated the efficacy and safety of CZP in adults subjects with adult-onset active and progressive PsA. The study had 5 treatment periods: screening (up to 5 weeks), double-blind treatment period (weeks 0-24), dose-blind treatment phase (weeks 24-48), open-label treatment period (weeks 48-158), and the safety follow-up phase 10 weeks after the last dose of study medication (Week 166). For the efficacy data component of this submission, only the screening and double-blind treatment periods were included. However, the latter phases of the study are ongoing.

Screening assessments were performed between weeks -5 and -1. The screening period was used to obtain baseline data (clinical and laboratory), to verify that the doses of allowed DMARD, NSAID, and CS therapy was stable (if used), and to enable washout of any medications not permitted for use during the study. The baseline visit was Day 0, and then during the 24-week double-blind treatment period assessments were scheduled to occur at weeks 1 and 2, and thereafter every 2 weeks up until Week 24.

During the 24-week, double-blind treatment phase, patients were randomly allocated in a 1:1:1 ratio to the following study treatments: CZP 400 mg Q2W at weeks 0, 2, and 4 followed by CZP 200 mg Q2W (starting at Week 6), CZP 400 mg Q2W at weeks 0, 2, and 4 followed by CZP 400 mg Q4W (starting at Week 8), or placebo injections. Subjects receiving placebo injections who did not achieve at least a minimal response (defined as a decrease of at least 10% in the number of tender and swollen joints) at both the Week 14 and 16 visits were allocated to blinded CZP escape therapy (randomized 1:1 to receive CZP 200 mg Q2W or CZP 400 mg Q4W) from Week 16 onwards. All of the placebo escape patients received CZP 400 mg on 3 occasions (weeks 16, 18 and 20) followed by their ongoing randomized CZP regimen (200 mg Q2W starting at Week 22, and 400 mg Q4W starting at Week 24). The IVRS was used to identify qualifying subjects for early escape therapy. Subjects in either of the 2 CZP treatment groups who qualified for escape treatment at Week 16, continued with their current treatment allocation for the duration of their participation in the study (that is they were not re-randomized).

The primary efficacy objectives of the study were to demonstrate the efficacy of CZP (given by SC injection at the dose of 200 mg Q2W or 400 mg Q4W after loading with 400 mg at weeks 0, 2, and 4) on the signs and symptoms of active PsA, and on the inhibition of progression of structural damage in adults with active PsA. The secondary efficacy objectives of the study included the assessment of the effects of CZP upon health related outcomes, psoriatic skin disease (in the subgroup of affected subjects with > 3% body surface area [BSA] affected at baseline), dactylitis, enthesitis, and axial involvement (in the subgroup of affected subjects with Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] > 4 at baseline).

The study was to be conducted at 117 sites, but only 92 centres enrolled subjects. Centres were pooled based on comparison of medical practice and geographical regions into: North America (USA and Canada), Latin America (Mexico, Brazil, and Argentina), Western Europe (United

Kingdom, Ireland, Belgium, Germany, Italy, and Spain), and Central/Eastern Europe (Czech Republic, Poland, and Hungary). In Study PsA001, the first subject was enrolled on 2 March 2010, and the last subject procedure for this interim efficacy dataset occurred on 7 December 2011.

There were 3 global and 2 country-specific amendments to the original protocol (dated 25 September 2009). The first global amendment was instituted before the commencement of patient recruitment, and all of the other amendments occurred after. The amendments contained clarifications about the statistical analysis plan (for example hierarchical test procedures for multiple endpoints), and explanations about the baseline and efficacy measures. None of the amendments resulted in major changes to the study design, which may have adversely affected the integrity of the study's outcomes or statistical analysis.

6.1.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be at least 18 years of age with a diagnosis of adult-onset PsA of at least 6 months duration as defined by the CASPAR criteria, and have failed at least 1 DMARD. Patients were allowed to be receiving stable non-biological DMARD treatment for at least 28 days prior to baseline with 1 of 3 specified treatments: Sulfasalazine (SSZ) < 3g daily, Methotrexate (MTX) < 25 mg weekly, and/or Leflunomide (LEF) < 20 mg daily. Subjects were also required to have either active psoriatic skin lesions or a documented history of psoriasis. To be included in the study, patients must have had active arthritis at baseline defined as > 3 tender and swollen joints at the screening and baseline visits; and to have fulfilled at least 1 of the following 2 serological criteria during the screening phase (Erythrocyte sedimentation rate [ESR] > 28 mm/hour by the Westergren method, or C-reactive protein [CRP] > ULN [Upper Limit of Normal]).

The exclusion criteria were extensive and involved 5 domains. Patients meeting any 1 of the criterion were to be excluded from study.

- Diagnosis – any other inflammatory arthritis such as RA or a known diagnosis of fibromyalgia, symptomatic osteoarthritis that in the investigator's opinion may interfere with evaluating the effect of study medication on the subject's primary diagnosis of PsA, permanently bedridden or wheelchair bound for any reason, and pregnancy/lactation;
- Past history – chronic alcohol abuse within the last year (defined as consuming more than 14 standard drinks/week for women, and more than 21 standard drinks/week for men); history of chronic or recurrent infections (more than 3 episodes requiring antimicrobial treatment during the preceding year), recent serious or life-threatening infection within 6 months of the baseline visit (including herpes Zoster), hospitalization for any infection in the last 6 months, or any current sign or symptom that may have indicated an infection; known TB disease, high risk of acquiring TB, or latent TB infection; high risk of infection in the investigator's opinion (such as subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections); history of an infected joint prosthesis at any time; major surgery (including joint surgery) within the 8 weeks prior to screening; concurrent infection with Hepatitis B or C virus or HIV; demyelinating disease; lymphoproliferative disorder; Class III or IV congestive heart failure; and malignancy within the last 5 years (except for up to 3 excised basal cell skin cancers or cervical carcinoma in situ successfully treated by surgery);
- Abnormal baseline laboratory results – liver function tests > 2 x ULN, serum creatinine > ULN, or total white blood cell count < 3.0 x 10^9/L;
- Recent or concurrent treatments - use of biologic DMARD therapy within 3 months prior to baseline (28 days for etanercept), oral prednisone > 10 mg/day (as well as, intra-articular or parenteral CS within 28 days), phototherapy for skin psoriasis within 28 days prior to baseline, topical therapy for skin psoriasis within 14 days of baseline, change in non-biologic

DMARD therapy within the last 28 days, any live (including attenuated) vaccination within the 8 weeks prior to baseline (however, inactivated influenza and pneumococcal vaccines were allowed but nasal influenza vaccination was not permitted); and

- Prior treatment – exposure to a maximum of 2 previous biological response modifiers for either PsA or skin psoriasis, including only 1 TNF antagonist treatment. In addition, the prior TNF antagonist experience must not have been a primary failure to such therapy (defined as no response within the first 12 weeks of treatment with the TNF antagonist). Prior treatment (at any time) with tocilizumab or anti-CD20 therapy was an exclusion.

6.1.1.1.3. Study treatments

Subjects were randomized in a 1:1:1 ratio to receive CZP 200 mg Q2W, CZP 400 mg Q4W, or placebo injections. CZP was supplied as a sterile, clear, and colourless to slightly yellow liquid solution in a 1mL pre-filled syringe containing 200 mg of the drug (injected with 25G needle). Placebo injections were supplied in a 1mL pre-filled syringe containing 0.9% saline (injected with the same type of 25G needle). There were minor differences in the presentation and viscosity between the CZP and placebo injections. All injections were given by SC injection into the lateral abdominal wall or upper outer thigh. During each dosing visit where 2 injections were administered, 2 different anatomical sites were injected. During the double-blind phase of the Study PsA001, study treatments (including placebo injections) were administered by pre-specified, unblinded, trained study centre personnel at fortnightly intervals between weeks 0 and 24. Patients did not self-administer therapy in this treatment period.

Only 3 concurrent non-biological DMARD treatments were permissible during Study PsA001: SSZ < 3g daily, MTX < 25 mg weekly, or LEF < 20 mg daily. The doses of all continued DMARD therapy had to be stable for at least 28 days prior to baseline. The use of DMARD combination therapy was forbidden. Patients were also able to continue with low dose CS (maximum oral dose of 10 mg/day of prednisone or equivalent) if they had been receiving a stable dose for at least 28 days prior to baseline. Similarly, NSAID (including COX-2 inhibitors) could be continued if these treatments were stable for at least 14 days prior to baseline. Analgesic medications (including paracetamol and narcotics) were permitted except for ad hoc use within 24 hours prior to any scheduled study assessments. No change in concurrent NSAID, CS or DMARD dose (or route of administration for MTX) was permitted in the first 48 weeks of the study, except for documented safety reasons. Phototherapy and/or topical agents for psoriasis, as well intra-articular CS injections for active PsA, will be permitted after the first 48 weeks of the study.

6.1.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- American College of Rheumatology (ACR) response criteria
- Modified Total Sharp Score (mTSS)
- Psoriasis Area and Severity Index (PASI).

Study PsA001 had 2 primary efficacy outcomes: ACR 20 response rate at Week 12, and the mean change from baseline to Week 24 in the mTSS.

In general, the key efficacy endpoints in Study PsA001 use validated metrics that have served as the basis of previous published studies, prior regulatory approvals, and are consistent with published guidelines. The endpoints studied were relevant to assess the proposed indication of "to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function in adult patients with active psoriatic arthritis."

The ACR response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with RA and PsA. A patient with an ACR 20 response to an intervention has demonstrated a 20% decrease in the combined number of swollen (maximum of 66) and tender

(maximum of 68) joint counts, as well as a 20% improvement in any 3 of the 5 core-set measures which include Patient's Global Assessment, Physician's Global Assessment of disease activity, Patient's Assessment of Pain score (on 10 cm VAS), Disability (Index of the HAQ), and acute phase reactants (ESR or CRP). The analyses of ACR 50 and ACR 70 included the same criteria as ACR 20, but with the use of a higher percentage improvement (50% or 70%) instead of 20%.

The Disability Index of the Health Assessment Questionnaire (HAQ-DI) is a validated method for measuring disability in inflammatory arthritis (range: 0-3 with higher score indicating more functional impairment). It assesses physical function by measuring the patient's ability to perform the following 8 activities (using 20 questions): -dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity. The measure uses a scale ranging from zero (best) to three (worst). A change in the HAQ-DI of -0.30 units is considered to be the minimal clinically important difference (MCID) in treatment studies of patients with PsA (Mease et al, 2004).

The Sharp-van der Heijde modified scoring method (modified Total Sharp Score, or mTSS) for PsA was used to assess structural joint damage, and its progression (van der Heijde et al, 2005). All enrolled subjects in Study PsA001 were required to have X-rays taken of both hands and both feet (a single postero-anterior view of each hand, and a single dorso-plantar view of each foot) at baseline, weeks 12 and 24, or upon early withdrawal. X-ray images of both hands and feet were obtained using a slotting approach, digitized, and assessed by physicians who were blinded to the treatment group and clinical status of the subject. The mTSS score is the sum of the joint space narrowing (JSN) score plus the erosion score (ES) and has a range of 0-528. In further detail, the mTSS consists of the composite of the JSN (range of 0-208; 26 sites on each side of the body scored from 0-4 for each site) and the ES (range of 0-320; 32 sites on each side of the body scored from 0-5 for each site). A higher score indicates more radiographic damage.

The Psoriasis Area and Severity Index (PASI) is an assessment of 4 anatomic sites (head, upper extremities, trunk, and lower extremities) for erythema, induration, and desquamation using a scale of zero (the best evaluation, no symptoms) to four (the worst evaluation, very marked). The extent of lesions in a given area is assigned a numerical value from one (< 10%) to six (90-100%). The PASI score is then calculated from a weighted average based on the % of body surface area (BSA) of the anatomic site (head, 10%; upper extremities, 20%; trunk, 30%; and lower extremities, 40%). The PASI score has a range from 0 (no disease) to 72 (maximal disease), and responses can be based on at least 50%, 75%, 90% and 100% improvement in scores from baseline.

The Psoriatic Arthritic Response Criteria (PsARC) contains a variation of 4 of the measures of the ACR 20 response (Swollen and Tender joint counts; as well as the Physician's and Patient's Global Assessment of Disease Activity) but does not include a measure of pain, function/disability, or an acute phase reactant (ESR or CRP). PsARC response is defined as no worsening in any of the criteria listed below, and an improvement from baseline in at least 2 of the following 4 criteria, one of which has to be either the tender or swollen joint count:

- Physician's Global Assessment of Disease Activity (PhGADA; decrease by 1 point in the 5-point Likert scale),
- Patient's Global Assessment of Disease Activity (PtGADA; decrease by 1 point in the 5-point Likert scale),
- Tender Joint Count (at least 30% improvement in the 68 joint count), and
- Swollen Joint Count (at least 30% improvement in the 66 joint count).

Worsening of criteria is defined as > 20% increase for global assessments, and > 30% increase for joint counts.

The 28 joint Disease Activity Score (DAS 28) is a widely used and validated method used in research trials and clinical practice for measuring outcome in patients with RA and PsA. It is a composite disease activity index of 4 clinical variables involving the tender joint count (up to 28 joints), swollen joint count (up to 28 joints), CRP, and the patient's assessment of general health using a 10 cm visual analogue scale. The final score is derived by a complex mathematical calculation of the individual elements. DAS 28 has a scale from 0 to 10, and most scores range from around 2 to a maximum of 10. According to EULAR guidelines, DAS 28 > 5.1 indicates high disease activity, < 3.2 indicates low disease activity, and "clinical remission" is indicated by a DAS 28 score of < 2.6.

6.1.1.1.5. Secondary efficacy endpoints

There were 3 key secondary efficacy variables in Study PsA001, all of which were measured at Week 24: ACR 20 response rate, mean change from baseline in the HAQ-DI score, and PASI 75 response rate. The PASI index is a validated and universally accepted tool for assessing extensive skin psoriasis (that is covering at least 3% BSA). The index takes into account redness, thickness and scaliness of the psoriatic skin lesions, weighted by the area of involvement. PASI responses were based on at least 50%, 75%, 90% and 100% improvement in the PASI score, in the subgroup of patients with skin psoriasis involving at least 3% BSA at baseline.

There were a very large number of other non-key secondary efficacy outcomes (grouped below by disease manifestation/category), which included:

- Signs and symptoms of PsA – ACR 20/50/70 responses (and the individual components) at various time points over 24 weeks; and change from baseline in the Leeds Dactylitis Index (LDI), Leeds Enthesitis Index (LEI), Psoriatic Arthritis Response Criteria (PsARC), DAS 28 score (using CRP), and BASDAI over time.
- Radiographic endpoints – Change from baseline in mTSS at 12 weeks, change from baseline in ES and JSN score at 12 and 24 weeks, and radiographic responder status at 24 weeks.
- Heath-related outcomes - Change from baseline at various time points over 24 weeks in SF-36 domains (as well as responder status), PsAQoL, fatigue (using FASCA), EQ-5D, DLQI, work productivity, and health resource utilization.
- Skin Effects - PASI 50/75/90/100 responses at various time points over 24 weeks; mean change from baseline PASI score; Physician's Global Assessment of Psoriasis and psoriatic nail changes.

6.1.1.1.6. Randomisation and blinding methods

Subject randomization was conducted using IVRS (Interactive Voice Response System), and stratified by treatment centre and prior TNF antagonist exposure. Patients were allocated to treatment in a 1:1:1 ratio (CZP 200 mg Q2W, CZP 400 mg Q4W, or placebo injections). Placebo subjects who qualified for escape treatment at Week 16 were re-randomized in a 1:1 ratio (stratified by prior TNF antagonist exposure) to either CZP 200 mg Q2W or CZP 400 mg Q4W. Subjects originally randomized to placebo who completed to Week 24 were re-randomized at that time point in a 1:1 ratio to either CZP 200 mg Q2W or CZP 400 mg Q4W, again stratified by prior TNF antagonist exposure.

Due to differences in the presentation and viscosity between the CZP and placebo injections, the sponsor states, "special precautions were taken to ensure blinding of the study". However, detail about the special precautions was limited in the submission. During the double-blind phase of the Study PsA001, study treatments (including placebo injections) were administered by pre-specified, unblinded, trained study centre personnel at fortnightly intervals between weeks 0 and 24. However, investigators and patients were blinded to study treatment assignment.

6.1.1.1.7. Analysis populations

The primary analysis of all efficacy variables was performed using the Randomized Set (RS), which consisted of all subjects randomized into the trial, analysed by imputation of missing values. For sensitivity analyses of the primary efficacy variables, the Full Analysis Set (FAS), Per-Protocol Set (PPS) and Completer Set were additionally explored. The FAS consisted of all patients in the RS who had received at least 1 dose of study medication, and who had valid baseline and post-baseline efficacy measurements for both the ACR20 through to Week 12, and the mTSS at Week 24. The PPS consisted of patients in the FAS who had a minimal exposure to medication of 12 weeks in the double-blind treatment phase without any major protocol deviations that may have affected the validity of the efficacy variables. The Completer Set consisted of subjects in the FAS who had completed 24 weeks of randomized treatment, with a valid 24-week efficacy measurement.

6.1.1.1.8. Sample size

The sample size was determined by the larger of the 2 sample size estimates for the co-primary efficacy endpoints. Based on published data examining the effect of other anti-TNF therapy in the treatment of PsA, it was anticipated that the difference between CZP and placebo for the mean change over 24 weeks in the mTSS was greater than 1.0 point. A sample size of 130 patients in each treatment group was sufficient to detect a statistically significant difference in the mean change in mTSS if both CZP arms were combined versus placebo, yielding at least 95% power, assuming a SD of 2.4 points. This sample size was also sufficient to detect a statistically significant difference between CZP and placebo at Week 48 with 90% power (and 80% for the individual CZP dose regimens), assuming a treatment difference of 2.0 points, SD of 5.6 points, and applying linear extrapolation. For each CZP treatment group comparison with placebo for the ACR20 response rate at Week 12, the power was 99%, assuming an anticipated treatment difference of 25% (40% response rate for CZP versus 15% response rate for placebo).

6.1.1.1.9. Statistical methods

Statistical analyses accounting for multiplicity were performed for the primary and key secondary efficacy variables. A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. The pre-defined order of hypothesis testing, each at a 2-sided 5% alpha level versus placebo (using Wald asymptotic test), was performed in the following sequence for dose regimen and endpoint:

- ACR 20 response at Week 12 for CZP 200 mg Q2W
- ACR 20 response at Week 12 for CZP 400 mg Q4W
- ACR 20 response at Week 24 for CZP 200 mg Q2W
- ACR 20 response at Week 24 for CZP 400 mg Q4W
- Change from baseline to Week 24 in HAQ-DI for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 24 in mTSS for CZP 200 mg Q2W and 400 mg Q4W combined
- PASI 75 response at Week 24 for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 48 in mTSS for CZP 200 mg Q2W and 400 mg Q4W combined (not included in this interim study report).

For the primary efficacy analysis, subjects who withdrew for any reason before Week 12 or who had missing data at Week 12 were considered non-responders. For the ACR response criteria, imputation was used after the Week 12 visit for the handling of missing data. For the X-ray criteria of mTSS, linear extrapolation of scores from the last 2 radiographs taken before Week 24 (post-hoc: at least 8 weeks apart) was used for the handling of missing data. Sensitivity

analyses using the removal of outliers (values +/- 3 SD outside observations for the mTSS) and potential unblinding (some investigators may have become clinically aware of treatment allocation [CZP versus placebo] by Week 16 because of patient response) were performed for the change from baseline in mTSS using ANCOVA with linear extrapolation. To verify the model assumption of similar effects across geographical regions, the ANCOVA model (with treatment, region, and prior anti-TNF exposure as factors) included an assessment of treatment by region interaction. The same procedure was done to investigate whether or not prior anti-TNF exposure was a determinant of treatment response.

6.1.1.1.10. Participant flow

A total of 603 patients were enrolled into the screening phase of the study, of which 409 subjects were randomized at Week 0 (138 to the CZP 200 mg Q2W group, 135 to the CZP 400 mg Q4W arm, and 136 to placebo). Overall, 32.2% (194/603) of subjects were screen failures. The most common reasons for screen failure were a failure to meet the inclusion criteria of sufficiently active disease (n = 164; 27.2% of 603) and withdrawal of consent (n = 19; 3.2% of 603). All of the 409 randomized subjects received at least 1 dose of study medication. At Week 16, 43.4% (59/136) of subjects treated with placebo did not achieve the minimal response criteria, and were therefore allocated to active escape therapy with CZP. Of these patients, 30 were re-randomized to CZP 200 mg Q2W and 29 were allocated to CZP 400 mg Q4W. The majority of patients (88-92%) in each of the 3 treatment groups completed the 24-week double-blind treatment period – refer to Figure 1. The most common reasons for premature discontinuation were withdrawal of consent (3.4%; 14/409) and adverse events (3.2%; 13/409), which were similarly distributed across the treatment groups.

6.1.1.1.11. Major protocol violations/deviations

Of the 409 patients who were randomized to, and received at least 1 dose of study treatment in Study PsA001, 115 were excluded from the PPS because of potentially significant protocol deviations. The proportion of subjects who were identified to have protocol deviations that may have affected their efficacy measurements was higher in the CZP 400 mg Q4W group (32.6%; 44/135) compared with the CZP 200 mg Q2W arm (25.4%; 35/138) and placebo (26.5%; 36/136). Some subjects were recorded to have more than 1 important protocol deviation. The most common reasons for efficacy related protocol deviations were procedural non-compliance (35.2%; 144/409), and receipt of a prohibited medication or treatment (21.3%; 87/409). Only 10 patients (4 in the placebo group, 4 in the CZP 200 mg Q2W arm and 2 in the CZP 400 mg Q4W group; total of 2.4% of 409) had less than 80% compliance with study medication. Two placebo-randomized subjects inadvertently received single doses of CZP at weeks 0 or 2.

6.1.1.1.12. Baseline data

The treatment groups were well balanced with respect to demographic characteristics. Overall, subjects had a mean and median age of 48 years (range: 19-75 years), just over half (55.3%; 226/409) were female, and the majority (97.8%; 400/409) were of Caucasian ethnicity. The overall mean BMI was 29.75 kg/m^2, with 40.3% (165/409) of subjects having a BMI greater than or equal to 30 kg/m^2. About half of all subjects (50.9%; 208/409) reported never having used alcohol, and 17.6% (72/409) were current tobacco users.

In Study PsA001, a diagnosis of adult-onset PsA of at least 6 months duration was defined using the CASPAR (Classification Criteria for Psoriatic Arthritis), which has a sensitivity of 98.7% and a specificity of 91.4% (Taylor et al, 2006). A maximum score of 6 is derived by adding points from 5 categories. A score of 3 or more is consistent with the diagnosis of PsA. Current evidence of psoriasis is assigned 2 points and the other 4 categories are each worth 1 point. The other categories are psoriatic nail dystrophy, negative Rheumatoid Factor blood test, dactylitis (current, or history of confirmed by rheumatologist), and radiographic evidence of juxta-articular new bone formation. All but 5 patients in Study PsA001 (1.2% of 409) fulfilled the CASPAR criteria of greater than or equal to 3 points, as defined by the study protocol. In

particular, 93.4% (382/409) of all subjects had current evidence of psoriasis, 36.9% (151/409) had current dactylitis, and 26.4% (108/409) had radiologic evidence of juxta-articular new bone formation at baseline.

The treatment groups were well balanced with respect to baseline PsA features. The mean duration of PsA for all subjects was 8.55 years, with 80.0% (327/409) of subjects having disease duration of at least 2 years. Most patients (82.2%; 336/409) were HLA-B27 negative. Overall, 84.8% (347/409) of subjects had a baseline BASDAI score of at least 4 suggesting possible axial involvement, 64.3% (263/409) had enthesitis present at baseline, and 34.0% (139/409) had recorded dactylitis. All of these disease manifestations occurred at a similar incidence across the treatment groups. However, the percentage of patients with nail and greater than or equal to 3% BSA skin psoriasis at baseline was somewhat unequal between the 3 treatment arms: CZP 200 mg Q2W group (66.7% and 65.2%, respectively), CZP 400 mg Q4W (77.8% and 56.3%, respectively) and placebo (75.7% and 63.2%, respectively). By geographic region, the largest percentage of patients came from Central/Eastern Europe (47.9%; 196/409), followed by North America (24.0%; 98/409), Latin America (14.7%; 60/409) and Western Europe (13.4%; 55/409). Recruitment site was a stratification factor in randomization, and patients from different geographical regions were equally distributed across the 3 treatment groups.

In terms of disease activity at baseline, the mean numbers of tender and swollen joints were similar for the CZP 200 mg Q2W (21.51 and 11.04, respectively), CZP 400 mg Q4W (19.55 and 10.48, respectively), and placebo groups (19.9 and 10.43, respectively). The mean HAQ-DI scores were similar between the treatment groups at 1.29-1.33, and consistent with moderate disease activity (supported by mean DAS 28 scores being 4.99-5.04). The mean CRP for all subjects was elevated at 15.88 mg/L, and the mean ESR was 40.6 mm/h. The mean (SD) mTSS score was slightly lower in the CZP 200 mg Q2W group (18.0 +/- 30.6) compared to the CZP 400 mg Q4W group (23.2 +/- 46.6) and placebo arm (24.5 +/- 49.7). In each of the treatment groups, the erosion score was a greater contributor to the overall composite mTSS score than the JSN score.

In total, 19.6% (80/409) of subjects had received previous treatment with anti-TNF drugs, and history of this prior medication use was equally distributed across the treatment groups. Similarly, prior and allowed concomitant use of non-biologic DMARD therapy at baseline was similar across the treatment groups. Just over half of all subjects (50.6%; 207/409) had prior use of 1 DMARD, another 25.2% (103/409) had experienced 2 previous DMARDs, and 22.0% (90/409) had used 3 or more previous DMARDs, reflecting a treatment refractory PsA population. The 2 most commonly used prior DMARDs were MTX (68.0%) and SSZ (25.2%), at a similar frequency in each of the treatment groups.

During Study PsA001, 70.7% (289/409) of all patients continued DMARD therapy. Use of concomitant DMARDs was higher in the combined CZP treated patients (73.6%; 201/273) compared to the placebo arm (64.7%; 88/136). The most common concurrent DMARD used in all groups was MTX (58.8% [80/136] in the placebo arm, and 63.0% [172/273] in the combined CZP subjects). In addition, the majority of patients (71.0-74.1%) in all treatment groups took concomitant NSAID during the trial, and approximately one quarter (24.3-26.7%) took low dose oral CS. About one third of all subjects (33.1-36.3%) were taking medicines for gastro-oesophageal reflux and/or peptic ulcer prevention. Past history of hypertension was recorded at a higher incidence in CZP treatment groups (40.6-44.4%) than the placebo arm (35.3%). Similarly, a past history of cardiac disorders was recorded at a higher incidence in CZP treatment groups (7.2-11.9%) than the placebo arm (5.9%).

6.1.1.1.13. Results for the primary efficacy outcomes

6.1.1.1.13.1. ACR 20 response rate at week 12

The ACR 20 responder rates at Week 12 were higher in the CZP 200 mg Q2W (58.0%; 80/138) and CZP 400 mg Q4W (51.9%; 70/135) groups compared with placebo therapy (24.3%;

33/136). The differences in response compared to placebo were statistically significant for both comparisons (differences of 27.6-33.7%; $p < 0.001$ for each comparison). These results demonstrate the efficacy of CZP for the treatment of signs and symptoms of active PsA. Secondary and sensitivity analyses of the ACR 20 responder rate at Week 12 provided similar trends to the primary analysis.

The ACR 20 response rate at Week 12 (and also Week 24) was analysed by subgroups of interest such as age (< 45 years versus greater than or equal to 45 years), gender, ethnicity, duration of disease (< 2 years versus greater than or equal to 2 years), geographic region, concomitant use of allowed DMARDs at baseline, prior use of conventional DMARDs, prior use of anti-TNF medications and anti-CZP antibody status. Only 2 subgroup analyses showed a difference in ACR 20 response rate at Week 12. Firstly, a difference in response was observed by geographic region, although the overall number of subjects per group was small in the Latin America and Western Europe regions. The treatment difference between CZP (combined) and placebo was 12.5% in Latin America, which is primarily explained by a larger placebo response rate (63.2%; 12/19) compared to control subjects in the 3 other regions (12.7-27.3% placebo response rates). All 3 of the other regions had approximately 30% differences in responder status between the CZP groups and placebo. Males tended to exhibit a higher rate of ACR 20 response than females, which is a common observation for trials involving patients with PsA. Interestingly, there was no difference in the ACR 20 response rate at 12 weeks based on prior exposure to anti-TNFα therapy.

6.1.1.1.13.2. Mean change from baseline to week 24 in mTSS

The second primary efficacy variable was the mean change from baseline to Week 24 in mTSS. All enrolled subjects were required to have X-rays taken of both hands and feet at baseline, Week 12 and 24, or upon early withdrawal. A total of 56 subjects (13.7% of 409) were missing values from 1 or more visits: 35 subjects were missing 1 visit, 17 subjects were missing 2 visits, and 4 subjects were missing all 3 visits. The 56 subjects were missing a total of 81 values: 10 were missing baseline X-ray values, 27 were missing values at Week 12, and 44 were missing values at Week 24.

Reasons for missing values included: images not taken due to site error or missed visit, lost X-ray images, subject withdrew from study within 4 weeks of a previous visit at which X-rays were taken (and therefore, not repeated at withdrawal), subject withdrew consent, no withdrawal visit performed because subject was lost to follow-up, and unreadable X-ray images that were not repeated.

The study's protocol-defined imputation rules led to physiologically implausible changes in the mTSS with the LS [Least Square] mean change being 18.28 points in the combined CZP group, and 28.92 points for the placebo group. This result does not accurately reflect response, and was not statistically significant ($p = 0.203$) for a treatment difference between combined CZP and placebo therapy. The original imputation rules combined with the lack of specified window period between radiographs, as well as an unequal distribution of subjects with no or only 1 radiograph across treatment groups (for example more than 50% of the placebo group had missing X-ray values), resulted in implausibly high LS mean changes from baseline across all groups (LS means ranged from 11.52 to 28.92 points). Furthermore, a comparison of Study PsA001 X-ray results with 4 published studies examining structural damage progression in PsA patients treated with placebo and anti-TNF therapy reveals that the expected values for mean LS change from baseline in mTSS are markedly lower (0.27 to 1.0 for placebo, and -0.70 to -0.03 for anti-TNF therapy). Hence, the mean LS values observed in Study PsA001 were implausibly high when the protocol-defined imputation rules were applied. The sponsor identified the analysis problem and to appropriately evaluate the X-ray data from Study PsA001, applied different post-hoc imputation rules along with a specified window between radiographs (minimum 8-week window). In the post-hoc analysis for the across-subject imputation, missing mTSS values were imputed by using the median change from baseline in the entire study

population. This imputation method and the rule to specify the minimum 8-week window between X-rays led to results that were realistic (LS means ranged from 0.01 to 0.28 points). This statistical approach yielded results that were consistent with the observed case data, and also was similar with the results from a placebo-controlled study in PsA with another anti-TNF drug (Kavanaugh et al, 2012). Using the observed case values, the LS mean changes in mTSS were substantially lower (LS means ranged from -0.04 to 0.13).

Using the post-hoc imputation method, less progression of X-ray changes was observed at Week 24 (as measured by the LS mean change from baseline in mTSS) in the combined CZP treatment group compared with the placebo arm (0.06 versus 0.28 points, respectively). The difference between CZP (combined) and placebo was -0.22 points (95% CI -0.38, -0.06; p = 0.007). The LS mean change in mTSS from baseline to Week 24 was smaller (that is , less progression of radiographic changes) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group (0.01 versus 0.11 points). However, both CZP treatment regimens appeared to be better compared with placebo (treatment difference of -0.27 and -0.17 points, respectively). The difference between CZP 200 mg Q2W and placebo was statistically significant at -0.27 points (95% CI -0.45, -0.08; p = 0.004). However, the difference between CZP 400 mg Q4W and placebo was not statistically significant at -0.17 points (95% CI -0.35, 0.02; p = 0.072). The above results were supported by multiple post-hoc sensitivity analyses (that is imputation of missing values using mean change or worst change from baseline in the entire study population, and also the same treatment group).

6.1.1.1.14. Results for other efficacy outcomes

The results of the 3 key secondary efficacy endpoints at Week 24 were statistically significant in favour of CZP therapy versus placebo. The differences in treatment response are also of a magnitude to be clinically meaningful.

6.1.1.1.14.1. ACR 20 response rate at week 24

The proportion of patients who achieved an ACR 20 response at 24 weeks were higher in the CZP 200 mg Q2W (63.8%; 88/138) and CZP 400 mg Q4W (56.3%; 76/135) groups compared with placebo (23.5%; 32/136). The differences between CZP therapy and placebo were statistically significant for both comparisons (treatment differences of 32.8-40.2%; p < 0.001 for each comparison). This result supports the primary clinical endpoint of ACR 20 response at 12 weeks, and indicates that CZP is effective in maintaining a reduction in the signs and symptoms of active PsA over 24 weeks of treatment follow-up.

Treatment results for the ACR 20 response by subgroup at Week 24 showed similar trends as observed at Week 12.

6.1.1.1.14.2. Mean change from baseline in HAQ-DI at week 24

At baseline, the mean HAQ-DI scores were similar between the combined CZP (1.31 points) and placebo (1.30 points) groups. At Week 24, the LS mean change from baseline in HAQ-DI was statistically greater in the combined CZP group (-0.50 points) compared with the placebo arm (-0.19 points). The difference between CZP therapy (combined dose regimens) and placebo was -0.31 points (95% CI -0.42, -0.20; p < 0.001). These results demonstrate that CZP treatment improves the physical function for subjects with active PsA. The LS mean change from baseline to Week 24 in HAQ-DI was similar in the CZP 200 mg Q2W (-0.54 points) and CZP 400 mg Q4W (-0.46 points) groups.

Subjects receiving CZP (either dose regimen) were observed to have statistically significant improvements (that is numerically decreased) in mean HAQ-DI score over placebo subjects at every visit from Weeks 2 to 24 (p < 0.005 for all visits beginning at Week 2). Most of the improvement in HAQ-DI was achieved by Week 12 in the CZP treatment groups, and maintained thereafter. Up to 24 weeks, the results were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W dosing groups. Placebo subjects who escaped to CZP 200 mg Q2W or CZP 400 mg Q4W

at Week 16 showed an improvement in mean HAQ-DI score from between weeks 16 to 18 (-0.05 to -0.29 points for those 30 subjects escaping to CZP 200 mg Q2W; and -0.11 to -0.22 points for those 29 subjects escaping to CZP 400 mg Q4W). The escape patients maintained or improved their HAQ-DI scores through to Week 24.

In a supplementary analysis, subjects were considered to be a HAQ-DI responder if they had a decrease of greater than or equal to 0.3 points from baseline. The percentage of HAQ-DI responders at Week 12 was greater in the combined CZP group (47.3%; 129/273) compared with placebo (21.3% [29/136]; treatment difference of 17.9% [p < 0.001]). The percentage of HAQ-DI responders was stable thereafter in all 3 treatment groups (at Week 24, combined CZP group response rate was 48.7% [133/273] versus 15.4% [21/136] for placebo. The proportion of HAQ-DI responders over time was similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups. By Week 24, 49.3% (68/138) of subjects in the CZP 200 mg Q2W, and 48.1% (65/135) of patients in the CZP 400 mg Q4W arm were HAQ-DI responders.

Placebo subjects who escaped to CZP 200 mg Q2W or CZP 400 mg Q4W at Week 16 had a > 20% increase in the percentage of HAQ-DI responders between weeks 16 and 18 (16.7% to 40.0% for those subjects escaping to CZP 200 mg Q2W; and 17.2% to 37.9% for those subjects escaping to CZP 400 mg Q4W group).

6.1.1.1.14.3. PASI 75 response rate at week 24

For the subset of subjects with at least 3% BSA psoriasis at baseline, more CZP-treated subjects (61.4%; 102/166) recorded a 75% improvement in skin psoriasis area and severity compared with placebo-treated subjects at Week 24 (15.1%; 13/86). However, the treatment difference between CZP and placebo was not considered to be statistically significant due to the hierarchical testing rules being breached at item 6 (that is using the predefined mTSS imputation rules). By applying post-hoc analytical rules, the PASI 75 response at Week 24 could have been regarded as statistically significant in favour of CZP combined, as well as each CZP dose regimen versus placebo (all 3 pair-wise comparisons showed p < 0.001). Regardless of statistical significance, the difference between CZP and placebo therapy (over 24 weeks of treatment) can be judged to be clinically meaningful. The percentage of PASI 75 responders at Week 24 was similar between the CZP 200 mg Q2W (62.2%; 56/90) and CZP 400 mg Q4W dosing groups (60.5%; 46/76).

Overall, these results demonstrate that treatment with CZP provides efficacy with regard to the skin manifestations of psoriasis for the subgroup of PsA subjects with psoriasis involving at least 3% BSA at baseline.

6.1.1.1.15. Other outcomes relating to the signs and symptoms of PsA

6.1.1.1.15.1. ACR response

The proportion of ACR 20 responders was greater for the combined CZP group compared with placebo at every scheduled visit through to Week 24 after baseline (p≤0.001 at each visit). There was no statistically significant difference in the ACR 20 response rate between the CZP 200 mg Q2W and CZP 400 mg Q4W groups at any visit.

The percentage of ACR 50 responders was statistically greater in the combined CZP arm compared with placebo starting at Week 2 through to Week 24 (at each visit, the p-value for the difference to placebo was p≤0.012). The proportion of CZP treated subjects who achieved an ACR 50 response increased steadily over time to Week 16 (38.1%; 104/273), and remained stable through to Week 24 (42.1%; 115/273). In comparison, the ACR 50 response rates were 6.6% (9/136) at Week 16, and 12.5% (17/136) at Week 24 in the control arm.

The percentage of ACR 70 responders was statistically higher in the combined CZP treatment group compared with placebo starting at Week 4, and continuing through to Week 24 (p-value for the difference to placebo was ≤0.005 at each visit). The proportion of ACR 70 responders at Week 16 was 23.9% (33/138) for CZP 200 mg Q2W, 12.6% (17/135) for CZP 400 mg Q4W, and

4.4% (4/136) for placebo. The proportion of ACR 70 responders at Week 24 was 28.3% (39/138) for CZP 200 mg Q2W, 23.7% (32/135) for CZP 400 mg Q4W, and 2.9% (6/136) for placebo. Overall, these results suggest that CZP 400 mg Q4W treatment appears to have a delayed achievement of ACR 50 and 70 responses in comparison to the CZP 200 mg Q2W, a pattern which was particularly evident for the ACR 70 response rates over time (up to 24 weeks of treatment follow-up).

Placebo subjects who escaped to CZP (either dose regimen) after Week 16 had a marked increase (by approximately 30%) in the proportion of subjects obtaining an ACR 20 improvement. For example, between weeks 16 and 18, the ACR 20 response rose from 3.3% (1/30) to 30.0% (9/30) for those subjects escaping to CZP 200 mg Q2W; and from 3.4% (1/29) to 34.5% (10/29) for those subjects escaping to CZP 400 mg Q4W group. Similar trends upon switching treatment from placebo to CZP were observed for the percentage of ACR 50 and ACR 70 responders.

All individual components comprising the ACR response criteria showed a consistent trend in favour of CZP treatment versus placebo, with no clinically meaningful differences in response between the 2 CZP dose regimens being observed.

6.1.1.1.15.2. Leeds Dactylitis Index (LDI)

At baseline, 34.0% (139/409) of all subjects had dactylitis with a mean LDI score of 2.27 (range: 0-3). The distribution of affected patients was similar across groups (32-34 subjects in each of the 3 treatment groups), as was the mean baseline scores (2.08-2.40). The mean change from baseline in LDI was minimal at all time points in both CZP treatment groups and the placebo arm, indicating no significant change in dactylitis severity across the 3 treatment groups.

6.1.1.1.15.3. Leeds Enthesitis Index (LEI)

At baseline, 64.3% (263/409) of all subjects had enthesitis with a mean LEI score of 3.0 (range: 0-4). The distribution of affected patients was similar across groups (84-91 subjects in each of the 3 treatment groups), as was the mean baseline scores (2.9-3.1). The mean change from baseline in the LEI score in the combined group showed a statistically greater decrease (that is clinical improvement) compared to placebo for all study visits between weeks 8 and 24 ($p < 0.005$ for each visit comparison). At Week 24, the mean change from baseline in the LEI score was -1.9 points in the combined CZP group and -1.1 points in the placebo arm ($p < 0.001$). Mean changes from baseline were similar between the 2 CZP dosing regimens.

6.1.1.1.15.4. Psoriatic Arthritis Response Criteria (PsARC)

The percentage of PsARC responders was greater in the combined CZP group (34.4%; 94/273) compared with placebo beginning at Week 1 (14.0% [19/136]; $p < 0.001$). The proportion of PsARC responders steadily increased over time (to 24 weeks) in the combined CZP group, but remained stable in the placebo group. By Week 24, 77.7% (212/273) of subjects in the combined CZP group were PsARC responders compared with 33.1% (45/136) of subjects in the placebo group ($p < 0.001$). The percentage of PsARC responders and the trends over time were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W dosing groups.

Placebo subjects who escaped to CZP at Week 16 had a marked increase (by approximately 60%) in the proportion of PsARC responders between weeks 16 and 20 (increasing from 3.3% to 66.7% for those subjects escaping to CZP200 mg Q2W; and from 0% to 62.1% for those subjects escaping to CZP 400 mg Q4W group). This rate of response continued to increase up to Week 24 in the escape group of patients.

All 4 elements comprising the PsARC criteria showed a consistent trend in favour of CZP treatment versus placebo, with no clinically meaningful differences in response between the 2 CZP dose regimens being observed.

6.1.1.1.15.5. DAS 28 score (using CRP)

At Week 24, the mean change from baseline in DAS 28 score in the combined CZP group (-1.92) was statistically greater compared to placebo (-0.45; $p < 0.001$). Statistically significant comparative improvements in disease activity in the combined CZP treatment cohort versus placebo were observed as early as Week 1.

Analysis of the DAS 28 scores by the EULAR classification of categorical responses (that is remission; and low, medium or high disease activity) showed a pattern towards lower disease activity over time in the combined CZP group as early as Week 1, whereas distribution of responses was generally similar over time for the placebo group. The improvements in disease activity over time were similar for the CZP 200 mg Q2W and CZP 400 mg Q4W groups. These results are consistent with the improvements observed in the rate of achieving ACR 20 response with CZP treatment.

A EULAR response of "good" was defined as an improvement in DAS 28 of > 1.2 and a score ≤3.2 (possible scores range from 0 to 10). The percentage of subjects achieving a "good" EULAR response increased over time in the combined CZP group through to Week 24. The placebo group also showed a trend towards an increase over time, but of smaller magnitude compared with the combined CZP group. At 24 weeks, the percentage of subjects with a "good" EULAR response was 52.4% (143/273) in the combined CZP group compared with 13.2% (18/136) of subjects in the placebo group. The percentage of subjects with a "good" EULAR response at Week 24 was similar between the CZP 200 mg Q2W (52.9%; 73/138) and CZP 400 mg Q4W groups (51.9%; 70/135).

6.1.1.1.15.6. BASDAI

At baseline, the majority of all subjects (84.8%; 347/409) had a BASDAI score of greater than or equal to 4, which was used in this study for suspected axial involvement. The distribution of affected subjects was similar across the 3 treatment groups (114-119 patients in each arm), and the mean baseline BASDAI was 6.39-6.58 (range: 0-10). The mean change from baseline in the BASDAI (for the subset of subjects with BASDAI greater than or equal to 4 at baseline) score improved in all treatment groups, although subjects treated with CZP (-2.65) had statistically greater improvement compared with placebo-treated subjects (-1.68; $p < 0.001$).

6.1.1.1.16. Other radiographic endpoints

For all of the secondary X-ray efficacy endpoint analyses, the sponsor applied a post-hoc analysis using median change from baseline in the entire study population in place of the pre-specified analysis, which led to physiologically implausible results.

6.1.1.1.16.1. Change from baseline in mTSS at week 12

At baseline, the mean mTSS was slightly lower in the combined CZP group (20.58 points) compared with the placebo arm (24.46 points). The mean change from baseline to Week 12 in the mTSS was minimally different (0.01 points), indicating little or no progression of X-ray changes in the combined CZP group, whereas the mTSS score worsened slightly in the placebo group (0.14 points; $p = 0.017$). The LS mean changes from baseline to Week 12 in the mTSS for the combined CZP group (-0.15 points) were numerically less (that is better) compared to placebo (-0.09 points).

6.1.1.1.16.2. Change from baseline in ES at weeks 12 and 24

The change from baseline in the ES at weeks 12 and 24 was defined as a secondary efficacy variable. At baseline, the mean erosion score was slightly lower in the combined CZP group (11.92 points) compared with the placebo arm (14.05 points). At Week 12, the mean change from baseline in the ES was near zero (0.02 points) in the combined CZP group, whereas the ES worsened in the placebo group by 0.12 points (LS mean difference between combined CZP and placebo was -0.10 points [$p = 0.027$]). At 24 weeks, the mean changes from baseline in the ES were 0.01 versus 0.21 for placebo ($p = 0.004$). Patients who received treatment with CZP 200

mg Q2W showed slightly less progression in the ES compared with those given CZP 400 mg Q4W (at Week 12, 0.00 for 200 mg Q2W versus 0.03 points for 400 mg Q4W; and at 24 weeks, -0.01 for 200 mg Q2W versus 0.04 points for 400 mg Q4W).

6.1.1.1.16.3. Change from baseline in JSN score at weeks 12 and 24

The change from baseline in the JSN score at weeks 12 and 24 was another secondary efficacy variable. At baseline, mean JSN scores were slightly lower in the combined CZP group (8.66 points) compared with the control arm (10.40 points). At Week 12, the mean change from baseline in the JSN score was near zero (that is indicating no significant progression of JSN) in both the combined CZP group (-0.01 points), and the placebo arm (0.01 points). There was no statistically difference between groups ($p = 0.129$) for JSN at 12 weeks. The results were similar at 24 weeks, indicating no significant progression of JSN over the limited follow-up time.

6.1.1.1.16.4. Radiographic responder status at week 24

A further supportive analysis of the mTSS response at Week 24 involved using the post-hoc imputation rules and applying them to subjects with a dichotomous outcome (responder versus non-responder status). Patients were considered an mTSS responder if they had a change from baseline to Week 24 in their mTSS of ≤0. Escape subjects were considered non-responders (that is their change from baseline to Week 24 in mTSS was > 0, indicating radiographic progression). The percentage of mTSS responders at Week 24 was greater in the combined CZP treatment group (79.9%; 218/273) compared to placebo (34.6%; 47/136). The difference between CZP therapy and placebo was 45.3% (95% CI 36.0, 54.6; $p < 0.001$). Pair-wise comparison between each of the CZP dose regimens and placebo were also statistically significant. These results suggest that CZP inhibits the progression of structural damage over 24 weeks in subjects with active PsA.

6.1.1.1.17. Other health-related outcomes

6.1.1.1.17.1. Mean changes and responder status in SF-36 domains

The mean changes from baseline in the SF-36 physical function domain, Physical Component Summary (PCS), and Mental Component Summary (MCS) scores were additional secondary efficacy variables. All scores were calculated as norm-based values, such that the general population in the USA has a mean value of 50 and a standard deviation of 10.

At baseline, the mean SF-36 physical function domain score was similar between the combined CZP (33.79 +/- 9.88 points) and placebo (33.74 +/- 10.27 points) groups. Subjects who received CZP (either dose) had an increase in physical function (as assessed by the mean change from baseline in the SF-36 physical function domain) over time compared with the placebo group beginning as early as Week 1, and continuing through to Week 24 ($p < 0.001$). At Week 24, the mean change from baseline in the SF-36 physical function domain was 7.30 (+/- 10.26) points in the combined CZP group and 1.50 (+/- 8.34) points in the placebo group ($p < 0.001$). Mean changes from baseline in the physical function domain, as well as all other domains (role physical, bodily pain, vitality, general health, social functioning, and role emotional) were generally greater (that is more improved) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W arm.

At baseline, the mean SF-36 PCS score was similar between the combined CZP (33.15 +/-7.60 points) and placebo (33.79 +/-7.93 points) groups. These mean values are indicative of a moderate impact upon physical functioning, as compared to the general population in the USA (mean PCS value of 50). Subjects in the combined CZP arm had an increase in physical functioning over time, compared with the placebo group beginning at Week 4 (first post-baseline assessment), and continuing through to Week 24 ($p < 0.001$). At Week 24, the mean change from baseline in the SF-36 PCS score was 8.01 (+/-9.14) points in the combined CZP group, versus 2.14 (+/-7.18) points in the placebo group ($p < 0.001$). In addition, Study PsA001 did an analysis of the SF-36 PCS responder rate (defined as the within-subject MCID of at least 2.5 points from baseline [Strand et al, 2005]). The percentage of SF-36 PCS responders was

greater in the combined CZP group compared with placebo at all time points between weeks 4 and 24 ($p < 0.001$). The proportion of SF-36 PCS responders in the combined CZP group markedly increased from baseline up until Week 8, and then remained stable thereafter. In contrast, the SF-36 PCS responder rate peaked at Week 12 for the placebo arm, and thereafter declined. By Week 24, 67.8% (185/273) of subjects in the combined CZP cohort were SF-36 PCS responders compared with 30.1% (41/136) of placebo-treated patients ($p < 0.001$). The percentage of SF-36 PCS responders and the trends over time were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups.

At baseline, the mean SF-36 MCS score was similar between the combined CZP (41.30 +/- 11.85 points) and placebo (42.36 +/- 12.45 points) groups. Subjects given CZP had a mean improvement from baseline in their SF-36 MCS score over time compared with the placebo group beginning at Week 4 (first assessment), and continuing through to Week 24 ($p < 0.05$ except at Week 8). At Week 24, the mean change from baseline in SF-36 MCS was 4.50 (+/-9.95) points in the combined CZP group, compared with 0.73 (+/-9.85) points in the placebo group ($p < 0.001$). The mean changes from baseline in the SF-36 MCS score were generally greater (that is more improved) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group. The rate of SF-36 MCS response (defined as increase of greater than or equal to 2.5 points from baseline [Strand et al, 2005]) was also evaluated. The percentage of SF-36 MCS responders was greater in the combined CZP group compared with placebo at all time points ($p < 0.05$ except at Week 8). The proportion of SF-36 MCS responders in the combined CZP group increased from baseline to Week 8, and remained stable through to Week 24; whereas the placebo group rate peaked at Week 8, then declined over time. By Week 24, 51.6% (141/273) of subjects in the combined CZP group were SF-36 MCS responders compared with 22.8% (31/136) in the placebo group ($p < 0.001$). The percentage of SF-36 MCS responders was higher in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group at all time points (assessed every 4 weeks).

Placebo subjects who escaped to CZP (either dose regimen) at Week 16 had increases in all of the SF-36 endpoints (physical function, PCS, MCS, responder status) from weeks 20 to 24, which matched the responses observed in patients who received CZP from the outset of the trial.

6.1.1.1.17.2. Mean change from baseline in PsAQoL

The use of the PsAQOL (20 items; range: 0-20) is recommended by the European Medicines Agency as a disease specific QOL measure. At baseline, the mean PsAQoL score was similar between the combined CZP (11.22 points) and placebo (10.86 points) groups. Subjects in the combined CZP group had improved QOL over time compared with the placebo group beginning as early as Week 1, and continuing through Week 24 ($p < 0.023$). At Week 24, the mean change from baseline in PsAQoL was -3.87 points in the combined CZP group, and -1.27 points in the placebo group ($p < 0.001$). Mean decreases from baseline in the PsAQoL were generally greater (that is more improved) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W groups.

6.1.1.1.17.3. Fatigue assessment scale

The FASCA is a validated 10 cm VAS (0 = ”no fatigue” and 10 = ”fatigue as bad as you can imagine”) used to evaluate fatigue severity in patients with PsA. At baseline, mean FASCA scores were similar between the combined CZP (6.3 points) and placebo (5.8 points) groups. From as early as Week 2, subjects treated with CZP had a significant reduction in tiredness/fatigue over time compared with the placebo arm. This treatment related difference continued through to Week 24 ($p < 0.012$ for all visits). At Week 24, the mean change from baseline in the FASCA was -2.0 points in the combined CZP group and -0.6 points in the placebo cohort ($p < 0.001$). Mean changes from baseline in the FASCA were similar between the CZP 200 mg Q2W (-2.2 at 24 weeks) and CZP 400 mg Q4W groups (-1.9 at 24 weeks).

The percentage of FASCA responders (defined as a within-subject decrease of greater than or equal to 1 point) was another efficacy variable. The proportion of FASCA responders was higher in the combined CZP group compared with control beginning at Week 1 (46.5% versus 33.8%; p = 0.013). The percentage of FASCA responders was increased or maintained over time in the combined CZP group, but remained fairly stable in the placebo group. By Week 24, 64.5% (176/273) of subjects in the combined CZP group were FASCA responders compared to 28.7% (39/136) of placebo-treated patients (p < 0.001). The percentage of FASCA responders over time was similar between the 2 CZP dose regimens (at 24 weeks; 65.9% [91/138] for 200 mg Q2W, and 63.0% [85/135] for 400 mg Q4W).

Placebo subjects who escaped to CZP at Week 16 had a significant increase in the percentage of FASCA responders between weeks 16 and 18 (from 46.7% to 60.0% for those subjects escaping to CZP 200 mg Q2W; and from 34.5% to 62.1% for those subjects escaping to CZP 400 mg Q4W). These results indicate that CZP therapy results in improvements in fatigue for subjects with active PsA.

6.1.1.1.17.4. Dermatology Life Quality Index (DLQI)

The DLQI is an assessment of the effect of psoriasis on the QOL of a subject. The range for the DLQI is 0-30, with a higher score indicating more impaired quality of life. At baseline, the mean DLQI score was similar between the combined CZP (8.9 points) and placebo (7.9 points) groups. Subjects in the combined CZP group had improved QOL related to their skin disease over time compared with the placebo group beginning as early as Week 2, and continuing through to Week 24. At Week 12, the mean change from baseline in the DLQI was -5.2 points in the combined CZP group, which is considered to be clinically meaningful, compared with -1.1 points in the placebo group. At Week 24, the mean change from baseline in the DLQI was further slightly improved in the combined CZP group (-5.8 points) compared with a change of -1.4 points in the placebo group. Mean changes from baseline in the DLQI were generally greater (that is more improved) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W groups. Placebo subjects who escaped to CZP (either dose) at Week 16 had marked improvements in their DLQI after Week 16, which continued through to Week 24. Overall, these results indicate that CZP provides improvement in QOL related to skin psoriasis for subjects with active PsA.

6.1.1.1.17.5. Health Status EuroQOL Questionnaire (EQ-5D)

The EQ-5D is comprised of a 5-item health status dimension, and a 20 cm vertical VAS (range: 0-100). The percentage of subjects reporting recording no difficulties in each of the EQ-5D categories (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) was greater in the combined CZP group compared with the control arm beginning at Week 4, and increased over time up to Week 24. In general, a greater proportion of subjects reporting no problems in each of the EQ-5D categories were observed in the CZP 200 mg Q2W dose group compared with the CZP 400 mg Q4W group. Placebo subjects who escaped to CZP at Week 16 had shifts towards improvement in each of the EQ-5D categories from Week 16 to Week 20, which continued to improve at Week 24.

At Week 24, the mean change from baseline in the EQ-5D VAS was 17.3 points in the combined CZP group, and 5.2 points in the placebo group. As noted for each of the EQ-5D dimensions, the mean change from baseline in EQ-5D VAS was generally greater in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group.

6.1.1.1.17.6. Work Productivity Scale (WPS)

The WPS (9 questions) assesses the impact of arthritis on a subject's productivity within and outside the home over the previous month. At baseline, the proportion of subjects employed outside the home in the combined CZP arm was 60.8% (166/273), and 56.6% (77/136) in the placebo group. The rate of employment for any treatment group did not change throughout the 24-week study. However, treatment –related improvements in productivity (within and outside

the home) were observed as early as Week 4, and maintained over 24 weeks in combined CZP group compared with the placebo arm. Among employed subjects, those treated with CZP versus placebo gained additional workdays per month (Question 2), reported less work days with productivity reduced by half or more due to arthritis compared with the placebo group (Question 3), and arthritis interfered to a lower extent with work productivity (Question 4). For all subjects regardless of employment status, subjects receiving CZP compared to placebo gained more household work days per month (Question 5), reported less household work days with productivity reduced by half or more due to arthritis (Question 6), missed fewer days of family, social, or leisure activities (Question 7), had fewer days with outside help hired because of arthritis (Question 8), and reported that arthritis interfered to a lower extent with their household work productivity (Question 9). Results for the WPS showed similar improvements in productivity in the CZP 200 mg Q2W and CZP 400 mg Q4W dose groups. Placebo subjects who escaped to CZP at Week 16 had improvements in the WPS between weeks 16 and 24, which were consistent with that observed in patients who received CZP at baseline.

6.1.1.1.17.7. Health resource utilization

The number of concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations, and emergency room visits with an onset during the double-blind treatment period were defined as another efficacy variable. The majority of subjects in the combined CZP and placebo groups received no concomitant medical procedures (81.3% and 76.5%, respectively), no unforeseen consultations (74.4% and 72.8% respectively), no hospitalizations (90.1% and 91.2%, respectively), and no emergency room visits (94.1% each) during the 24 week study. Resource utilization was slightly less in the combined CZP group compared with the placebo group with regard to fewer concomitant medical procedures (on average, 0.364 versus 0.441 procedures), and fewer unforeseen consultations (on average, 0.564 versus 0.765 consultations). It should be noted that these results are based on observed data during the entire double-blind treatment phase, and were not adjusted for drug exposure, which is less in the placebo group than in the CZP treatment groups.

6.1.1.1.18. Skin effects

6.1.1.1.18.1. PASI response

The proportion of subjects achieving PASI 75 response was statistically higher in the combined CZP cohort compared with placebo beginning at Week 2, and maintained through to Week 24 ($p < 0.02$ at each visit). The percentage of PASI 90 responders was greater in the combined CZP group compared with placebo at all time points beginning at Week 8. At 24 weeks of treatment follow-up, only 5.8% (5/86) placebo-treated patients compared with 41.6% (69/166) of combined CZP subjects achieved PASI 90 response ($p < 0.001$). Both dose regimens of CZP (200 mg Q2W and 400 mg Q4W) recorded a similar percentage of PASI 75 and PASI 90 responders over 24 weeks of follow-up, although the proportion of PASI 90 responders at Week 24 was somewhat higher in the CZP 200 mg Q2W group (46.7%; 42/90) compared to CZP 400 mg Q4W arm (35.5%; 27/76).

Placebo subjects who escaped to CZP at Week 16 had a marked increase in the proportion of subjects attaining PASI 75 (from < 10% to 30%) and PASI 90 response (from 0 to 15%) between weeks 16 and 20, which further increased at Week 24 (PASI 75 response rate was 42.1% [16/38], and PASI 90 response rate was 23.7% [9/38]).

The same treatment response trend in favour of CZP therapy was observed for the percentage of subjects achieving other levels of PASI responders (PASI 50 and 100). The percentage of PASI 50 and PASI 100 responders increased over time and was greater in the combined CZP group compared with placebo at all visits. The percentage of PASI 50 and PASI 100 responders at Week 24 in the combined CZP cohort was 73.5% (versus 27.9% for placebo), and 22.3% (versus 2.3% for placebo). The proportion of PASI 50 responders were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups, although the percentage of PASI 100 responders was

smaller in the CZP 400 mg Q4W group compared with the CZP 200 mg Q2W group at most visits.

6.1.1.1.18.2. Mean change from baseline in PASI score

At baseline, the mean PASI scores in subjects with psoriasis BSA of at least 3% were similar between the combined CZP (12.0 points) and placebo (11.1 points) groups. The mean change from baseline in PASI score in the combined CZP group progressively decreased over 24 weeks, and showed a greater decrease (that is improvement) from baseline compared with placebo at all study visits (Week 2 onwards). The mean change from baseline to Week 24 was -9.3 points in the combined CZP 200 mg Q2W+CZP 400 mg Q4W cohort compared with -1.3 points in the placebo group. The results were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W dose regimen groups. Placebo subjects who escaped to CZP (either regimen) at Week 16, showed a marked improvement in PASI score between weeks 16 and 24 (baseline score of +2.73 to -6.79 points for those subjects escaping to CZP 200 mg Q2W; and -0.10 to -6.94 points for those subjects escaping to CZP 400 mg Q4W group).

6.1.1.1.18.3. Physician's Global Assessment of Psoriasis (PhGAP)

A PhGAP responder was defined as having a response of "clear" or "almost clear" on a 6-point scale. For the subgroup of subjects with at least 3% psoriasis BSA at baseline, the proportion of PhGAP responders was higher in the combined CZP group compared with placebo beginning at Week 4 of therapy (22.9% [38/166] versus 7.0% [6/86]; $p < 0.001$). The percentage of PhGAP responders steadily increased over time (to 24 weeks) in the combined CZP group. The placebo group also showed a trend towards an increase in proportion of PhGAP responders with time, but the increase was much smaller than that observed in the combined CZP group. By Week 24, 60.2% (100/166) of subjects in the combined CZP group were PhGAP responders compared with 15.1% (13/86) in the placebo arm ($p < 0.001$). The proportion of PhGAP responders was typically higher at all time points in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group (at Week 24, 64.4% [58/90] receiving CZP 200 mg Q2W versus 55.3% [42/76] taking CZP 400 mg Q4W).

Placebo subjects who escaped to CZP treatment at Week 16 had a marked increase in the percentage of PhGAP responders between weeks 16 and 24 (increasing from 16.7% to 44.4% for those escaping to CZP 200 mg Q2W; and increasing from 25.0% to 65.0% for subjects escaping to CZP 400 mg Q4W group).

6.1.1.1.18.4. Psoriasis nail changes

In the subgroup of subjects with psoriatic nail disease at baseline (73.3%; 300/409), the change from baseline in mNAPSI (modified Nail Psoriasis Severity Index) score was recorded every 4 weeks during 24-week, double-blind treatment phase of Study PsA001. Mean changes in the mNAPSI over time were small in all 3 treatment groups. At 24 weeks, the mean change from a baseline score of 3.3 in the mNAPSI score was slightly greater in the combined CZP group (-1.9 points) compared with the placebo group (-1.1 points), but this result was not statistically significant or clinically meaningful. The duration of follow-up (24 weeks) for this type of evaluation is not sufficient to assess clinically relevant improvements in nail disease.

6.1.1.2. Studies C87040 and C87044

6.1.1.2.1. Study design, objectives, locations and dates

Study C87040 was a Phase II randomized, double-blind, parallel-group, placebo-controlled trial which evaluated the efficacy and safety of CZP in adults subjects with moderate to severe chronic plaque psoriasis who were candidates for systemic treatment and/or phototherapy. The study had a screening period of 1 week, followed by double-blind treatment period of 12 weeks. Study C87044 was a follow-up trial to Study C87040, whereby those subjects who responded to treatment in Study C87040 (defined as achieving at least a PASI 75 response), and who subsequently relapsed within 24 weeks could receive the same therapy for an additional 12

weeks. Relapse was defined as a > 50% reduction in maximum improvement in PASI from baseline achieved by a subject during Study C87040. Both studies had a safety follow-up phase of up to 24 weeks after the last dose of study medication. Assessments (efficacy and safety) in both studies were done weekly for the first 4 weeks, and fortnightly thereafter.

Study C87040 was conducted at 15 European centres (5 in France, and 10 in Germany). Study C87044 was conducted in 12 of the original centres (4 in France, and 8 in Germany). In Study C87040, the first subject was enrolled on 17 October 2005, and the last subject procedure for Study C87044 occurred on 9 May 2007.

6.1.1.2.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be at least 18 years of age with a diagnosis of chronic plaque psoriasis of at least 6 months duration (stable severity in the last 3 months). Subjects were required to have active skin psoriasis with a PASI score at least 12, and an affected BSA of at least 10%. Subjects were required to be candidates for systemic treatment and/or phototherapy. Patients were allowed to have a prior history of receiving the following treatments: biologic therapy (nil for 6 months; 3 months for etanercept and 2 months for efalizumab); conventional systemic treatments such as retinoids, immunosuppressants such as MTX and cyclosporine, and oral CS (nil for 4 weeks); phototherapy (nil for 4 weeks); and topical CS (nil for 4 weeks if high potency; nil for 2 weeks if medium potency).

The exclusion criteria involved 3 domains, and patients meeting any 1 of the criterion were to be excluded from study.

- Diagnosis – any other type of psoriasis such as erythrodermic, guttate, or pustular; severe progressive and/or uncontrolled renal, cardiac, pulmonary, or neurologic disease; and pregnancy/lactation;
- Past history –chronic or recurrent infections (more than 3 episodes requiring antimicrobial treatment during the preceding year), recent serious or life-threatening infection within 6 months of the baseline visit (including herpes Zoster), hospitalization for any infection in the last 6 months, or any current sign or symptom that may have indicated an infection; known TB disease, high risk of acquiring TB, or latent TB infection; concurrent infection with Hepatitis B or C virus or HIV; demyelinating disease; lymphoproliferative disorder; Class III or IV congestive heart failure; SLE and malignancy within the last 5 years (except for up to 3 excised basal cell skin cancers successfully excised);
- Abnormal baseline laboratory results – liver function tests > 3 x ULN, serum creatinine > ULN, or total white blood cell count < 4.0 x 10^9/L.

6.1.1.2.3. Study treatments

In Study C87040, all patients were scheduled to receive SC injections (of CZP or placebo) at Week 0, and every 2 weeks until Week 10. The CZP 200 mg treatment group received a single 400 mg CZP injection at Week 0, followed by 200 mg every 2 weeks thereafter. The CZP 400 mg treatment group received 400 mg at Week 0, followed by 400 mg every 2 weeks until Week 10. CZP was provided in the commercial formulation as a single pre-filled syringe containing 200 mg/mL. Low-potency topical corticosteroids and emollients were permitted during both studies, but were not to be used within 12 hours of efficacy assessments. Use of moderate potency topical corticosteroids, topical retinoids, coal tar, keratolytics, and vitamin D analogues was permitted only on the scalp, palms, groin, anal fold and soles. They were not to be used within 12 hours of efficacy assessments. Topical dermatological therapies were used by 86.4% (51/59) of placebo subjects, 78.0% (46/59) of patients in the CZP 200 mg group, and 75.9% (44/58) in the CZP 400 mg arm.

In Study C87044, relapsed subjects with a recent history of PASI 75 response were re-treated with their original treatment allocation for a further 12 weeks (that is 6 doses of treatment

given at weeks 0, 2, 4, 6, 8 and 10). The rules for permissible concurrent therapies were the same as Study C87040.

6.1.1.2.4. Efficacy variables and outcomes

The main efficacy variables were:

- PASI score (as detailed earlier in this report).
- Psoriasis Global Assessment (PGA).

The 2 co-primary efficacy outcomes in Study C87040 were the proportion of subjects achieving at least a 75% decrease from baseline in PASI score at Week 12, and the proportion of subjects with a PGA rating of 'clear' or 'almost clear' (that is 0 or 1) at Week 12. The PGA is a 6-point scale that grades psoriasis from 'clear' (= 0) to 'very severe' (= 5). It has validated reliability as an outcome measure is evaluating changes in psoriasis.

Secondary efficacy parameters in Study C87040 were based on the PASI and included:

- Time from baseline to first achievement of PASI 75 response.
- Time to relapse, defined as the time from last dose to when maximal improvement had reduced by > 50%. This parameter only applied to patients who achieved PASI 75 response at Week 12.
- The proportion of subjects achieving greater than or equal to 50% decrease from baseline in PASI (that is PASI 50) and greater than or equal to 90% decrease from baseline in PASI (that is PASI 90) at the end of the 12 week treatment period.
- The proportion of subjects with rebound effect (PASI score > 125% of baseline value) within 2 months of stopping treatment.
- BSA covered by psoriasis at Week 12, and change in BSA from baseline.
- Time to discontinuation from the treatment period due to lack of efficacy.

The primary efficacy outcome in Study C87044 was the median difference in PASI scores between Week 12 of Study C87040 (first treatment period) and Week 12 of Study C87044 (re-treatment phase). Secondary efficacy parameters assessed in Study C87044 included the proportion of PASI 50/75/90 responders at Week 12 upon re-treatment, median best PASI score (and median time to best PASI score) in each treatment period, and the proportion of PGA responders (defined as those with a score of 0 or 1) in each treatment period.

6.1.1.2.5. Randomisation and blinding methods

In Study C87040, subjects were randomized 1:1:1 to receive one of the 2 doses of CZP or matching placebo injections. Randomization was centralized and stratified by 3 factors: study centre, severity of psoriasis at baseline (severe [PASI > 20 or BSA involvement > 20%] or moderate [PASI 12-20 or BSA involvement 10-20%), and previous receipt of systemic treatment and/or photodynamic therapy for psoriasis. The study was conducted in a double-blind manner. To maintain blinding, each subject received 2 SC injections at each visit. Matching placebo injections were presented in the same manner (single use pre-filled syringes containing 1mL with no label identifying its content).

In Study C87044, patients were not re-randomized but resumed their original treatment allocation (as per Study C87040). The re-treatment trial had a double-blind design.

6.1.1.2.6. Analysis populations

In both studies, the primary efficacy analyses were conducted on the Intention-To-Treat (ITT) population, which consisted of all randomized subjects. Supporting efficacy analyses were

conducted using the PPS, which is a subset of the ITT population consisting of all subjects who had no major protocol deviations that may have affected the primary efficacy parameter.

6.1.1.2.7. Sample size

Study C87040 was anticipated to recruit 150 subjects in total. Given this patient number, Fisher's exact test had a power of 92% to detect a difference between the assumed placebo response rate of 10% compared with the assumed CZP response rate of 40%, at the end of the 12-week treatment period, for each of the co-primary efficacy endpoints, assuming a Type I error of 5%. The overall statistical power was about 85%, since the PASI and the PGA endpoints both needed to show a statistically significant result for the study to be declared successful. There was no sample size calculation for Study C87044 as patient enrolment was dependent on the number of patients who achieved PASI 75 response at the end of 12 weeks of therapy.

6.1.1.2.8. Statistical methods

In Study C87040, the 2 primary efficacy parameters were each analysed using a logistic regression model including terms for treatment (3 groups), and severity of psoriasis (moderate or severe). In order to limit the inflation of the overall Type I error rate, the global null hypothesis of equality between the 3 treatment groups was tested first. If the global treatment effect was significant at the 5% significance level, pair-wise comparisons between CZP and placebo were performed, each at 5% significance level. For each dose of CZP, the odds ratio versus placebo was calculated with its 95% CI. Study C87040 was declared successful if at least 1 dose of CZP compared to placebo was statistically significant for the PASI and PGA endpoints. A sensitivity analysis of the primary efficacy parameters in Study C87040 was performed using randomization based statistical tests, and to verify the impact of missing assessment values. For secondary endpoint analysis in Study C87040, a logistic regression model was used for the percentage of PASI 50 and PASI 90 responses; and time to PASI results and relapse were analysed by a Kaplan-Meier product limit method.

Descriptive statistics were used in Study C87044 with no inferential analyses to compare the 2 CZP dose treatment groups. In addition, Study C87044 was not designed to test any hypothesis regarding re-treatment effect.

6.1.1.2.9. Participant flow

In Study C87040, a total of 215 subjects were screened, and 176 were randomized to 1 of 3 treatment groups: 59 allocated to placebo, 59 randomized to CZP 200 mg Q2W, and 58 to CZP 400 mg Q2W. The majority of subjects in each group completed the 12-week treatment period: 67.8% (40/59) in the placebo group, 91.5% (54/59) in the CZP 200 mg arm, and 93.1% (54/58) in the CZP 400 mg group. Of the 28 patients who prematurely discontinued, the main non-safety reason was lack of efficacy (14 placebo patients, 3 subjects in the CZP 200 mg group, and 1 patient in the CZP 400 mg arm). In addition, 2 placebo subjects were lost to follow-up.

At Week 12 in Study C87040, a total of 96 subjects (4 placebo, 44 CZP 200 mg and 48 CZP 400 mg) achieved a PASI 75 response. To be eligible for enrolment in Study C87044, patients had to achieve a PASI 75 response by Week 12 in Study C87040, and then also meet the relapse criteria following cessation of treatment. A total of 71 subjects (34 in the CZP 200 mg Q2W group, and 37 in the CZP 400 mg Q2W arm) were eligible to enter into Study C87044, and all were re-treated with their original treatment dose in Study C87044. None of the 4 placebo subjects met the relapse criteria within 24 weeks of treatment follow-up in Study C87040, so none were eligible to enter into Study C87044. The majority of subjects in each treatment group completed the 12 weeks of follow-up in Study C87044 – 94.1% (32/34) of subjects in the CZP 200 mg group, and 94.6% (35/37) in the CZP 400 mg arm. Of the 4 subjects who prematurely withdrew from Study C87044, 1 did so for lack of efficacy (CZP 200 mg group – withdrew at Day 56), and the other 3 discontinued for other reasons (2 moved away, and 1 patient was non-compliant).

6.1.1.2.10. Major protocol violations/deviations

In total, 26 subjects (14.8% of 176) in the ITT population had at least 1 major protocol deviation during Study C87040 that excluded them from the PP population for analysis. Each treatment group had a similar frequency of protocol deviations that may affect efficacy assessments. The most common reasons for efficacy related protocol deviations were errors in attributing study medication (5.1%; 9/176), and receipt of a prohibited medication or treatment (5.1%; 9/176). Seven patients (2 in the placebo group, 1 in the CZP 200 mg Q2W arm and 4 in the CZP 400 mg Q4W group; total of 4.0% of 176) had less than 80% compliance with study medication.

6.1.1.2.11. Baseline data

At baseline in Study C87040, the mean age of the ITT population was 43.4 years (range: 18.8 to 73.3 years). Most recruited subjects (59.7%; 105/176) were aged between 35 and 55 years. The majority of subjects were Caucasian (97.7%; 172/176), and more than two thirds (69.9%; 123/176) were male. The mean weight was 82.2 kg (range: 45.0-150.0 kg). The mean BMI of subjects was 27.12 kg/m^2. Baseline demographic characteristics were similar for each of the 3 treatment groups.

Patients had a mean duration of psoriasis at screening of 20.1 years. Psoriasis was graded as severe in 60.8% (107/176) of subjects, and moderate in 38.6% (68/176) subjects. At baseline, the mean (+/- SD) PASI score was 22.55 (+/- 8.83) for the placebo group, 21.36 (+/- 8.20) for the CZP 200 mg arm, and 21.95 (+/- 8.05) for the CZP 400 mg group. The mean (+/- SD) BSA for the extent of skin involvement in psoriasis was 30.07% (+/- 17.65) for the placebo group, 26.6% (+/- 16.46) for the CZP 200 mg arm, and 28.42% (+/- 14.28) for the CZP 400 mg group. At baseline, all subjects had a PGA rating of at least moderate (= 4, on the 6-point scale). In total, 14.8% (26/176) of subjects had a baseline PGA rating of moderate, 51.1% (90/176) had a rating of moderate to severe (= 5), and 33.5% (59/176) had a rating of severe (= 6). A total of 167 subjects (94.9%) had received at least 1 prior systemic treatment and/or phototherapy for psoriasis. The most commonly used prior treatments were MTX (34.7%; 61/176) and PUVA (41.5%; 73/176). Around one quarter of all subjects (23.3%; 41/176) reported prior use of anti-TNF treatment for psoriasis, and 39.8% (70/176) had no response to, or were intolerant of, at least 2 previous treatments, reflecting a treatment refractory group of patients. Of relevance to this application, 21.6% (38/176) of patients had a history of PsA – 13 in the placebo group, 15 in the CZP 200 mg arm, and 10 in the CZP 400 mg group. However, no arthritis related efficacy endpoints were collected in Studies C87040 and C87044. The demographic and baseline psoriasis characteristics of the ITT population in Study C87044 were similar to the characteristics described above for the population that entered into Study C87040.

6.1.1.2.12. Results for the primary efficacy outcome

In Study C87040, CZP (either dose) showed statistically significant and clinically relevant improvements of psoriasis symptoms in subjects suffering from moderate to severe chronic plaque psoriasis. At 12 weeks, a greater percentage of subjects treated with CZP (74.6% [44/59] with 200 mg Q2W, and 82.8% [48/58] with 400 mg Q2W) achieved PASI 75 response compared with 6.8% (4/59) of patients given placebo injections. The rates of obtaining a PGA 'clear' or 'almost clear' response after 12 weeks with CZP treatment was also higher (52.5% [31/59] with 200 mg Q2W, and 72.4% [42/58] with 400 mg Q2W) compared to placebo (1.7%; 1/59). The odds ratios and 95% CIs for each co-primary variable and CZP dose versus placebo confirmed the same outcome in favour of CZP therapy. Sensitivity analyses supported the nature of the primary efficacy analysis in demonstrating that CZP (either dose) was effective in comparison to placebo in improving psoriasis activity over 12 weeks of treatment follow-up. The interaction between previous use of anti-TNF drugs (yes/no) and study treatment was not significant for the rate of PASI 75 ($p = 0.30$) and PGA response ($p = 0.289$) at Week 12. Similarly, no interaction between treatment response and prior use of systemic therapy (yes/no) could be demonstrated.

The median difference in PASI scores (range: 0-72) between the first treatment period and the re-treatment phase was 1.25 (95% CI 0.10, 4.40) for CZP 200 mg Q2W, and 0.20 (95% CI 0.00, 0.70) for CZP 400 mg Q2W. The median difference in response between the 2 treatment periods was not clinically significant for either dose of CZP.

6.1.1.2.13. Results for other efficacy outcomes

In Study C87040, significant improvements were shown for both doses of CZP versus placebo in the relative rates of PASI 50 and PASI 90 response, percentage BSA affected by psoriasis, time to achievement of PASI 75 response, and also upon the rate of withdrawal from study treatment due to lack of efficacy. At Week 12, the proportion of patients achieving a PASI 50 response was statistically higher in the CZP treatment groups (86.4% [51/59] for 200 mg Q2W, and 93.1% [54/58] for 400 mg Q2W) compared to placebo (11.9%; 7/59). At Week 12, the proportion of patients achieving a PASI 90 response was statistically higher in the CZP treatment groups (39.0% [23/59] for 200 mg Q2W, and 46.6% [27/58] for 400 mg Q2W) compared to placebo (1.7%; 1/59).

At Week 12, the mean BSA affected by psoriasis was 28.8% (versus baseline of 30.1%) for placebo, 7.1% (versus baseline of 26.7%) for CZP 200 mg Q2W, and 5.6% (versus baseline of 28.4%) for CZP 400 mg Q2W. The adjusted mean difference in BSA change during treatment with CZP versus placebo was 17.79 % (95% CI 12.57, 23.00; $p < 0.001$) for the CZP 200 mg group, and 20.29% (95% CI 15.14, 25.43; $p < 0.001$) for the CZP 400 mg arm.

The onset of PASI response was quicker in active treatment groups compared to placebo. For subjects that obtained PASI 75 response at Week 12, the median time from first dose to clinical response was 77.5 days (95% CI 42.0, 99.0) for the control group, 42.5 days (95% CI 28.0, 56.0) for the CZP 200 mg Q2W arm, and 55.5 days (95% CI 42.0, 69.0) for the CZP 400 mg Q2W group. For subjects that were PASI 75 responders at Week 12, the median time to relapse from last dose was 22.1 weeks (95% CI 17.0, 26.0) for CZP 200 mg, and 20.1 weeks (95% CI 17.0, 22.3) for CZP 400 mg. The proportion of subjects who rebounded within 2 months of stopping treatment was 15.3% (9/59) in the placebo arm, and 1.7% (1 subject) in each of the CZP treatment groups. During Study C87040, 15 (25.4% of 59) patients withdrew from the control group due to a lack of efficacy at a median time of 42.0 days, 4 (6.8% of 59) discontinued from CZP 200 mg Q2W at a median time of 59.5 days, and 2 (3.4% of 58) withdrew from CZP 400 mg Q2W at a median time of 49.0 days.

The proportions of PASI 50/75/90 responders at Week 12 of re-treatment in Study C87044 for those subjects who received CZP 200 mg Q2W was 76.5%, 67.6% and 35.3%, respectively; versus 97.1%, 97.1% and 52.9%, respectively, at Week 12 in Study C87040. The proportions of PASI 50/75/90 responders at Week 12 of re-treatment in Study C87044 for those subjects who received CZP 400 mg Q2W was 89.2%, 86.5% and 48.6%, respectively; versus 100%, 97.3% and 56.8%, respectively, at Week 12 in Study C87040. For the CZP 200 mg group, the median best PASI score was 1.60 (95% CI 0.80, 2.70) in Study C87040, and 2.00 (95% CI 1.20, 4.20) upon re-treatment. For the same treatment group, the median time to best PASI score was 11.0 weeks (95% CI 10.0, 12.0) in the first treatment period, and 8.0 weeks (95% CI 6.0, 10.0) upon re-treatment. For the CZP 400 mg cohort, the median best PASI score was 1.60 (95% CI 0.80, 2.00) in Study C87040, and 1.80 (95% CI 0.60, 2.80) upon re-treatment. For the same treatment group (400 mg Q2W), the median time to best PASI score was 12.0 weeks (95% CI 10.3, 12.0) in the first treatment period, and 9.9 weeks (95% CI 8.0, 10.1) upon re-treatment. The median best PASI scores were similar during the first and second treatment periods for both doses of CZP, but the median time to reach the best PASI score tended to be shorter for both CZP dose groups upon re-treatment. The proportions of PGA responders at Week 12 of re-treatment in Study C87044 for those subjects who received CZP 200 mg Q2W was 52.9% (18/34) versus 64.7% (22/34) at Week 12 in Study C87040. The proportions of PGA responders at Week 12 of re-treatment in Study C87044 for those subjects who received CZP 400 mg Q2W was 56.8% (21/37) versus 81.1% (30/37) at Week 12 in Study C87040.

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

A pooled efficacy analysis was not appropriate for the indication of PsA as there is only 1 pivotal study in patients with active PsA, and the 2 supporting trials focussed on assessing efficacy in skin psoriasis.

6.1.3. Evaluator's conclusions on clinical efficacy for Psoriatic Arthritis

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

This submission is seeking an indication in active PsA, and in general is consistent with the TGA adopted regulatory guideline pertaining to the requested extension of indication: EMEA guideline CPMP/EWP/438/04 "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Psoriatic Arthritis" (effective 5 February 2008). In addition, the single pivotal study (PsA001) had a design that met the criteria for single pivotal study applications. For Study PsA001, the choice of clinical and functional efficacy endpoints and statistical analysis were appropriately performed. However, although the radiographic endpoints were appropriate, the statistical analysis plan was modified post-hoc to demonstrate statistical significance in favour of CZP as the primary statistical analysis was observed to be erroneous. This is a major deficiency of the current submission for the additional claim of reducing the rate of radiographic progression in patients with PsA.

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

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

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

primary radiographic endpoint (mean change from baseline to 24 weeks in mTSS), as well as several supporting X-ray endpoints (such as, the proportion of mTSS responders at Week 24).

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

6.2. Indication 2

Indication 2:

> *Cimzia is indicated for the treatment of adult patients with active axial spondyloarthritis, including patients with ankylosing spondylitis and patients with non-radiographic axial spondyloarthritis.*

6.2.1. Pivotal efficacy study

6.2.1.1. Study AS001

6.2.1.1.1. Study design, objectives, locations and dates

Study AS001 was a Phase III randomized, double-blind, parallel-group, placebo-controlled trial which evaluated the efficacy and safety of CZP in adults subjects with active axial SpA. The study had 5 treatment periods: screening (up to 5 weeks), double-blind treatment period (weeks 0-24), dose-blind treatment phase (weeks 24-48), open-label treatment period (weeks 48-158), and the safety follow-up phase 10 weeks after the last dose of study medication (Week 166). For the efficacy data component of this submission, only the screening and double-blind treatment periods were included. However, the latter phases of the study are ongoing.

Screening assessments were performed between weeks -5 and -1. The screening period was used to obtain baseline data (clinical and laboratory), to verify that the doses of allowed DMARD, NSAID, and corticosteroid (CS) therapy was stable (if used), and to enable washout of any medications not permitted for use during the study. The baseline visit was Day 0, and then during the 24-week double-blind treatment period assessments were scheduled to occur at weeks 1 and 2, and thereafter every 2 weeks up until Week 24.

During the 24-week, double-blind treatment phase, patients were randomly allocated in a 1:1:1 ratio to the following study treatments: CZP 400 mg Q2W at weeks 0, 2, and 4 followed by CZP 200 mg Q2W (starting at Week 6), CZP 400 mg Q2W at weeks 0, 2, and 4 followed by CZP 400 mg Q4W (starting at Week 8), or placebo injections. Subjects receiving placebo injections who did not achieve at least a minimal response (defined as the Axial Spondyloarthritis International Society 20% response criteria, or ASAS 20) at both the Week 14 and 16 visits were re-allocated to blinded CZP escape therapy (randomized 1:1 to receive either CZP 200 mg Q2W, or CZP 400 mg Q4W) from Week 16 onwards. These subjects continued to be treated with this dose regimen for the duration of their participation in the study. The IVRS was used to identify qualifying subjects for early escape therapy. Subjects in either of the 2 CZP treatment groups who qualified for escape treatment at Week 16, continued with their current treatment allocation for the duration of their participation in the study (that is they were not re-randomized).

The primary efficacy objective of the study was to demonstrate the efficacy of CZP (given by SC injection at the dose of 200 mg Q2W or 400 mg Q4W after loading with 400 mg at weeks 0, 2, and 4) on the signs and symptoms of active axial SpA. The secondary efficacy objectives of the study were to assess the effects of CZP on: health related outcomes, partial remission, spinal mobility, and structural damage and inflammation in a subpopulation that underwent MRI.

The study was to be conducted at 128 sites (83 enrolled subjects) located in North America, Latin America, Western Europe, and Central/Eastern Europe. In Study AS001, the first subject was enrolled on 9 April 2010, and the last subject procedure for this interim efficacy dataset occurred on 14 January 2012.

There were 4 global and 14 country-specific amendments to the original protocol (dated 25 September 2009). The first global amendment was instituted before the commencement of patient recruitment, and all of the other amendments occurred after. The amendments contained clarifications about the inclusion and exclusion criteria, statistical analysis plan (for example hierarchical test procedures for multiple endpoints), and explanations about the baseline and efficacy measures. The amendments were also to adapt to the most recent scientific developments in the field. None of the amendments resulted in major changes to the study design, which may have adversely affected the integrity of the study's outcomes or statistical analysis.

6.2.1.1.2. Inclusion and exclusion criteria

To be eligible for inclusion, patients had to be at least 18 years of age with a documented diagnosis of adult-onset axial SpA of at least 3 months duration as defined by the ASAS criteria. The protocol specified that 50% of the study population had to fulfil both the modified NY criteria for a definite diagnosis of AS, as well as the ASAS criteria. The other 50% of subjects should not have met the modified NY criteria, but at least 50% of those patients (that is at least 25% of the overall study population) had to meet the new ASAS imaging criteria, and the remainder (up to 25% of the overall population) could be enrolled based on meeting the ASAS clinical criteria only. The design allowed for the recruitment of a mix of patients with AS and nr-SpA.

Subjects had to have been intolerant to, or have had an inadequate response to at least 1 NSAID. Inadequate response to an NSAID was defined as lack of response to at least 30 days of continuous NSAID therapy at the highest tolerated dose of the administered NSAID, or the lack of response to treatment with at least 2 NSAIDs at the maximum tolerated dose for 2 weeks each. Patients were also allowed to be receiving stable non-biological DMARD treatment for at least 28 days prior to baseline with 1 of 3 specified treatments: SSZ less than or equal to 3g daily, MTX less than or equal to 25 mg weekly, and/or Hydroxychloroquine (HCQ) less than or equal to 400 mg daily. Subjects were also required to have active disease at baseline with the BASDAI score being greater than or equal to 4, spinal pain greater than or equal to 4 on a 0 to 10 Numerical Rating Scale (NRS), CRP > ULN and/or current evidence (that is , within the last 3 months from Screening) for sacroiliitis on MRI as defined by the ASAS criteria. The spinal pain NRS is item 2 of the BASDAI.

The original ASAS criteria require a patient to have back pain of at least 3 months duration with an age of symptom onset before 45 years. In addition, 1 of the following 3 criteria need to be true:

- Active acute inflammation on MRI suggestive of sacroiliitis + 1 clinical feature,
- Definitive sacroiliitis (grade 2 or higher bilateral or 3 or higher unilateral) on plain X-ray + 1 clinical feature, or
- Positive HLA-B27 status + 2 clinical features.

The clinical features are: inflammatory back pain, inflammatory arthritis (with synovitis), enthesitis, uveitis, dactylitis, psoriasis, Crohn's colitis, elevated CRP, good response to NSAID in the past and family history of SpA. The modified NY criteria for diagnosing AS excludes the last 2 clinical features (prior good response to NSAID, and family history of SpA) from its decision algorithm. There were 2 approaches for evaluating the modified NY criteria in Study AS001 (Sieper et al, 2009). Firstly, the subject had to meet the radiological criterion. Secondly, at least 1 of the 3 clinical criteria regarding back pain and stiffness, limitation of lumbar movement, or limitation of chest movement had to be positively answered. The subgroup which answered yes (investigator decision) to the modified NY criteria were regarded as the AS population, whereas those which answered no were assumed to have nr-SpA. A plain X-ray of the sacroiliac joints was performed on all subjects at baseline (or within 12 weeks of the baseline visit if recently done). The X-rays were centrally read by 2 blinded independent experts. If their assessments differed, an adjudication reader also assessed the images. For each reader, the presence of definitive sacroiliitis on plain X-ray required the subject to have either grade greater than or equal to 2 bilateral or grade 3-4 unilateral sacroiliitis. Both readers, or at least 2 of the 3 adjudicated readers, had to concur on the presence of sacroiliitis at baseline for this diagnosis to be established. The plain X-ray reading process was robust in nature to optimise the integrity of classifying patients at baseline as either having AS or nr-SpA.

The exclusion criteria were extensive and involved 5 domains. Patients meeting any 1 of the criterion were to be excluded from study.

- Diagnosis – total spinal ankylosis ("bamboo spine"); any other inflammatory arthritis such as RA or a known diagnosis of fibromyalgia; symptomatic osteoarthritis that in the investigator's opinion may interfere with evaluating the effect of study medication on the subject's primary diagnosis of axial SpA; permanently bedridden or wheelchair bound for any reason; pregnancy/lactation; subjects with a current or recent history, as determined by the investigator, of severe, progressive, and/or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, or neurological disease;
- Past history – chronic alcohol abuse within the last year (defined as consuming more than 14 standard drinks/week for women, and more than 21 standard drinks/week for men); history of chronic or recurrent infections (more than 3 episodes requiring antimicrobial treatment during the preceding year); recent serious or life-threatening infection within 6 months of the baseline visit (including Herpes Zoster); hospitalization for any infection in the last 6 months; known TB disease, high risk of acquiring TB, or latent TB infection; high risk of developing infection in the investigator's opinion (such as subjects with leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections); history of an infected joint prosthesis at any time; major surgery (including joint surgery) within the 8 weeks prior to screening; concurrent infection with Hepatitis B or C virus or HIV; demyelinating disease; lymphoproliferative disorder; Class III or IV congestive heart failure; malignancy within the last 5 years (except for up to 3 excised basal cell skin cancers or cervical carcinoma in situ successfully treated by surgery);
- Abnormal baseline laboratory results – liver function tests > 2 x ULN, serum creatinine > ULN, or total white blood cell count < 3.0 x 10^9/L;
- Recent or concurrent treatments – Any ad hoc analgesic use in the 24 hours prior to the baseline visit (stable doses of analgesics were permitted); any change in dose of NSAID regimen in the 14 days prior to the baseline visit; use of biologic DMARD therapy within 3 months prior to baseline (28 days for etanercept); oral prednisone > 10 mg/day (as well as, intra-articular or parenteral CS within 28 days); any live (including attenuated) vaccination within the 8 weeks prior to baseline (however, inactivated influenza and pneumococcal vaccines were allowed but nasal influenza vaccination was not permitted); and

- Prior treatment – exposure to a maximum of 2 previous biological response modifiers for axial SpA, including only 1 TNF antagonist treatment. In addition, the prior TNF antagonist experience must not have been a primary failure to such therapy (defined as no response within the first 12 weeks of treatment with the TNF antagonist). Prior treatment (at any time) with tocilizumab or anti-CD20 therapy was an exclusion.

The study protocol stipulated that no more than 40% of the enrolled subjects could have a history of secondary efficacy failure to anti-TNF therapy, which is an acceptable limit to apply so that a broader representative SpA population is enrolled versus those with treatment refractory SpA.

6.2.1.1.3. Study treatments

Subjects were randomized in a 1:1:1 ratio to receive CZP 200 mg Q2W, CZP 400 mg Q4W, or placebo injections. CZP was supplied as a sterile, clear, and colourless to slightly yellow liquid solution in a 1mL pre-filled syringe containing 200 mg of the drug (injected with 25G needle). Placebo injections were supplied in a 1mL pre-filled syringe containing 0.9% saline (injected with the same type of 25G needle). There were minor differences in the presentation and viscosity between the CZP and placebo injections. All injections were given by SC injection into the lateral abdominal wall or upper outer thigh. During each dosing visit where 2 injections were administered, 2 different anatomical sites were injected. During the double-blind phase of the Study AS001, study treatments (including placebo injections) were administered by pre-specified, unblinded, trained study centre personnel at fortnightly intervals between weeks 0 and 24. Patients did not self-administer therapy in this treatment period.

Only 3 concurrent non-biological DMARD treatments were permissible during Study AS001: SSZ less than or equal to 3 g daily, MTX less than or equal to 25 mg weekly, or HCQ less than or equal to 400 mg daily. The doses of all continued DMARD therapy had to be stable for at least 28 days prior to baseline. The use of DMARD combination therapy was forbidden. Patients were also able to continue with low dose CS (maximum oral dose of 10 mg/day of prednisone or equivalent) if they had been receiving a stable dose for at least 28 days prior to baseline. Similarly, NSAID (including COX-2 inhibitors) could be continued if these treatments were stable for at least 14 days prior to baseline. Analgesic medications (including paracetamol and narcotics) were permitted except for ad hoc use within 24 hours prior to any scheduled study assessments. No change in concurrent NSAID, CS or DMARD dose (or route of administration for MTX) was permitted in the first 48 weeks of the study, except for documented safety reasons. Intra-articular CS injections for active SpA were permitted after the first 48 weeks of the study.

6.2.1.1.4. Efficacy variables and outcomes

The main efficacy variables were:

- Axial Spondyloarthritis International Society (ASAS) response criteria, and some of its components (the BASFI [Bath Ankylosing Spondylitis Functional Index] and BASDAI measures).
- Bath Ankylosing Spondylitis Metrology Index (BASMI).
- MRI parameters (SPARCC and ASspiMRI-a scores).

The primary efficacy variable in Study AS001 was the ASAS 20 response rate at Week 12.

There were 5 key secondary efficacy variables in Study AS001:

- ASAS 20 response rate at Week 24,
- Mean change from baseline in the BASFI score at 12 and 24 weeks,
- Mean change from baseline in the BASDAI score at 12 and 24 weeks,
- Mean change from baseline in the BASMI score at 12 and 24 weeks, and

- MRI parameters - SPARCC (sacroiliac joint) and ASspiMRI-a (spinal) scores at Week 12.

In general, the key efficacy endpoints in Study AS001 use validated metrics that have served as the basis of previous published studies, prior regulatory approvals, and are consistent with published guidelines. The endpoints studied were relevant to assess the proposed indication of reducing the signs and symptoms of active axial SpA.

The ASAS response criterion is a composite endpoint, which quantifies the clinical response to therapy in patients with axial SpA (Anderson et al, 2001). A patient with an ASAS 20 response has demonstrated an improvement of 20% and absolute increase of at least 1 unit on the 0-10 NRS in at least 3 of the following 4 domains: Patient's Global Assessment of disease activity, spinal pain score (on 0-10 NRS), function (represented by BASFI), and inflammation (the mean of questions 5 and 6 of the BASDAI, concerning morning stiffness intensity and duration). The ASAS 50 and ASAS 70 response criteria include the same criteria as ASAS 20, but with the use of a higher percentage improvement (50% or 70%) instead of 20%, as well as an absolute improvement of at least 2 units on the 0-10 NRS in at least 3 of the 4 domains, and no worsening at all in the remaining domains.

The BASFI is a validated, disease-specific tool for assessing physical function. The index comprises 10 items (occurring in the past week), which are rated on a scale of 0-10. The BASFI is the mean of the 10 scores, with lower scores indicating better physical function. The first 8 questions relate to functional anatomical limitations due to active spinal disease (for example question 1 asks "can you put your socks or tights on without help?"), and the final 2 questions evaluate a patient's ability to cope with everyday life. The MCID used in Study AS001 to interpret score changes is a 1-unit improvement from baseline on the NRS.

The BASDAI is a validated, self-reported instrument consisting of 6 questions (all rated on a 10-unit horizontal NRS) relating to fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration) over the last week. To give each symptom equal weighting, the mean of the 2 scores relating to morning stiffness (questions 5 and 6) is taken. The resulting 0-50 score is divided by 5 to give a final 0-10 BASDAI score. Scores of 4 or more (out of 10) indicate active axial SpA. In Study AS001, an MCID of 1 was selected for the NRS version used.

The BASMI characterises the spinal mobility of patients with AS. It consists of 5 clinical measures reflecting axial movement: cervical rotation, tragus to wall distance, lumbar flexion (modified Schober test), intermalleolar distance, and lateral lumbar flexion. The mean of the 5 scores provides the final BASMI score with a range of 0-10. In Study AS001, the linear version of the BASMI was utilised.

MRI scans of the spine and sacroiliac joints were performed at baseline and 12 weeks (+/- 2 weeks) in a subset of patients in Study AS001. Scoring was done by 2 independent readers, who were blinded to both the order of the scans and treatment allocation, using a standardized approach. For analysis, the average of the scores from the 2 readers was utilized. The SPARCC (Spondyloarthritis Research Consortium of Canada) scoring method identifies lesions consistent with bone marrow oedema (abnormally increased bone marrow signal on a T2-weighted sequence). The total sacroiliac joint SPARCC scores can range from 0-72, with higher scores indicating more extensive bony oedema. The other MRI parameter assessed in Study AS001 was the Berlin modification of the ASspiMRI-a (Braun and Baraliakos, 2011). This scoring method quantifies bone marrow oedema changes in 23 vertebral units of the spine from the C2 to S1 vertebral body. Each vertebral unit is scored from 0-3, and the total score ranges from 0-69.

There were a very large number of other non-key secondary efficacy outcomes (grouped below by disease manifestation/category), which included:

- Signs and symptoms of axial SpA – ASAS 40, 5/6 and partial remission responses (and the individual components of the ASAS criteria) at various time points over 24 weeks; enthesitis (using the MASES index), and BASDAI 50 response time.
- Heath-related outcomes - Change from baseline at various time points over 24 weeks in SF-36 domains, ASQoL, fatigue, sleep (using MOS Sleep Scale), work productivity, and health resource utilization.
- Radiographic endpoints - mean change from baseline, as well as the rates of radiographic progression according to the mSASSS (modified Stoke Ankylosing Spondylitis Spine Score).

6.2.1.1.5. Randomisation and blinding methods

Subject randomization was conducted using IVRS, and stratified by 3 variables: treatment centre, fulfilment of modified NY criteria (yes/no) and prior anti-TNF exposure (yes/no). Patients were allocated to treatment in a 1:1:1 ratio (CZP 200 mg Q2W, CZP 400 mg Q4W, or placebo injections). Placebo subjects who qualified for escape treatment at Week 16 were re-randomized in a 1:1 ratio (stratified by prior TNF antagonist exposure and fulfilment of modified NY criteria) to either CZP 200 mg Q2W or CZP 400 mg Q4W. Subjects originally randomized to placebo who completed to Week 24 were re-randomized at that time point in a 1:1 ratio to either CZP 200 mg Q2W or CZP 400 mg Q4W, again stratified by fulfilment of modified NY criteria and prior anti-TNF use.

Due to differences in the presentation and viscosity between the CZP and placebo injections, the sponsor states, "special precautions were taken to ensure blinding of the study". However, detail about the special precautions was limited in the submission. During the double-blind phase of the Study AS001, study treatments (including placebo injections) were administered by pre-specified, unblinded, trained study centre personnel at fortnightly intervals between weeks 0 and 24. However, investigators and patients were blinded to study treatment assignment.

6.2.1.1.6. Analysis populations

The primary analysis of all efficacy variables was performed using the Randomized Set (RS), which consisted of all subjects randomized into the trial, analysed by imputation of missing values. For sensitivity analyses of the primary efficacy variable, the Full Analysis Set (FAS), Per-Protocol Set (PPS) and Completer Set were additionally explored. The FAS consisted of all patients in the RS who had received at least 1 dose of study medication, and who had valid baseline and post-baseline efficacy measurements for both the ASAS 20 through to Week 12. The PPS consisted of patients in the FAS who had a minimal exposure to medication of 12 weeks in the double-blind treatment phase without any major protocol deviations that may have affected the validity of the efficacy variables. The Completer Set consisted of subjects in the FAS who had completed 24 weeks of randomized treatment, with a valid 24-week efficacy measurement.

6.2.1.1.7. Sample size

The sample size was determined on both the estimate for the primary efficacy endpoint in the entire axial SpA population, as well as the modified NY criteria stratum. Based on published data of other anti-TNF therapy in the treatment of axial SpA, it was anticipated that the difference between CZP and placebo for the rate of ASAS 20 response over 12 weeks was 38% (Inman et al, 2008). However, the comparator trial had a lower percentage of anti-TNF failures included compared to Study AS001 (up to 40% of subjects with prior anti-TNF failure were allowed), so the treatment difference was expected to be slightly lower at 33% in Study AS001. Furthermore, although the treatment effect was not expected to be less for the entire axial SpA cohort versus the true AS group (meeting modified NY criteria), a more conservative assumption of 30% for the difference in treatment response was concluded in Study AS001.

A sample size of 105 patients in each treatment group was considered sufficient to detect a statistically significant difference in the ASAS 20 response rate if both CZP arms were combined versus placebo, yielding at least 99% power. This sample size was also sufficient to detect a statistically significant difference between CZP and placebo at 12 weeks with 90% power if the anticipated treatment difference was 33%.

6.2.1.1.8. Statistical methods

Statistical analyses accounting for multiplicity were performed for the primary and key secondary efficacy variables. A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. The pre-defined order of hypothesis testing, each at a 2-sided 5% alpha level versus placebo (using Wald asymptotic test), was performed in the following sequence for dose regimen and endpoint:

- ASAS 20 response at Week 12 for CZP 200 mg Q2W.
- ASAS 20 response at Week 12 for CZP 400 mg Q4W
- ASAS 20 response at Week 24 for CZP 200 mg Q2W
- ASAS 20 response at Week 24 for CZP 400 mg Q4W
- Change from baseline to Week 12 in BASFI for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 12 in BASDAI for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 24 in BASFI for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 24 in BASDAI for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 12 in BASMI for CZP 200 mg Q2W and 400 mg Q4W combined
- Change from baseline to Week 24 in BASMI for CZP 200 mg Q2W and 400 mg Q4W combined

For the primary efficacy analysis, subjects who withdrew for any reason before Week 12 or who had missing data at Week 12 were considered non-responders. For the ASAS response criteria, imputation with LOCF (Last Observation Carried Forward) was used after the Week 12 visit for the handling of missing data. Secondary analyses using the FAS, PPS and CS populations were also undertaken for the primary efficacy outcome. To verify the model assumption of similar effects across geographical regions, the ANCOVA model (with treatment, fulfilling modified NY criteria, and prior anti-TNF exposure as factors) included an assessment of treatment by region interaction. The same procedure was done to investigate whether or not prior anti-TNF exposure was a determinant of treatment response.

6.2.1.1.9. Participant flow

A total of 591 patients were enrolled into the screening phase of the study, of which 325 subjects were randomized at Week 0 (111 to the CZP 200 mg Q2W group, 107 to the CZP 400 mg Q4W arm, and 107 to placebo). Overall, 45.0% (266/591) of subjects were screen failures. The most common reasons for screen failure were a failure to meet the eligibility criteria (n = 236; 39.9% of 591) and withdrawal of consent (n = 14; 2.4% of 591). All of the 325 randomized subjects received at least 1 dose of study medication. An additional 2 subjects were randomized in error, were not treated, and were censored from the RS. At Week 16, 52.3% (56/107) subjects treated with placebo did not achieve the minimal response criteria, and were therefore allocated to active escape therapy with CZP. Of these patients, 27 were re-randomized to CZP 200 mg Q2W and 29 were allocated to CZP 400 mg Q4W. Most patients (91.7%; 298/325) completed the 24-week double-blind treatment period – refer to Figure 2. The 2 most common

reasons for premature discontinuation were protocol violations (2.2%; 7/325) and adverse events (2.2%; 7/325).

In the modified NY criteria AS subpopulation of Study AS001, a total 178 patients were randomized: 65 to the CZP 200 mg Q2W group, 56 to the CZP 400 mg Q4W arm, and 57 to placebo. At Week 16, 52.6% (30/57) subjects treated with placebo did not achieve the minimal response criteria, and were therefore allocated to active escape therapy with CZP. Of these patients, 16 were re-randomized to CZP 200 mg Q2W and 14 were allocated to CZP 400 mg Q4W. All but 1 of the escape patients completed study follow-up at Week 24. Most patients treated with CZP (60/65 [92.3%] in the 200 mg Q2W group; and 52/56 [92.9%] in the 400 mg Q4W arm) completed 24 weeks of treatment follow-up; yet only 40.4% (23.57) of the patients originally randomized to placebo completed the double-blind phase.

6.2.1.1.10. Major protocol violations/deviations

Of the 325 patients who were randomized to, and received at least 1 dose of study treatment in Study AS001, 70 (21.5%) were excluded from the PPS because of potentially significant protocol deviations. The proportion of subjects who were identified to have protocol deviations that may have affected their efficacy measurements was similar between the 3 treatment groups (19.6% [21/107] in the CZP 400 mg Q4W group, 22.5% [25/111] in the CZP 200 mg Q2W arm, and 22.4% [24/107] in the placebo group. Some subjects were recorded to have more than 1 important protocol deviation. The most common reasons for efficacy related protocol deviations were failure to meet the inclusion criteria at baseline (11.7%; 38/325), and failure to meet the exclusion criteria at baseline (6.2%; 20/325). Only 2 patients (1 in the placebo group [escaping to CZP 400 mg Q4W], and 1 in the CZP 200 mg Q2W arm) had less than 80% compliance with study medication.

6.2.1.1.11. Baseline data

The treatment groups were well balanced with respect to demographic characteristics. In the overall axial SpA population, subjects had a median age of 38 years (range: 19-78 years; 78.8% [256/325] were aged between 25 and 54 years), more than half (61.5%; 200/325) were male, and the majority (90.2%; 293/325) were of Caucasian ethnicity. Subjects with AS were slightly older (median age of 41.0 years versus 35.0 years for the nr-SpA patient subset), and expectedly more were male (61.5% overall versus 48.3% for the nr-SpA group). The overall mean BMI was 27.6 kg/m^2, with 28.9% (94/325) of subjects having a BMI greater than or equal to 30 kg/m^2.

In Study AS001, the entry criteria required subjects fulfil a diagnosis of axial SpA according to the ASAS criteria. All but 7 subjects (3 in the placebo group, and 2 in each CZP dose arm) met the ASAS diagnostic criteria. All of those patients were deemed to be protocol violations. Consistent with the stratification rule which specified that 50% of subjects in Study AS001 also meet the modified NY criteria for a diagnosis of AS, sacroiliitis was confirmed by X-ray in 54.8% (178/325) of patients. In the AS subset of subjects, all patients (n = 178) had evidence of sacroiliitis on X-ray. In the nr-SpA subpopulation, 54.4% (80/147) of subjects had sacroilliitis detected on MRI. With the exception of sacroiliitis on imaging, fulfilment of the ASAS criteria was similar between the AS and nr-SpA subpopulations.

Regarding the clinical ASAS features at baseline, most (97.8%; 318/325) reported current inflammatory back pain, 80.3% (261/325) had elevated CRP levels, and 41.5% (135/325) had evidence of peripheral joint synovitis. Collectively, 21.2% (69/325) had a current or past history of uveitis, 10.2% (33/325) reported dactylitis, 6.2% (20/325) suffered psoriasis, and 5.5% (18/325) had a current or past history of Crohn's colitis. A good past response to NSAID was recorded in 33.2% (108/325) of patients, and 12.9% (42/325) had a family history of SpA. In total, 71.4% (232/325) of subjects were HLA-B27 positive. Expectedly, in the AS subset, HLA-B27 was positive in a greater proportion of subjects (81.5%; 145/178) compared to the nr-SpA subpopulation (74.8%; 110/147). There were no clinically relevant differences between the 3 treatment groups for baseline ASAS criteria. In the AS population subset, additional baseline

features according to the modified NY criteria were: 83.1% (148/178) of patients had limited lumbar spine motion, and 77.0% (137/178) of subjects had restricted chest wall expansion.

The treatment groups were well balanced with respect to other baseline disease features. The mean time since diagnosis of axial SpA for all subjects was 6.73 years, with 61.2% (199/325) of subjects reporting back pain for at least 5 years. Patients in the AS subset had a longer mean time since diagnosis (8.24 years) compared to those in the nr-SpA subpopulation (mean of 4.91 years). At baseline in the overall axial SpA population, subjects in the placebo group had a higher mean CRP level (22.35 mg/L) compared to the combined CZP cohort (17.25 mg/L). This difference was also evident in the AS (25.22 mg/L for placebo versus 19.48 mg/L for combined CZP), and nr-SpA subsets (19.08 mg/L for placebo versus 14.47 mg/L for combined CZP).

In terms of disease activity at baseline, the mean baseline BASDAI, BASMI and BASFI scores for the overall axial SpA population, as well as the AS and nr-SpA subsets were similar for the CZP 200 mg Q2W, CZP 400 mg Q4W, and placebo groups. The mean BASDAI score was 6.44, mean BASMI score was 3.84, and the mean BASFI score was 5.38, all of which are consistent with moderate disease activity. In general, the mean baseline BASDAI scores were similar between the AS and nr-SpA subsets (6.39 for AS, and 6.50 for nr-SpA), whereas the mean BASMI and BASFI scores were lower in the nr-SpA (3.15 for BASMI and 4.94 for BASFI) versus AS subpopulations (4.40 for BASMI and 5.74 for BASFI), which probably reflects a shorter time since diagnosis and less structural damage.

In total, 16.0% (52/325) of subjects had received previous treatment with anti-TNF drugs, and history of this prior medication use was higher in the placebo group (24.3%; 26/107) compared to the combined CZP treatment group (11.9%; 26/218). In the AS subset, a history of anti-TNF use was 20.2% (36/178) compared to the nr-SpA subpopulation (10.9%; 16/147). Similarly, prior anti-TNF use was higher in the placebo group (28.1% [16/57] in the AS subset, and 20.0% [10/50] in the nr-SpA subset) compared with the combined CZP treatment group (16.5% [20/121] in the AS subset, and 6.2% [6/97] in the nr-SpA subset). The mis-match between active and control therapy for a past history of anti-TNF use (indicative of treatment refractory disease) is a significant consideration in interpretating the relative rates of treatment response.

Just under half of all subjects (49.2%; 160/325) had prior use of DMARD, with a higher proportion of placebo subjects recording this history (57.0%; 61/107) compared to those treated with CZP (45.0% [50/111] for 200 mg Q2W, and 45.7% [49/107] for 400 mg Q4W). The 2 most commonly used prior DMARDs were SSZ (43.7%) and MTX (28.6%). The majority (85.2%; 277/325) of subjects in the overall axial SpA population reported past NSAID use, most commonly with diclofenac (27.4%), meloxicam (21.2%) and ibuprofen (18.5%), at a similar frequency in each of the treatment groups. Past use of NSAID was similar between the AS and nr-SpA subgroups.

During Study AS001, concomitant NSAID use was recorded in 87.7% (285/325) of patients in the overall axial SpA population, mainly with diclofenac (23.4%) and meloxicam (16.3%). The incidence of concurrent NSAID use was similar in the AS and nr-SpA patient subsets, as well between treatment groups. Continued DMARD therapy was recorded in 32.3% (105/325) of patients overall, primarily with SSZ (17.2%) and MTX (15.4%), and the incidence of use was similar in both the AS and nr-SpA patient subpopulations. Use of concomitant analgesics other than NSAID was higher in the placebo (44.9%) versus CZP treated groups (33.3% for 200 mg Q2W, and 26.2% for 400 mg Q4W). Overall, use concurrent CS was recorded in 16.9% (55/325) of patients, at a similar frequency in all 3 treatment groups.

By geographic region, the largest percentage of patients came from Eastern Europe (43.4%; 141/325), followed by North America (27.1%; 88/325), Western Europe (19.4%; 63/325), and Latin America (10.2%; 33/325). Recruitment site was a stratification factor in randomization, and patients from different geographical regions were equally distributed across the 3 treatment groups. Whereas the largest percentage of subjects in the AS subpopulation came

from Eastern Europe (55.1%; 98/178), subjects in the nr-SpA subset were recruited more evenly across the geographical areas (34.7% [n = 51] from Western Europe, 27.2% [n = 40] from North America, and 29.3% [n = 43] from Eastern Europe). The sponsor explains this observation was due to Eastern European sites starting enrolment first, and that AS patient recruitment was quick versus slow and difficult in the nr-SpA subpopulation.

6.2.1.2. Results for the primary efficacy outcomes

In the overall axial SpA population, the ASAS 20 responder rates at Week 12 were higher in the CZP 200 mg Q2W (57.7%; 64/111) and CZP 400 mg Q4W (63.6%; 68/107) groups compared with placebo therapy (38.3%; 41/107). The differences in response compared to placebo were statistically significant for both comparisons (difference of 19.3% for 200 mg Q2W [$p < 0.004$], and difference of 25.2% for 400 mg Q4W [$p < 0.001$]). In both of the subpopulations (AS and nr-SpA), statistically significant differences in favour of CZP (either dose regimen) versus placebo were additionally observed. These results demonstrate the efficacy of CZP for the treatment of the signs and symptoms of active axial SpA in patients with confirmed AS, as well as those with nr-SpA. Secondary and sensitivity analyses of the ASAS 20 responder rate at Week 12 provided similar trends to the primary analysis

The ASAS 20 response rates at Week 12 for the overall axial SpA population, as well as the 2 subpopulations (AS and nr-SpA) were analysed by subgroups of interest such as age (< 45 years versus greater than or equal to 45 years), gender, ethnicity, symptom duration (< 5 years versus greater than or equal to 5 years), geographic region, baseline CRP category (less than or equal to 15 mg/dL versus > 15 mg/dL), prior use of anti-TNF medications and anti-CZP antibody status. Two subgroup analyses showed a difference in ASAS 20 response rate at Week 12 for the overall axial SpA population. Firstly, a difference in response was observed by geographic region, whereby patients recruited in Latin America exhibited a significantly higher placebo response rate (58.3%; 7/12) compared to subjects who received placebo (23.2-43.2%) in the 3 other regions (12.7-27.3% placebo response rates). In addition, males tended to exhibit a higher rate of ASAS 20 response than females, which is a common finding in AS trials. Interestingly, there was no difference in ASAS 20 response rate at 12 weeks based on prior exposure to anti-TNFα therapy. The 2 patient subpopulations showed the same pattern of subgroup analysis as the overall axial SpA cohort.

6.2.1.2.1. Results for other efficacy outcomes

The results of the key secondary efficacy endpoints at weeks 12 and 24 were also statistically significant in favour of CZP therapy versus placebo. The differences in treatment response are of a magnitude to be clinically meaningful.

6.2.1.2.2. ASAS 20 response rate at week 24

The proportion of patients who achieved an ASAS 20 response at 24 weeks were higher in the CZP 200 mg Q2W (66.7%; 74/111) and CZP 400 mg Q4W (70.1%; 75/107) groups compared with placebo (29.0%; 31/107). The differences between CZP therapy and placebo were statistically significant for both comparisons (treatment differences of 37.7-41.1%; $p < 0.001$ for each comparison). In the AS subpopulation, the ASAS 20 response rate at 24 weeks were greater in the CZP 200 mg Q2W (67.7%; 44/65) and CZP 400 mg Q4W groups (69.6%; 39/56) compared to placebo (33.3%; 19/57). In the nr-SpA patient subset, the ASAS 20 response rate at 24 weeks were higher in the CZP 200 mg Q2W (65.2%; 30/46) and CZP 400 mg Q4W groups (70.6%; 36/51) compared to placebo (24.0%; 12/50). These results support the primary clinical endpoint of ASAS 20 response at 12 weeks, and indicate that CZP is effective in maintaining a reduction in the signs and symptoms of active axial SpA over 24 weeks of treatment follow-up.

6.2.1.2.3. Mean change from baseline in BASFI at weeks 12 and 24

At baseline, the mean BASFI scores were similar between the combined CZP (5.33) and placebo (5.49) groups. At Week 12, the LS mean change from baseline in BASFI was statistically greater in the combined CZP group (-2.02) compared with the placebo arm (-0.53). The difference between CZP therapy (combined dose regimens) and placebo was -1.49 (95% CI -1.96, -1.01; $p < 0.001$). Likewise, at Week 24, the LS mean change from baseline in BASFI was statistically greater in the combined CZP group (-2.28) compared with the placebo arm (-0.40). The difference between CZP therapy (combined dose regimens) and placebo was -1.88 (95% CI -2.38, -1.38; $p < 0.001$). These results demonstrate that CZP treatment improves the physical function for subjects with active axial SpA. The LS mean change from baseline to Week 24 in BASFI was similar in the CZP 200 mg Q2W (-2.36) and CZP 400 mg Q4W (-2.20) groups.

The treatment effect with CZP appeared to be greater in those with nr-SpA versus patients in the AS subpopulation. Comparative treatment improvements (that is numerically decreased) with CZP versus placebo in the mean BASFI scores were -1.14 at Week 12 and -1.58 at Week 24 in the AS subset, compared with -1.87 at Week 12 and -2.23 at Week 24 in the nr-SpA subgroup.

Placebo subjects who escaped to CZP 200 mg Q2W or CZP 400 mg Q4W at Week 16 showed an improvement in mean HAQ-DI score from between weeks 16 to 18 (-0.05 to -0.29 points for those 30 subjects escaping to CZP 200 mg Q2W; and -0.11 to -0.22 points for those 29 subjects escaping to CZP 400 mg Q4W). The escape patients maintained or improved their HAQ-DI scores through to Week 24.

The MCID (Minimal Clinical Important Difference) in HAQ-DI scores for PsA subjects is 0.3 points (Mease et al, 2004). In a supplementary analysis on Study PsA001, subjects were considered to be a HAQ-DI responder if they had a decrease of greater than or equal to 0.3 points from baseline. The percentage of HAQ-DI responders at Week 12 was greater in the combined CZP group (47.3%; 129/273) compared with placebo (21.3% [29/136]; treatment difference of 17.9% [$p < 0.001$]). The percentage of HAQ-DI responders was stable thereafter in all 3 treatment groups (at Week 24, combined CZP group response rate was 48.7% [133/273] versus 15.4% [21/136] for placebo. The proportion of HAQ-DI responders over time was similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups. By Week 24, 49.3% (68/138) of subjects in the CZP 200 mg Q2W, and 48.1% (65/135) of patients in the CZP 400 mg Q4W arm were HAQ-DI responders.

Placebo subjects who escaped to CZP 200 mg Q2W or CZP 400 mg Q4W at Week 16 had a > 20% increase in the percentage of HAQ-DI responders between weeks 16 and 18 (16.7% to 40.0% for those subjects escaping to CZP 200 mg Q2W; and 17.2% to 37.9% for those subjects escaping to CZP 400 mg Q4W group).

6.2.1.2.4. Mean change from baseline in BASDAI at weeks 12 and 24

At baseline, the mean BASDAI scores were similar between the combined CZP (6.44) and placebo (6.42) groups, and consistent with active disease. At Week 12, the LS mean change from baseline in BASDAI was statistically greater in the combined CZP group (-2.81) compared with the placebo arm (-1.22). The difference between CZP therapy (combined dose regimens) and placebo was -1.60 (95% CI -2.07, -1.12; $p < 0.001$). Likewise, at Week 24, the LS mean change from baseline in BASDAI was statistically greater in the combined CZP group (-3.05) compared with the placebo arm (-1.05). The difference between CZP therapy (combined dose regimens) and placebo was -1.99 (95% CI -2.49, -1.50; $p < 0.001$). The LS mean change from baseline to Week 24 in BASDAI was similar in the CZP 200 mg Q2W (-2.03) and CZP 400 mg Q4W (-1.96) groups. Like the BASFI results, the treatment benefit with CZP appeared to be greater in those with nr-SpA versus patients in the AS subpopulation. Comparative treatment improvements (that is numerically decreased) with CZP versus placebo in the mean BASDAI scores were -1.45 at Week 12 and -1.86 at Week 24 in the AS subset, compared with -1.84 at Week 12 and -2.21 at Week 24 in the nr-SpA subgroup.

6.2.1.2.5. Mean change from baseline in BASMI linear scale at weeks 12 and 24

At baseline, the mean BASMI linear scores were similar between the combined CZP (3.76) and placebo (3.99) groups. At Week 12, the LS mean change from baseline in BASMI was statistically greater in the combined CZP group (-0.51) compared with the placebo arm (-0.13). The difference between CZP therapy (combined dose regimens) and placebo was -0.40 (95% CI -0.60, -0.20; $p < 0.001$). Likewise, at Week 24, the LS mean change from baseline in BASMI was statistically greater in the combined CZP group (-0.52) compared with the placebo arm (-0.07). The difference between CZP therapy (combined dose regimens) and placebo was -0.44 (95% CI -0.65, -0.23; $p < 0.001$). The LS mean change from baseline to Week 24 in BASDAI was similar in the CZP 200 mg Q2W (-0.47) and CZP 400 mg Q4W (-0.41) groups. Like the other Bath indices, the treatment benefit with CZP appeared to be greater in those with nr-SpA versus patients in the AS subpopulation. Comparative treatment improvements (that is numerically decreased) with CZP versus placebo in the mean BASMI scores were -0.21 at Week 12 and -0.32 at Week 24 in the AS subset, compared with -0.60 at Week 12 and -0.59 at Week 24 in the nr-SpA subgroup.

6.2.1.2.6. MRI changes from baseline at week 12

The MRI subgroup involved a total of 153 patients: 49 (29 with AS, and 20 with nr-SpA) in the CZP 200 mg Q2W group, 54 (30 with AS, and 24 with nr-SpA) in the CZP 400 mg Q4W arm, and 50 (32 with AS, and 18 with nr-SpA) in the placebo group. The demographic and baseline disease characteristics of the MRI subpopulation were similar to that of the overall axial SpA cohort.

At baseline, the mean sacroiliac joint SPARCC scores were higher in the placebo group (17.10 points) compared with both CZP groups (10.05 points for 200 mg Q2W and 11.31 points for 400 mg Q4W). This baseline imbalance may have affected the integrity of the results interpretation. At Week 12, the LS mean change from baseline in SPARCC scores was statistically greater in the combined CZP group (-5.20) compared with the placebo arm (0.35). The difference between CZP therapy (combined dose regimens) and placebo was -5.54 (95% CI -7.90, -3.19; $p < 0.001$). The Pearson's coefficient of correlation in actual scores between readers was 0.782. The LS mean change (improvement) from baseline to Week 12 in SPARCC scores was greater in the CZP 400 mg Q4W (-6.16) compared to the CZP 200 mg Q2W dosing group (-4.93). Like the clinical indices, the treatment benefit with CZP appeared to be greater in those with nr-SpA versus patients in the AS subpopulation. Comparative treatment improvements (that is numerically decreased) with CZP versus placebo in the mean SPARCC scores were -5.06 for the AS subpopulation, compared with -6.71 at Week 12 in the nr-SpA subgroup.

At baseline, there was an imbalance in the mean spinal ASspiMRI-a scores between the treatment groups: 5.38 points in the placebo group, 5.97 points in the CZP 200 mg Q2W arm, and 3.79 points for CZP 400 mg Q4W group. In addition, patients with AS had higher mean spine ASspiMRI-a scores than those with nr-SpA, which reflects the earlier disease stage of the nr-SpA patients. At Week 12, the LS mean change from baseline in spinal ASspiMRI-a scores was statistically greater in the combined CZP group (-1.78) compared with the placebo arm (1.23. The difference between CZP therapy (combined dose regimens) and placebo was -3.00 (95% CI -4.29, --1.71; $p < 0.001$). The Pearson's coefficient of correlation in actual scores between readers was 0.731. The LS mean change (improvement) from baseline to Week 12 in spine ASspiMRI-a scores was greater in the CZP 200 mg Q2W (-3.26) compared to the CZP 400 mg Q4W dosing group (-2.75). In contrast to all of the other indices, the treatment benefit with CZP appeared to be greater in those with AS versus patients in the nr-SpA subpopulation. Comparative treatment improvements (that is numerically decreased) with CZP versus placebo in the mean spine ASspiMRI-a scores for AS patients were -3.32, compared with -2.13 in the nr-SpA subgroup.

6.2.1.2.7. Other cutcomes relating to the signs and symptoms of axial SpA

6.2.1.2.7.1. ASAS 40, ASAS 5/6 and ASAS partial remission response.

At Week 12, the percentage of subjects achieving an ASAS 40 response was greater in the combined CZP group (45.9%; 100/218) compared with the placebo arm (17.9%; 19/106). The treatment difference in comparison to placebo was 27.9% (95% CI 18.1, 37.8; p < 0.001). At 24 weeks, the percentage of subjects reaching an ASAS 40 response was higher in the combined CZP group (51.8%; 113/218) compared with placebo (15.1%; 16/106). The treatment difference between CZP and placebo was 36.7% (95% CI 27.2, 46.3; p < 0.001).

At Week 12 in the AS subpopulation, the proportion of subjects with an ASAS 40 response was higher in the combined CZP group (44.6%; 54/121) compared with control (19.3%; 11/57) - treatment difference was 25.3% (95% CI 11.8, 38.0; p < 0.001). At Week 24, the percentage of subjects with an ASAS 40 response was greater in the combined CZP group (52.9%; 64/121) compared with the placebo group (15.8%; 9/57) - treatment difference was 37.1% (95% CI 24.1, 50.1; p < 0.001).

Comparable treatment differences were seen in the nr-axSpA subpopulation. At Week 12, the percentage of subjects with an ASAS 40 response was greater in the combined CZP group (47.4%; 46/97) compared with placebo (16.3%; 8/49) - treatment difference to placebo was 31.1% (95% CI 16.7, 45.4; p < 0.001). At Week 24 the effect was continued, with the proportion of patients with an ASA S40 response being higher in the combined CZP group (50.5%; 49/97) compared with the placebo group (14.3%; 7/49) - treatment difference to placebo was 36.2% (95% CI 22.3, 50.2; p < 0.001).

The ASAS 5/6 improvement criteria have been a more recent evaluation method proposed by the ASAS group as a means of assessing potential disease-modifying drugs. The 5/6 criteria include another 2 domains (spinal mobility and serum inflammation markers) compared to the standard ASAS criteria. To achieve the ASAS 5/6 criteria a subject must demonstrate an improvement of at least 20%, and an absolute improvement of at least 10 on a 0-100 scale in at least 5 of 6 of the following domains: patient global, pain, function, morning stiffness, spinal mobility and CRP.

For the overall population at Week 12, the percentage of subjects with an ASAS 5/6 response was greater in the combined CZP group (43.1%; 94/218) compared with the placebo group (8.5%; 9/106). The difference between CZP and placebo was 34.6% (95% CI 26.2, 43.1; p < 0.001). The treatment effect continued to Week 24. The proportion of subjects with an ASAS 5/6 response at Week 24 was higher in the combined CZP group (42.2%; 92/218) compared with the control group (4.7%; 5/106). The treatment difference was 37.5% (95% CI 29.8, 45.2; p < 0.001).

At Week 12 in the AS subpopulation, the percentage of subjects with an ASAS 5/6 response was greater in the combined CZP group (42.1%; 51/121) compared with the placebo group (8.8%; 5/57). The difference between CZP and placebo was 33.4% (95% CI 21.9, 44.8; p < 0.001). At Week 24, the percentage of subjects with as ASAS 5/6 response was higher in the combined CZP group (39.7%; 48/121) compared with the placebo group (5.3%; 3/57). The treatment difference was 34.4% (95% CI 23.9, 44.9; p < 0.001).

Treatment related differences in the rate of ASAS 5/6 response were also seen in the nr-axSpA subpopulation. At Week 12, the percentage of subjects with an ASAS 5/6 response was higher in the combined CZP group (44.3%; 43/97) compared with the placebo group (8.2%; 4/49). The treatment difference was 36.2% (95% CI 23.7, 48.7; p < 0.001). The response at 24 weeks showed a similar result with the percentage of subjects achieving an ASAS 5/6 response being greater in the combined CZP group (45.4%; 44/97) compared with placebo (4.1%; 2/49). The difference between CZP and placebo was 41.3% (95% CI 29.9, 52.6; p < 0.001).

ASAS partial remission is another was to measure response. It is defined as end-of-trial improvement to a value below 20 on a 0-100 scale in each of the 4 domains (patient global, pain, function, and inflammation based on 1 of either BASDAI questions 5/6 or morning stiffness). At Week 12 in the overall axial SpA population, the percentage of subjects with partial remission was higher in the combined CZP group (23.9%; 52/218) compared with the placebo group (3.8%; 4/106). The treatment difference was 20.1% (95% CI 13.4, 26.8; $p < 0.001$). At 24 weeks, the proportion of subjects with partial remission was higher in the combined CZP group (30.3%; 66/218) compared with placebo (8.5%; 9/106) - treatment difference was 21.8% (95% CI 13.7, 29.9; $p < 0.001$). At Week 12 in the AS subpopulation, the percentage of subjects with partial remission was greater in the combined CZP group (19.8%; 24/121) compared with the placebo group (1.8%; 1/57). The difference between CZP and placebo was 18.1% (95% CI 10.2, 26.0; $p < 0.001$). At 24 weeks, the proportion of subjects with partial remission was higher in the combined CZP group (28.1%; 34/121) compared with placebo (7.0%; 4/57). The treatment difference was 21.1% (95% CI 10.7, 31.5; $p < 0.001$). Treatment differences in rate of ASAS partial remission were also seen in the nr-axSpA subpopulation. At Week 12, the percentage of subjects with partial remission was greater in the combined CZP group (28.9%; 28/97) compared with the placebo group (6.1%; 3/49). The difference between CZP and placebo was 22.7% (95% CI 11.5, 34.0; $p < 0.001$). Partial remission was maintained through to Week 24, with the proportion of subjects achieving a partial remission being higher in the combined CZP group (33.0%; 32/97) compared with the control group (10.2%; 5/49). The treatment difference was 22.8% (95% CI 10.2, 35.4; $p < 0.001$).

6.2.1.2.7.2. Change from baseline in ASAS components

The components of the ASAS are the PTGADA (Patient Global Assessment of Disease Activity), total spinal pain (past 2 days) using the NRS, BASFI, and the mean of the BASDAI questions 5 and 6 concerning morning stiffness.

Baseline morning stiffness, assessed as the mean response on a 0 to 10 NRS of BASDAI Questions 5 and 6, was 6.59 in the overall axial SpA population, and 6.60 in the AS subpopulation. No baseline differences were seen between treatment groups. These results are consistent with significant morning stiffness. Clinically meaningful improvements in morning stiffness were seen in the overall axial SpA population at 12 weeks. The mean change from baseline to Week 12 was greater in the combined CZP group (-3.15 points) compared with placebo (-1.22 points); the difference to placebo was -1.94 (95% CI -2.48, -1.41; $p < 0.001$). The same degree of improvement in morning stiffness was also observed at Week 24. The mean change from baseline to Week 24 in the overall axial SpA population was greater in the combined CZP group (-3.54 points) compared with placebo (-1.23 points); the difference to placebo was -2.25 (95% CI -2.80, -1.70; $p < 0.001$).

At baseline, the mean PTDADA was 7.00 in the overall axial SpA population, and 7.01 in the AS subpopulation, reflecting active disease. No baseline differences were seen between treatment groups. The mean improvement from baseline to Week 12 was significantly greater in the combined CZP group (-3.05 points) compared with placebo (-1.19 points); the difference to placebo was -1.71 (95% CI -2.30, -1.11; $p < 0.001$). The mean change from baseline to Week 24 in the overall axial SpA population was greater in the combined CZP group (-3.36 points) compared with placebo (-0.92 points); the difference to placebo was -2.24 (95% CI -2.83, -1.66; $p < 0.001$).

At baseline, the mean total spinal pain score (0-10) was 7.02 in the overall axial SpA population. No baseline differences were seen between treatment groups. The mean improvement from baseline to Week 12 in total spinal pain was higher in the combined CZP group (-2.97 points) compared with placebo (-1.40 points); the difference to placebo was -1.61 (95% CI -2.17, -1.04; $p < 0.001$). The mean change from baseline to Week 24 in the overall axial SpA population was greater in the combined CZP group (-3.23 points) compared with placebo (-1.33 points); the difference to placebo was -1.91 (95% CI -2.49, -1.33; $p < 0.001$).

6.2.1.2.7.3. BASDAI 50 response rate

The BASDAI 50 response is defined as an improvement of at least 50% in the BASDAI compared with baseline. By Week 1, a greater proportion of patients receiving CZP (either regimen) compared to placebo were achieving a BASDAI 50 response, and this observation continued throughout the 24-week, double-blind period in the overall axial SpA population, as well as the AS subpopulation.

The difference in response rates for the BASDAI 50 were clinically meaningful at Week 12 – 44.5% (97/218) in the combined CZP group compared to 13.2% (14/106) in the placebo arm; the difference between CZP and placebo was 31.3% (95% CI 22.1, 40.5; $p < 0.001$). The same trend was also seen at Week 24, with higher response rates in the combined CZP group (52.3%; 114/218) compared with the placebo group (17.9%; 19/106). The treatment difference was 34.4% (95% CI 24.5, 44.2; $p < 0.001$).

6.2.1.2.7.4. Enthesitis

The MASES (Maastricht Anklyosing Spondylitis Enthesitis Score) is an index that measures the extent of enthesitis at 13 defined anatomical sites, with each site scored as 0 or 1 for absence/presence of enthesitis (total score range: 0-13, higher score indicates more enthesitis). At both 12 and 24 weeks of follow-up, the mean change from baseline in the MASES score showed a statistically significant improvement for CZP-treated patients versus placebo subjects.

6.2.1.3. Other health-related outcomes

6.2.1.3.1. SF-36 domains

At baseline in the overall axial SpA population, the mean SF-36 PCS score was 32.48, and the mean SF-36 Physical Functioning (PF) domain score was 34.94. These SF-36 baseline scores represent substantial impairment in physical function compared to the US population. No differences were observed between treatment groups in SF-36 PCS and PF domain scores at baseline. Both indices of physical function showed greater improvement in CZP treated subjects in the overall axial SpA population compared with placebo subjects at Week 12. The mean change from baseline in PCS at Week 12 was 8.61 points in the combined CZP group compared with 2.36 points in the placebo arm; the difference between CZP and placebo was 6.07 points ($p < 0.001$). The mean change from baseline to Week 12 in the mean PF score was also greater in the combined CZP group (7.12 points) compared with placebo (2.27 points); treatment difference being 4.88 points ($p < 0.001$). A similar degree of improvement in physical functioning was also seen at Week 24. The mean change from baseline to Week 24 in PF score was 8.05 points in the combined CZP group compared to 1.82 points in the placebo group; the treatment related difference was 6.30 points ($p < 0.001$).

The within-subject MCID for SF-36 PCS score is 2.5 points. A subject was considered a PCS responder if the subject had an increase of > 2.5 points from baseline. In the overall axial SpA population, a higher percentage of subjects treated with CZP were SF-36 PCS responders at Week 12 (78.4% [87/111] in the CZP 200 mg Q2W group, and 73.8% [79/107] in CZP 400 mg Q4W arm) compared with the placebo group (42.5%; 45/106). The MCID responder rate was maintained through to Week 24, with a higher percentage of subjects being responders in the CZP 200 mg Q2W (76.6%; 85/111) and CZP 400 mg Q4W (70.1%; 75/107) compared with in the placebo group (27.4%; 29/106).

Mean changes from baseline in the other SF-36 domains (such as MCS, role physical, bodily pain, general health, vitality, social functioning, role emotional, mental health) by visit, or Week 12 and 24, demonstrated statistically significant improvements with CZP treatment (either regimen) versus placebo throughout the 24-week study.

6.2.1.3.2. Fatigue

Fatigue was assessed via question 1 of the BASDAI, which is a NRS for overall level of fatigue/tiredness, where 0 = none and 10 = very severe. The mean baseline fatigue score was 6.66 in the overall axial SpA population, indicating moderate fatigue. No differences were noted between the treatment groups in baseline fatigue scores. In the overall axial SpA population, the mean improvement (lower score) in fatigue from baseline to Week 12 was greater in the combined CZP group (-2.23 points) compared with placebo (-0.85 points); the treatment difference being -1.28 ($p < 0.001$). The mean change in fatigue scores from baseline to Week 24 was also greater in the combined CZP group (-2.68 points) compared with placebo (-0.85 points); the difference between CZP and placebo was -1.72 points ($p < 0.001$).

6.2.1.3.3. ASQoL

The ASQoL asks 18 health-related questions scored either as 0 or 1 (equally weighted), and has a range of 0-18. The baseline ASQoL score in the overall axial SpA population was 11.75, which represents a moderate diminishment in health related QOL. The mean change from baseline to Week 12 in the ASQoL score was -4.38 points in the combined CZP group compared with -1.31 points in the control arm. The treatment difference was -3.19 points ($p < 0.001$). At Week 24, the mean change from baseline in the ASQoL score was -5.11 points in the combined CZP group compared with -1.70 points in the control arm. The treatment difference was -3.53 points ($p < 0.001$)

6.2.1.3.4. Work productivity scale

The WPS (9 questions) assesses the impact of arthritis on a subject's productivity within and outside the home over the previous month. At baseline, the proportion of subjects employed outside the home in the combined CZP arm was 72.0% (157/218), and 63.2% (67/106) in the placebo group. The rate of employment for any treatment group did not change throughout the 24-week study. However, treatment –related improvements in productivity (within and outside the home) were observed as early as Week 4, and maintained over 24 weeks in combined CZP group compared with the placebo arm. Among employed subjects, those treated with CZP versus placebo gained additional workdays per month (Question 2), reported less work days with productivity reduced by half or more due to arthritis compared with the placebo group (Question 3), and arthritis interfered to a lower extent with work productivity (Question 4). For all subjects regardless of employment status, subjects receiving CZP compared to placebo gained more household work days per month (Question 5), reported less household work days with productivity reduced by half or more due to arthritis (Question 6), missed fewer days of family, social, or leisure activities (Question 7), had fewer days with outside help hired because of arthritis (Question 8), and reported that arthritis interfered to a lower extent with their household work productivity (Question 9). Results for the WPS showed similar improvements in productivity in the CZP 200 mg Q2W and CZP 400 mg Q4W dose groups.

6.2.1.3.5. Sleep

The MOS Sleep Scale (range: 0-100) is a validated, generic, self-administered scale measuring specific aspects of sleep. The mean baseline MOS Sleep Scale score was 49.48 in the overall axial SpA population, indicating moderately severe difficulties with sleep. No significant differences were noted between treatment groups at baseline for sleep disturbance. At both weeks 12 and 24, patients treated with CZP showed a greater reduction (that is improvement) from baseline in the MOS Sleep Scale score compared with placebo.

6.2.1.3.6. Health resource utilization

There was no statistically significant differences between the treatment groups for the number of concomitant medical procedures, health care provider consultations not foreseen by the protocol, hospitalizations, and emergency room visits with an onset during the 24-week, double-blind treatment period.

6.2.1.4. Radiographic endpoints

At 12 weeks, Study AS001 assessed the mean change from baseline, as well as the rates of radiographic progression according to the mSASSS (modified Stoke Ankylosing Spondylitis Spine Score). This tool uses plain-X-rays of the spine to evaluate the anterior vertebral edges of the cervical (C2 to T1 vertebrae) and lumbar (T12 to S1 vertebrae) spine by grading for the presence of bony changes (erosions, sclerosis and syndesmophyte formation) between 0 and 3. The total score has range of 0-72, with a higher score indicating more bony damage. There was no statistically significant difference between CZP and placebo for mean changes in the mSASSS or responder rates at 12 weeks. This outcome may reflect an insufficient period of follow-up for this efficacy variable.

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

Not applicable as only a single pivotal study has been submitted for the indication of axial SpA.

6.2.3. Evaluator's conclusions on clinical efficacy for Axial Spondyloarthritis

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

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

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

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

The pivotal trial enrolled patients with moderately active axial SpA, and demonstrated that CZP is an effective treatment in those who have either failed to respond to conventional treatment options, such as NSAIDs and/or DMARDs (SSZ or MTX). The primary efficacy endpoint of Study AS001 was the proportion of subjects who achieved an ASAS 20 response at 12 weeks, and this was reached. Overall, 63.6% (68/107) of patients treated with CZP 400 mg Q4W and 57.7% (64/111) of subjects treated with CZP 200 mg Q2W achieved this outcome versus 38.3% (41/107) of patients in the placebo group. Many secondary efficacy measures of clinical relevance such as various rates of ASAS response (20, 40, 5/6 and partial remission) at 12-24 weeks, as well as BASDAI response confirmed that CZP is effective in treating the symptoms and signs of active axial SpA. Improvements in measures of inflammation (CRP), imaging (MRI parameters), physical functioning (BASFI), spinal mobility (BASMI), and health related quality

of life were also attained with CZP therapy. Clinically meaningful improvements with CZP compared with placebo were observed in the overall axial SpA population, as well as the 2 subpopulations (AS and nr-SpA), with no significant differences between the 2 CZP dosing regimens.

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

7. Clinical safety

7.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

7.1.1. Pivotal efficacy studies

In the pivotal efficacy studies PsA001 and AS001, the following safety data was collected:

- General adverse events (AEs) were assessed by completion of the AE Case Report Form (CRF) at fortnightly intervals over 24 weeks of treatment follow-up, as well as physical examination assessments performed every 4 weeks during the active treatment phase.
- AEs of particular interest, including local injection site reactions (ISR), systemic hypersensitivity reactions, infections (overall and serious), cardiovascular events, autoimmune and demyelinating AEs and malignancies were assessed by CRF and physical examination as per the schedule for general AE evaluation.
- Laboratory tests, including haematology, biochemistry and urinalysis, were performed at baseline; weeks 1 and 2; and every 4 weeks thereafter in the 24-week double-blind treatment phase.
- Screening tests for tuberculosis were taken at baseline (Chest X-ray and PPD skin test), and a tuberculosis questionnaire was performed every 12 weeks during the studies.
- Vital signs such as blood pressure, heart and respiratory rate, and temperature were performed at each scheduled study visit
- Serum for anti-CZP antibodies was collected at baseline; and weeks 2, 4, 12, 16 and 24.

7.1.2. Pivotal studies that assessed safety as a primary outcome

No studies assessed safety as the primary outcome.

7.1.3. Dose-response and non-pivotal efficacy studies

No dose-response study was provided in this submission. The 2 supporting, non-pivotal efficacy studies (C87040 and C87044) provided safety data on general AEs, blood parameters (haematology and clinical chemistry), physical examination, ECG parameters, urinalysis and autoantibodies.

7.1.4. Other studies evaluable for safety only

Nil

7.1.5. Pivotal studies that assessed safety as a primary outcome

No study in the CZP inflammatory arthritis program has assessed safety as the primary outcome.

7.1.6. Patient exposure

7.1.6.1. Study PsA001

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

7.1.6.2. Study AS001

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

7.1.6.3. Study C87040

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

7.1.6.4. Study C87044

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

7.2. Adverse events

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

7.2.1.1. Pivotal studies

7.2.1.1.1. Study PsA001

The overall incidence of treatment emergent AEs was 62.3% (207/332) in the combined CZP group and 67.6% (92/136) in the placebo arm. The overall incidence of AEs was similar between the 2 CZP regimens (68.1% [94/138] in 200 mg Q2W group, and 71.1% [96/135] in the 400 mg Q4W cohort). In the CZP-treated group of patients, AEs were most commonly reported in the SOC of infections and infestations (35.8% [119/332] versus 38.2% [52/136] in

the placebo group), followed by the SOCs of investigations (14.2% [47/332] versus 10.3% [14/136] in the control arm), gastrointestinal disorders (13.6% [45/332] versus 14.0% [19/136] in the placebo group), and general disorders and administration site conditions (12.3% [41/332] versus 8.1% [11/136] in the control arm). The most commonly reported individual types of AE (by Preferred Term [PT]) in the combined CZP group were nasopharyngitis (8.7%; 29/332) and upper respiratory tract infection (7.8%; 26/332). Of the common occurring AEs (that is greater than or equal to 2% incidence in the combined CZP cohort), those that occurred in a higher percentage of subjects treated with CZP compared with the placebo group (difference of greater than or equal to 2%) were upper respiratory tract infection (7.8% versus 5.1%[7/136]), increased serum ALT (3.6% [12/332] versus 1.5% [2/136]), increased serum AST (3.0% [10/332] versus 0.7% [1/136]), headache (3.6% [12/332] versus 1.5% [2/136]), and sinusitis (2.7% [9/332] versus 0.7% [1/136]). The incidences of the most commonly reported AEs (by SOC) were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups with the exceptions of the SOCs of gastrointestinal disorders (18.8% [26/138] and 13.3% [18/135], respectively), and general disorders and administration site conditions (9.4% [13/138] and 19.3% [26/135], respectively). The incidence of individual events were generally similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups with the exception of nasopharyngitis, which was reported in 13.0% (18/138) of subjects in the CZP 200 mg Q2W group and 6.7% (9/135) of subjects in the CZP 400 mg Q4W group.

7.2.1.1.2. Study AS001

The overall incidence of treatment emergent AEs was higher at 70.4% (193/274) in the combined CZP group compared to 62.6% (67/107) in the placebo arm. The overall incidence of AEs was similar between the 2 CZP dose groups (76.6% [85/111] for 200 mg Q2W, and 74.8% [80/107] for 400 mg Q4W). Most AEs (> 80% in all 3 treatment groups) were judged to be of mild to moderate severity. Most AEs (> 66% in all 3 treatment groups) were considered to be unrelated to study medication.

In the combined CZP group, the most frequently reported type of AEs (at least 2% incidence) by SOC were infections and infestations (34.7% [95/274] versus 23.4% [25/107] in the placebo group), followed by gastrointestinal disorders (13.9%[38/274] versus 14.0% [15/107] in the placebo group), and general disorders and administration site conditions (12.4% [34/274] versus 7.5% [8/107] in the placebo group).

The most commonly reported individual types of AEs in the combined CZP cohort were nasopharyngitis (8.8%; 24/274), headache (6.2%; 17/274), and increased blood creatine phosphokinase (5.1%; 14/274). Of the common individual type of AEs, the incidence was similar between the combined CZP and placebo groups with the exception of raised blood creatine phosphokinase (5.1% [14/274] versus 1.9% [2/107]), and nasopharyngitis (8.8% [24/274] versus 6.5% [7/107]), where the incidence was > 2% higher in the combined CZP group compared to placebo. The most frequently reported AEs by SOC, as well as individual types of AEs, showed the same pattern in the 2 subpopulations (AS and nr-SpA) as the overall axial SpA cohort.

7.2.1.2. Other studies

7.2.1.2.1. Study C87040

The overall number and incidence of treatment emergent AEs was similar in each of the 3 treatment groups: 71.7% (43/60) subjects in the CZP 200 mg group experienced 156 AEs, 70.2% (40/57) of patients in the CZP 400 mg arm reported 125 AEs, and 70.7% (41/58) of subjects in the placebo arm recorded 133 AEs. The most frequently reported AEs by SOC (overall incidence greater than or equal to 20% of subjects) were infections and infestations (38.3%; 67/175), nervous system disorders (22.9%; 40/175) and general disorders and administration site conditions (21.1%; 37/175). All of the most common AEs by SOC occurred at similar frequency in active versus control treatment. The most commonly reported infection

was nasopharyngitis, which was recorded in 17.2% (10/58) of placebo patients, 6.7% (4/60) of subjects given CZP 200 mg Q2W, and 21.1% (12/57) of patients in the CZP 400 mg Q2W arm. Headache was the most common nervous system disorder recorded in 15.5% (9/58) of subjects in the placebo arm, 21.7% (13/60) of patients in the CZP 200ng group, and 14.0% (8/57) of subjects in the CZP 400 mg cohort.

7.2.1.2.2. Study C87044

Fewer subjects reported AEs during the re-treatment period (41.2% [14/34] of subjects given CZP 200 mg Q2W recorded 36 AEs; and 48.6% [18/37] of patients receiving CZP 400 mg Q2W experienced 36 AEs) compared to the initial 12-week treatment phase (67.6% [23/34] of subjects given CZP 200 mg Q2W recorded 93 AEs; and 64.9% [24/37] of patients receiving CZP 400 mg Q2W experienced 76 AEs). The most frequently reported AEs by SOC during the re-treatment period were infections (21.1%; 15/71), nervous system disorders (12.7%; 9/71) and skin and subcutaneous disorders (11.3%; 8/71). Consistent with the primary treatment period, nasopharyngitis and headache were the 2 most commonly reported individual types of AEs.

7.2.2. Treatment-related adverse events

7.2.2.1. Pivotal studies

7.2.2.1.1. Study PsA001

Treatment related AEs were those considered by the site investigator to be "related", "possibly related", or those with missing responses. The incidence of treatment related AEs were similar between the combined CZP (25.9%; 86/332) and placebo group (27.2%; 37/136), as well as between the CZP 200 mg Q2W (28.3%; 39/138) and CZP 400 mg Q4W groups (30.4%; 41/135).

The incidences of treatment related AEs (by SOC) that occurred in a higher percentage of subjects treated with CZP compared with placebo (difference of greater than or equal to 2%) were in the SOC of general disorders and administration site conditions (7.8% [26/332] versus 3.7% [5/136]), which was largely attributable to the higher incidence of injection site reactions. The incidences for all other SOCs were similar to or lower in the CZP treated subjects than the placebo group. In the CZP treated subjects, the most commonly reported AEs (by PT) were upper respiratory tract infection (2.1% [7/332] versus 2.2% [3/136] in the placebo group), and increased serum ALT values (2.1% [7/332] versus 1.5% [2/136] in the placebo group).

The overall incidence of treatment related AEs was similar between the CZP 200 mg Q2W (28.3%; 39/138) and CZP 400 mg Q4W groups (30.4%; 41/135). Differences (greater than or equal to 2%) in the incidences of treatment related AEs (by SOC) between the CZP 200 mg Q2W and CZP 400 mg Q4W groups were observed in the SOCs of general disorders and administration site conditions (7.2% [10/138] and 11.1% [15/135], respectively), investigations (8.0% [11/138] and 5.9% [8/135], respectively), nervous system disorders (3.6% [5/138] and 0.7% [1/135], respectively), blood and lymphatic system disorders (0 and 3.7% [5/135], respectively), and gastrointestinal disorders (0.7% [1/138] and 3.0% [4/135], respectively). Incidences of the most common treatment related AEs (by PT) were similar between the CZP 200 mg Q2W and CZP 400 mg Q4W groups.

The pre-defined AEs of special interest in Study PsA001 were:

- Local injection site reactions (ISRs), as determined by the investigator, which were reported in 6.6% (22/332) of subjects in the combined CZP group and 2.2% (5/136) of patients in the placebo arm. Subjects receiving CZP 400 mg Q4W had a higher incidence of ISRs (3.0%; 4/135) compared with those receiving CZP 400 mg Q4W (1.4%; 2/138). None of the local ISRs were considered serious.
- The incidence of acute systemic hypersensitivity reactions was very low (1 subject in the placebo group (0.9% of 107), as was the incidence of delayed systemic hypersensitivity reactions (1.5% [5/332] in the combined CZP group, and 0.7% [1/136] in the placebo

group). The overall incidence of systemic hypersensitivity reactions was similar in the CZP 200 mg Q2W group (1.4%; 2/138) and CZP 400 mg Q4W dosing arm (1.5%; 2/135).

- Cardiovascular events can be divided into cardiac and vascular AEs. The incidence of AEs in the cardiac disorders SOC was low in the combined CZP (1.5%; 5/332) and placebo (0.7%; 1/136) groups. The incidence of cardiac AEs was similar between the 2 CZP regimens (2.2% [3/138] for 200 mg Q2W, and 1.5% [2/135] for 400 mg Q4W groups. No individual type of cardiac AE (by PT) was reported in more than 1 subject. Four serious cardiac AEs were reported (all in patients receiving CZP) – acute myocardial infarction and fatal cardiac arrest (200 mg Q2W); as well as unstable angina and cerebrovascular accident (400 mg Q4W). Hypertension (including new onset or worsening of pre-existing hypertension) was the most commonly reported vascular AE in all groups, with little difference in incidence between the placebo (3.7%; 5/136) and CZP treatment groups (2.9% [4/138] in the 200 mg Q2W group, and 1.5% [2/135] in the 400 mg Q4W arm. All other types of vascular AEs (for example hypotension, haematoma and hot flush) were reported as single cases.
- No autoimmune or demyelinating disease AEs were recorded in the 24-week period of Study PsA001. However, 1 subject (64-year-old female) treated with CZP 200 mg Q2W recorded an AE of subacute cutaneous lupus 45 days after starting CZP. The AE was considered to be moderate in intensity, and possibly related to study medication. Concomitant medications included meloxicam, MTX, omeprazole, and chloramphenicol. The AE had not resolved by the end of the 24-week treatment period, and no interruption of study medication was recorded.

7.2.2.1.2. Study AS001

The overall incidence of treatment related AEs was higher in the combined CZP group (33.2%; 91/274) compared with the placebo arm (20.6%; 22/107). The difference is mainly attributable to a higher incidence of infections, and administration site conditions (particularly, injection site erythema) in CZP treated subjects compared to placebo.

No overall difference in incidence was seen in treatment related AEs between the CZP 200 mg Q2W (36.9%; 41/111) and CZP 400 mg Q4W groups (33.6%; 36/107). However, a higher incidence of treatment related AEs in the SOC of General disorders and administration site conditions was seen in the CZP 200 mg Q2W group (12.6%; 14/111) compared with the CZP 400 mg Q4W group (5.6%; 6/107).

The pre-defined AEs of special interest in Study AS001 were:

- Local ISRs were reported in 6.6% (18/274) of subjects in the combined CZP group and 0.9% (1/107) of patients in the placebo arm. The most frequently reported type of ISR (by Preferred Term) was injection site erythema (2.6% [7/274] in the combined CZP group compared with 0% in the placebo group). Subjects receiving CZP 200 mg Q2W had a higher incidence of ISRs (9.0%; 10/111) compared with those receiving CZP 400 mg Q4W (4.7%; 5/107). None of the local hypersensitivity reactions were considered serious.
- The incidence of acute systemic hypersensitivity reactions was low (1 AE of hypersensitivity in the CZP 400 mg Q4W group (0.9% of 107), and 1 AE of circulatory collapse in the placebo group (0.9% of 107), as was the incidence of delayed systemic hypersensitivity reactions (1.5% [4/274] in the combined CZP group, and 1.9% [2/107] in the placebo group). The overall incidence of systemic hypersensitivity reactions was similar in the CZP 200 mg Q2W group (2.7%; 3/111) and CZP 400 mg Q4W dosing arm (1.9%; 2/107).
- Autoimmune AEs were rare although there was a single case of pustular psoriasis reported in a 32-year-old female treated with CZP 200 mg Q2W. The AE was not considered serious, and was judged to be possibly related to CZP. The AE began 7 days after their first injection of CZP and was unresolved. CZP was interrupted but the subject did not dropout.

- Cardiovascular events can be divided into cardiac and vascular AEs. The incidence of AEs in the cardiac disorders SOC was low in the combined CZP (1.8%; 5/274) and placebo (0.9%; 1/107) groups. The incidence of cardiac AEs was similar between the 2 CZP regimens (1.8% [2/111] for 200 mg Q2W, and 1.9% [2/107] for 400 mg Q4W groups. No individual type of cardiac AE (by Preferred Term) was reported in more than 2 subjects. There were no AEs of cardiac failure. Only 1 cardiac AE was rated as serious (supraventricular tachycardia in a patient receiving CZP 400 mg Q4W). Hypertension was the most commonly reported vascular AE in all groups, with little difference in incidence between the placebo (3.7%; 4/107) and CZP treatment groups (2.7% [3/111] in the 200 mg Q2W group, and 1.9% [2/107] in the 400 mg Q4W arm. All other types of vascular AEs (for example hypotension, haematoma and hot flush) were reported in 2 or less subjects.

7.2.2.1.3. Other studies

7.2.2.1.3.1. Study C87040

Treatment related AEs were recorded at a higher frequency in the CZP 200 mg group (35.0%; 21/60) compared to the CZP 400 mg arm (26.3%; 15/57) and placebo group (24.1%; 14/58). This finding is mainly attributable to a higher incidence of general disorders and administration site conditions (by SOC) being recorded in the CZP 200 mg group (16.7% [10/60] versus 5.2% [3/58] for placebo, and 7.0% [4/57] for CZP 400 mg). When considered further (by Preferred Term), this is mainly due to 4 reports of fatigue (versus 0 in the other 2 treatment groups) and 3 cases of ISR (versus 0 with placebo, and 1 with CZP 400 mg). Infections 9.1%; 16/175) and nervous system disorders (8.0% [14/175]; mainly, headache [6.3%; 11/175]) were the 2 most commonly reported treatment related AEs, affecting similar numbers in each of the 3 groups.

AEs occurring within 2 hours of injection was a pre-defined AE of special interest in Study C87040. A total of 7 patients (1 treated with placebo, 4 with CZP 200 mg, and 2 with CZP 400 mg) reported various types of AEs within 2 hours of SC injection of study treatment. Three patients who received CZP 200 mg recorded injection site irritation as an AE.

7.2.2.1.3.2. Study C87044

The incidence of treatment related AEs was lower during the re-treatment period (14.7% [5/34] of subjects given CZP 200 mg Q2W; and 18.9% [7/37] of patients receiving CZP 400 mg Q2W) compared to the initial 12-week treatment phase (32.4% [11/34] of subjects given CZP 200 mg Q2W; and 21.6% [8/37] of patients receiving CZP 400 mg Q2W). The most frequently reported AEs by SOC during the re-treatment period did not differ from the initial 12-week treatment phase.

7.2.3. Deaths and other serious adverse events

7.2.3.1. Pivotal studies

7.2.3.1.1. Study PsA001

Two deaths were recorded during the 24-week, double-blind treatment period of Study PsA001. Both fatalities were considered to be unrelated to study medication. A 50-year-old white male in the CZP 200 mg Q2W group died of a cardiac arrest due to atherosclerotic cardiovascular disease. The death occurred 74 days after starting CZP. The subject collapsed after jogging and could not be revived through cardiopulmonary resuscitation. Toxicological tests were negative. There was no evidence of trauma or criminal activity that led to his death. Autopsy revealed atherosclerotic cardiovascular disease. The subject did not have any history of or risk factors for coronary artery disease (apart from a high serum cholesterol at screening). He had been taking low dose aspirin once daily for approximately 7 years for cardiac prophylaxis. There was no evidence of abnormal ECG at screening. Laboratory assessments performed during the study were unremarkable, except for an elevated serum creatine phosphokinase at Week 4 (203 U/L; normal range: 0 to 174 U/L), which returned to normal 4 weeks later (112 U/L). Sudden death occurred in a 42-year-old white female who received CZP 400 mg Q4W for 60 days. The cause of

death was unknown, and no autopsy was performed. The family refused to provide additional information after her death. The patient was a non-smoker with a history of well-controlled hypertension, and obese (BMI of 29.4 kg/m^2). She had been taking low dose aspirin once daily for approximately 7 years for cardiac prophylaxis. There was no evidence of an abnormal ECG at screening.

In addition to the 2 deaths, 1 patient (31 year old female given CZP 400 mg Q4W) developed malignancy (early stage cervical carcinoma) during the 24-week trial. The patient withdrew from the study. Another subject (54 year old female receiving CZP 200 mg Q2W) developed a pre-malignant condition, reported as an SAE of vulval dysplasia (onset 72 days after commencing CZP).

The overall incidence of SAEs was slightly higher in the combined CZP group (6.6%; 22/332) compared to the placebo arm (4.4%; 6/136). In the combined CZP cohort, SAEs were reported most often in the SOC of infections and infestations (1.2% [4/332] versus 0.7% [1/136] for placebo). For all other SOCs, the incidence of SAEs was < 1%. No individual type of SAE (by Preferred Term) was reported for more than 1 subject. The overall incidence of SAEs was somewhat lower in the CZP 200 mg Q2W group (5.8%; 8/138) compared with the CZP 400 mg Q4W arm (9.6%; 13/135), although there were no notable differences in incidences for SOCs and Preferred Terms between the 2 CZP dosing groups.

7.2.3.1.2. Study AS001

There were no recorded deaths in Study AS001, and no malignancies were reported in any subjects.

The overall incidence of SAEs was the same in the combined CZP and placebo groups (both 4.7% - 13/274 for CZP combined, and 5/107 for placebo). No subject reported more than 1 SAE. The types of SAEs observed in subjects who received CZP included 2 cases of cholelithiasis (both received 400 mg Q4W), and the rest were single cases of supraventricular tachycardia, appendicitis, oesophageal candidiasis, Haemophilus infection, laryngitis, raised GGT level, retinal vein occlusion, hypersensitivity reaction, renal colic, nasal polyps and Morton's neuroma. Overall, serious infections were recorded in 3 subjects (1.1%) in the combined CZP group (2 subjects in the CZP 200 mg Q2W group, and 1 subject in the placebo arm who escaped to CZP 200 mg Q2W therapy). No patients in the placebo group developed an infection related SAE, although 1 person was reported to have had a drug hypersensitivity reaction. No rare or opportunistic infections (including tuberculosis) were reported in Study AS001.

7.2.3.2. Other studies

7.2.3.2.1. Study C87040

No deaths or malignancies occurred in this trial. The overall incidence of SAEs was higher in the CZP 400 mg group (8.8%; 5/57) than the CZP 200 mg (3.3%; 2/60) and placebo groups (1.7%; 1/58). The SAE in the patient receiving placebo involved haemorrhagic diarrhoea. Two patients receiving CZP 400 mg Q2W became pregnant. Both patients underwent elective abortion, and 1 subject (who discontinued treatment) subsequently became pregnant again in the post-treatment period. Three CZP treated patients experienced 4 infection related SAEs including 1 case of disseminated tuberculosis, 2 reports of gastroenteritis and 1 case of urinary tract infection. The other SAEs affecting CZP treated patients involved anxiety (2 reports), contusion, and flare of skin psoriasis.

7.2.3.2.2. Study C87044

No deaths occurred during the 12 week treatment period but 1 subject died of cerebral haemorrhage 18 weeks after taking his last dose of CZP in Study C87044. The death was considered unrelated to CZP. No patients developed malignancy in Study C87044. No SAEs were recorded during this re-treatment study. However, 1 patient scheduled to enter into this trial

failed screening after registering a positive PPD test consistent with latent tuberculosis after receiving CZP in Study C87040.

7.2.4. Discontinuation due to adverse events

7.2.4.1. Pivotal studies

7.2.4.1.1. Study PsA001

The overall incidence of AEs leading to permanent study medication discontinuation was low in Study PsA001 affecting 3.0% (10/332) of patients in the combined CZP group, and 1.5% (2/136) of those in the placebo arm. Apart from 2 cases of raised serum transaminases affecting subjects given CZP 200 mg Q2W, no individual type of AE leading to study withdrawal was reported for more than 1 subject. The additional withdrawals from CZP included pregnancy, cerebrovascular accident, and sinusitis. One patient each in the placebo group withdrew because of allergic oedema and dyspnoea.

The overall incidence of AEs leading to temporary study medication discontinuation was similar between the combined CZP (16.9%; 56/332) and the placebo groups (14.0%; 19/136), as well as between the 2 CZP dose regimens (21.7% [30/138] for 200 mg Q2W, and 18.5% [25/135] for 400 mg Q4W). The most common AEs leading to temporary study medication discontinuation in all groups were in the SOC of infections and infestations (10.5% [35/332] in the combined CZP group, and 8.8% [12/136] in the placebo arm). There were no notable differences in incidences (greater than or equal to 2% difference) for SOCs and Preferred Terms between all 3 of the treatment groups.

7.2.4.1.2. Study AS001

The incidence of AEs leading to discontinuation was low and similar between the combined CZP (2.2%; 6/274) and placebo groups (1.9%; 2/107). There was slightly higher incidence of AEs leading to withdrawal in the CZP 400 mg Q4W group (3.7%; 4/107) versus the CZP 200 mg Q2W arm (1.8%; 2/111), although the absolute numbers are small. Two infections (both in the CZP 200 mg Q2W group) led to premature discontinuation – folliculitis and upper respiratory tract infection. The 4 AEs in patients receiving 400 mg Q4W were cholelithiasis, hypersensitivity reaction, increased CRP and gynaecomastia.

7.2.4.1.3. Other studies

7.2.4.1.3.1. Study C87040

The incidence of AEs leading to discontinuation was similar between the CZP (3.3% [2/60] for 200 mg Q2W, and 5.3% [3/57] for 400 mg Q2W) and placebo groups (5.2%; 3/58). One patient in each of the 3 treatment groups discontinued due to psoriasis, which is really a treatment failure that has been coded as an AE. The 2 other placebo subjects permanently discontinued due to individual reports of haemorrhagic diarrhoea and vertigo. Two of the CZP treatment discontinuations were pregnancy (subject receiving CZP 400 mg Q2W), and a patient taking CZP 200 mg Q2W experiencing urinary tract infection and gastroenteritis. One patient in the CZP 400 mg group developed an SAE of disseminated tuberculosis before Week 12 after having received all 6 CZP injections between weeks 0 and 10.

AEs requiring temporary discontinuation of study medication were reported in 1 individual in the placebo and CZP 200 mg groups, and 3 subjects (5.3%) in the CZP 400 mg arm. Most of the temporary treatment discontinuations were due to intercurrent infection.

7.2.4.1.3.2. Study C87044

No patients withdrew from CZP in this re-treatment trial because of an AE.

7.3. Laboratory tests

7.3.1. Liver function

7.3.1.1. Pivotal studies

7.3.1.1.1. Study PsA001

Treatment with CZP resulted in greater mean changes in liver function tests compared to placebo, specifically, mean increases in serum transaminases (AST and ALT). For AST, the combined CZP group had mean increase from baseline at each assessment (means ranged 1.2 to 4.1 U/L), whereas the placebo group had mean decreases from baseline at each assessment (means ranged from -0.8 to -5.3U/L). A similar trend was observed for ALT values with mean increases from baseline in the combined CZP group (means ranged 2.9 to 7.1U/L) and mean decreases from baseline in the placebo group (means ranged from -9.1 to 0.6 U/L). Placebo subjects escaping to CZP had mean increases from baseline in AST and ALT after starting CZP treatment. Similar trends were not observed for alkaline phosphate, GGT or bilirubin.

Treatment with CZP also resulted in a higher frequency of shifts from normal or low at baseline to high post-baseline (corresponding to the maximum post-baseline value) than with placebo for AST (15.7% [52/331] versus 7.4% [10/135]), and ALT (19.6% [65/331] versus 13.3% [18/135]). Elevations in AST and ALT have been observed with other anti-TNF medications used in patients with PsA. Most of the elevations in AST and ALT were non-significant shifts (that is from normal at baseline to a post-baseline values of > 1 to < 2xULN). There was no difference in incidence and pattern of abnormal liver function tests between the 2 CZP dosing regimens.

Significant elevations in AST or ALT (that is greater than or equal to 3xULN) were greater in the combined CZP group (3.6%; 12/332) compared with placebo (2.2%; 3/136). Many of the subjects with elevations in serum transaminases were taking concurrent MTX, and 3 receiving CZP were receiving concomitant isoniazid for treatment of latent tuberculosis. A greater proportion of subjects in the combined CZP group had an elevation in bilirubin compared with the placebo group (greater than or equal to 1xULN: 4.8% [16/332] versus 2.9% [4/136]). Three subjects (all in the CZP 400 mg Q4W group) had elevations of serum bilirubin greater than or equal to 1xULN in conjunction with greater than or equal to 3xULN increase in either AST or ALT. Of note, 1 subject (19 year old male) treated with CZP 200 mg Q2W without concomitant MTX, had elevation of ALT and AST of up to 3xULN starting at Week 16 which persisted through to Week 20, before CZP was withdrawn and reported as an AE.

7.3.1.1.2. Study AS001

There was a higher rate of post-baseline shifts from normal to high in the combined CZP group versus placebo for AST (2.6% [7/274] versus 0.9% [1/107]), ALT (4.7% [13/274] versus 0.9% [1/107]), and bilirubin (1.8% [5/274] versus 0%). The majority of maximal increases in serum AST and ALT were in the category of < 2xULN. When clinically relevant shifts (that is, > 3xULN) were assessed, the percentage of AST or ALT elevations in the combined CZP group was 1.8% (5/274) compared with 0.9% (1/107) for placebo. One patient treated with CZP 200 mg Q2W had an elevation of serum transaminases > 10xULN. There were no cases of elevated serum bilirubin (> 1xULN) in conjunction with ALT or AST > 3xULN. Two SAEs of increased AST were reported in the CZP 200 mg Q2W group, 1 patient of which developed a concurrent > 3xULN increase in ALT. One SAE of increased GGT was reported in the CZP 200 mg Q2W group, but the rise in GGT was considered unrelated to CZP, the subject was asymptomatic and he completed the 24-week study (26 year old male with AS, and no history of alcohol use).

7.3.1.2. Other studies

7.3.1.2.1. Studies C87040 and C87044

In Study C87040, 3 CZP treated subjects (2 received 400 mg Q2W, and 1 was given 200 mg Q2W) developed new onset, transient increases in serum GGT at the Week 12 assessment, all of which resolved during the safety follow-up phase (off therapy). No abnormalities of liver function tests were identified in the re-treatment Study C87044.

7.3.2. Kidney function

7.3.2.1. Pivotal studies

7.3.2.1.1. Study PsA001

Treatment with CZP was associated with a slightly higher frequency of shifts from normal or low at baseline to high post-baseline (corresponding to the maximum post-baseline value) in serum creatine than with placebo (5.1% [17/331] versus 3.0% [4/134]), but this was not of clinical relevance. One patient in the placebo group had 2 recorded AEs related to renal function (increased serum creatine and blood urea nitrogen; occurring concurrently) that quickly resolved without specific intervention. In addition, no clinically meaningful changes in urinalysis over time were observed.

7.3.2.1.2. Study AS001

A total 5 placebo treated patients (4.7% of 107) and 4 CZP treated subjects (1.5% of 274) developed transient increases in blood urea nitrogen during Study AS001. No clinically meaningful changes in urinalysis parameters over time were observed.

7.3.2.1.3. Other studies: Studies C87040 and C87044

No patients developed rises in serum creatinine or blood urea nitrogen, as well as abnormalities on urinalysis.

7.3.3. Other clinical chemistry

7.3.3.1. Pivotal studies

7.3.3.1.1. Study PsA001

A higher proportion of subjects treated with CZP (26.3%; 87/331) developed transient elevations in serum creatine kinase than those receiving placebo (15.6%; 21/135). All results returned to normal within 2 weeks of the abnormality being detected. One patient treated with CZP developed a transient increase in serum creatine kinase to 3474 U/L, which resolved without any associated AEs. Patients receiving CZP also recorded a higher incidence of new elevations in serum cholesterol (29.9% [99/331] versus 17.8% [24/135] for placebo). Other significant changes in blood chemistry (for example hypokalaemia and hypocalcaemia) were sporadic and affected no more than 3 patients in total, and were considered unrelated to study medication.

7.3.3.1.2. Study AS001

No patients in this trial developed significantly abnormal laboratory values for the following parameters: sodium, potassium, calcium, urate, chloride, bicarbonate and total serum cholesterol. However, abnormalities were reported for both the placebo and combined CZP groups in elevations in serum creatine phosphokinase (3.7% versus 4.4%, respectively), and glucose (1.9% versus 1.5%, respectively).

7.3.3.2. Other studies

7.3.3.2.1. Studies C980404 and C87044

Both trials did not reveal any significant changes in serum chemistry.

7.3.4. Haematology

7.3.4.1. Pivotal studies

7.3.4.1.1. Study PsA001

Haematology values at baseline were similar across the treatment groups. Regardless of treatment allocation, mean (and median) changes over time were small, and were not of clinical significance.

The proportion of subjects experiencing shifts from normal at baseline, to high or low post-baseline values, in any haematology parameter were similar between the treatment groups with few exceptions. A greater percentage of subjects in the combined CZP versus placebo group shifted from normal or high at baseline to low post-baseline for total leukocyte count (16.9% [56/331] for CZP versus 5.9% [8/135] for placebo), and neutrophils (8.5% [28/331] for CZP versus 0.7% [1/135] for placebo). However, a lower proportion of subjects in the combined CZP group shifted from normal or high at baseline to low post-baseline values for haemoglobin (7.3% [24/331] for CZP versus 22.2% [30/135] for placebo) and lymphocyte count (3.9% [13/331] for CZP versus 9.6% [13/135] for placebo). Shifts to low neutrophils and lymphocytes were generally transient and returned to normal values spontaneously.

Five subjects experienced 7 AEs relating to abnormal haematology values which included 2 subjects with marked thrombocytopenia, 1 patient having 2 AEs relating to significant neutropenia, another subject with neutrophilia (2 AEs), and 1 case of increased eosinophil count increased. All 7 of these AEs occurred in patients receiving CZP. The 2 AEs of thrombocytopenia were considered to be possibly related to CZP, but the remaining 5 AEs were judged to be not related.

7.3.4.1.2. Study AS001

There were no SAEs of bone marrow dysfunction reported during the 24-week, double-blind treatment period of Study AS001. Reports of anaemia (1.1% [3/274] in combined CZP group versus 3.7% [4/107] in placebo group), leukopenia (1.1% [3/274] in the combined CZP group versus 0% in the placebo arm), and neutropenia (1.1% [3/274] in the combined CZP group versus 0% in the placebo group were recorded. No thrombocytopenia AEs were reported in the study.

All of the above haematology AEs were rated as non-serious, mild or moderate in severity, and transient. None of these AEs led to permanent discontinuation from study medication.

7.3.4.2. Other studies

7.3.4.2.1. Studies C87040 and C87044

One patient treated with CZP 200 mg Q2W in Study C87040 developed moderate severity (grade 3) neutropenia during treatment, but the subject continued CZP and the neutrophil count normalized. No other significant haematology finding (mean change or individually significant events) occurred in either of the skin psoriasis trials.

7.3.5. Anti-CZP antibody formation

7.3.5.1. Pivotal studies

7.3.5.1.1. Study PsA001

A positive anti-CZP antibody level was defined as > 2.4 units/mL measured on at least 1 visit. Serum samples for anti-CZP antibodies were collected at baseline; and weeks 2, 4, 12, 16 and 24. At baseline, 3 subjects (2 in the placebo group, and 1 in the CZP 200 mg arm) tested positive for anti-CZP antibodies, which is unexpected but reflects the assay variability and low level cross-reactivity of the test to other endogeneous antibodies. The percentage of subjects developing anti-drug antibodies was similar between the 2 CZP dose regimens (11.6% [16/138] of subjects

in the 200 mg group, and 11.9% [16/135] of patients in the 400 mg arm), but higher than that recorded in the placebo group (3.7%; 5/136). The first occurrence of anti-CZP antibodies was greatest at Week 12 (6.5% [9/138] of patients in the CZP 200 mg group, and 8.1% [11/135] of subjects in the CZP 400 mg cohort), but the percentage of subjects who did test positive for anti-CZP antibodies did incrementally increase over time (between weeks 12 and 24) in the double-blind treatment period. Four placebo subjects who escaped to CZP also tested positive for anti-CZP antibodies at Week 24, however, 1 of those patients did so at baseline. A total of 27 subjects (75.0% of 36) exposed to CZP tested positive for anti-CZP antibodies and in total they reported 33 AEs, which is a higher frequency than the anti-drug antibody negative CZP-exposed patient group (60.8%; 180/296). The only individual type of AE reported at a higher rate in the anti-CZP antibody positive subjects was nasopharyngitis or pharyngitis (6 subjects in total). The frequency of drug-related AEs was also slightly higher in the antibody positive subgroup (33.3% [12/36] versus 25.0% [74/296] for CZP exposed, antibody negative subjects), however, the rates of SAEs and discontinuations due to AEs was similar in the antibody positive and negative subgroups of CZP treated patients.

7.3.5.1.2. Study AS001

A positive anti-CZP antibody level was defined as > 2.4 units/mL measured on at least 1 visit. Serum samples for anti-CZP antibodies were collected at baseline; and weeks 2, 4, 12, 16 and 24. At baseline, no subjects tested positive for anti-CZP antibodies. The percentage of subjects developing anti-drug antibodies was low in all treatment groups: 3.6% (3/83) of subjects in the CZP 200 mg group, 1.2% (1/83) of patients in the CZP 400 mg arm, and 1.2% (1/81) patients in the placebo group. One additional patient initially treated with placebo who escaped to CZP 400 mg after Week 16, also developed positive anti-CZP antibodies at Week 24. Apart from the 1 escape treatment patient, all subjects developed their first occurrence of anti-CZP antibodies at Week 12. A total of 4 AEs were reported in the CZP-exposed subjects (n = 274) after the onset of positive antibody status. Two of these AEs were considered to be drug related, and none were serious or severe.

7.3.5.2. Other studies

7.3.5.2.1. Study C87040

Serum samples for anti-CZP antibodies were taken at screening and every 4 weeks during the 12-week active treatment phase, as well as the safety follow-up phase. Less than 5% of subjects treated with CZP (5.0% [3/60] in the 200 mg group, and 3.5% [2/57] in the 400 mg arm) during the 12-week treatment period of Study C87040 tested positive for anti-CZP antibodies (that is at least 1 serum sample by screening ELISA assay > 2.4 units/mL). However, this increased to approximately 30% during the treatment-free follow-up period of 24 weeks (28.7% [17/60] in the 200 mg group, and 31.6% [18/57] in the 400 mg arm). The anti-CZP antibodies were directed against the CZP idiotype, and approximately one third (10/31 tested) had neutralizing activity in an in vitro assay. The presence of anti-CZP antibodies was not associated with increased incidence or type of AE.

7.3.5.2.2. Study C87044

Like Study C87040, serum samples for anti-CZP antibodies were taken at screening and every 4 weeks during the 12-week active treatment phase, as well as the safety follow-up phase. The majority of subjects remained anti-CZP antibody negative throughout this re-treatment study (63.4%; 45/71 - 20 subjects in the 200 mg group, and 25 patients in the 400 mg arm). However, 15 subjects (6 in the 200 mg group, and 9 in the 400 mg arm) developed transient positive anti-CZP antibodies, and 11 patients developed persistently positive anti-drug antibodies (8 subjects in the 200 mg arm, 3 in the 400 mg group). The presence of anti-CZP antibodies was not associated with AEs, but appeared to result in a lack or loss of re-treatment efficacy with both doses of CZP, particularly CZP 200 mg Q2W.

7.3.6. Vital signs

7.3.6.1. Pivotal studies

7.3.6.1.1. Study PsA001

The incidence of hypertension (defined as either systolic blood pressure greater than or equal to 140mmHg and/or diastolic blood pressure greater than or equal to 90mmHg at 2 or more consecutive visits) was similar between the combined CZP (36.4%) and placebo groups (34.6%). Mean changes from baseline in heart rate, respiratory rate, and temperature were minimal, and not of clinical relevance.

7.3.6.1.2. Study AS001

Clinically meaningful changes from baseline in vital signs measurements over the 24-week study period were not noted. Mean changes in heart rate, respiratory rate, and temperature from the baseline (pre-dose) values were minimal, and not of clinical relevance. The incidence of hypertension was similar between the combined CZP (2.9%; 8/274) and placebo groups (3.7%; 4/107).

7.3.6.2. Other studies

7.3.6.2.1. Studies C87040 and C87044

Apart from 1 placebo subject developing a new right bundle branch block by the end of Study C87040, no significant changes in sequential ECG recordings or vital signs was observed in either trial.

7.4. Post-marketing experience

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

7.5. Safety issues with the potential for major regulatory impact

7.5.1. Risk of Infection, including opportunistic infection

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

7.5.2. Malignancies, including lymphoma and melanoma

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

7.5.3. Injection site and hypersensitivity reactions

This has already been addressed in this report.

7.5.4. Cardiovascular safety, including heart failure and ischaemic events

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

7.5.5. Unwanted immunological events

The rate and consequences of developing anti-CZP antibodies has already been discussed in sections 8.5.5 and 4.2.3 of this report. The formation of anti-drug antibodies does not appear to be associated with experiencing AEs, but results in increased plasma clearance of the drug, which potentially may affect efficacy.

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

7.6. Other safety issues

7.6.1. Safety in special populations

In Study PsA001, 1 pregnancy (35 year old receiving CZP 400 mg Q4W at Day 142), and 1 pregnancy of a partner (27 year old male in the CZP 400 mg Q4W group at Day 101) was reported. The female subject permanently discontinued CZP after the pregnancy was confirmed. The patient gave birth to a healthy infant at full term by spontaneous vaginal delivery. The partner of the male subject had an abortion at 10 weeks of gestation, and the abortion was classified as “congenital anomaly/birth defect”. No further information was available as the partner refused consent to provide additional information. No pregnancies were reported in Studies AS001 and C87044. Two patients receiving CZP 400 mg Q2W in Study C87040 became pregnant. Both patients underwent elective abortion, and 1 subject (who discontinued treatment) subsequently became pregnant again in the post-treatment period.

The submission did not present information regarding an assessment of risk of AE by subgroups of special interest, such as those aged > 65 years, increased BMI, concomitant treatment (for example CS use), concurrent co-morbidities or gender.

7.7. Evaluator’s overall conclusions on clinical safety

In this submission, the total clinical safety dataset for the use of CZP in adult patients with active PsA (n = 332) or axial Spa (n = 274) consists of 606 patients in 2 pivotal studies, all of whom received maintenance CZP by SC injection either at a dose of 200 mg Q2W or 400 mg Q4W. Most of the patients in the dataset received concurrent MTX and/or NSAID, and approximately 17-25% were taking concurrent low dose oral CS. In the pivotal PsA study, the overall exposure to CZP was 132.7 patient-years, and the total exposure to CZP in the pivotal SpA trial was 108.8 patient-years. In the 2 supporting skin psoriasis studies (C87040 and C98044) more than 90% of patients (n = 71) received CZP for 24 weeks in total (as part of a first, and then re-treatment period study design). Overall, there is sufficient volume of data to make a meaningful

assessment of safety for up to 24 weeks of treatment in newly proposed treatment indications of active PsA and axial SpA.

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

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

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

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

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

In summary, the safety data indicates that CZP has an acceptable overall short-term safety profile in the treatment of adult patients with moderately to severely active PsA and axial SpA. There is insufficient long-term safety data in the current submission to assess the risk of some types of AEs such as malignancy and adverse cardiovascular events, which will require longitudinal safety follow-up. There are some significant identified safety concerns including the risk of serious infection, opportunistic infection, injection site reactions, and abnormal liver function tests. These safety concerns are consistent with known profile of CZP in other approved indications, mainly active RA. Significant pharmacovigilance would be required if approval is granted for extension of treatment indications. This would include vigilance for opportunistic infections, adverse cardiovascular events and malignancy.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of CZP in the proposed usage are:

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

8.2. First round assessment of risks

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

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

8.3. First round assessment of benefit-risk balance

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

8.4. First round recommendation regarding authorisation

This evaluator recommends acceptance of the sponsor's proposed extension of treatment indications for CZP to include the treatment of active PsA and axial SpA. The proposed wording of treatment extension in patients with PsA has 2 additional elements: reducing the rate of progression of peripheral joint damage by X-ray, and improving physical functioning. The current submission provides robust evidence of improving physical functioning in patients with active PsA, however, the radiographic claim has not been sufficiently proven at this stage, and requires further evidence of justification before licensing is approved. In particular, the current X-ray data is limited to 24 weeks of assessment which is an insufficient time frame to evaluate such a claim. Furthermore, the current X-ray data only shows a positive effect with CZP at 24 weeks when post-hoc imputation rules with a specified minimum 8-week period between X-ray assessments was applied. A robust treatment effect requires at least 12 months (ideally 2 years) of follow-up (as per regulatory guideline advice in RA), and the statistical analysis plan should be pre-specified.

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

- Satisfactory response to the questions in this report,
- Regular periodic safety update reports, and
- When available, the sponsor provides the TGA with the final clinical study reports for Studies PsA001 and AS001.

9. Clinical questions

9.1. Pharmacokinetics

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

9.2. Pharmacodynamics

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

9.3. Efficacy

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

9.4. Safety

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

10. Second round evaluation

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

10.1. Pharmacokinetics

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

The sponsor also states the recent literature showing that the expression of cytochrome P450 enzymes may be down-regulated by increased levels of pro-inflammatory cytokines (eg TNF) during chronic active inflammation. Therefore, when chronic inflammation is successfully reduced this may impact upon the relative expression of cytochrome P450 enzymes. The sponsor has made no specific comment about how the "normalisation" of P450 enzyme expression (with effective anti-TNF treatment) may affect the PK of medications metabolised by this system. For example, the exposure to concurrent HMG Co-A reductase inhibitors may be increased once chronic inflammation is reduced. Patients with PsA and AS have an increased

risk of cardiovascular disease and hyperlipidaemia requiring treatment (Han et al, 2006). The evaluator concurs with the sponsor opinion but recommend post-marketing pharmacovigilance of this potential issue if registration in Australia is granted.

10.2. Pharmacodynamics

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

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

10.3. Efficacy

In the sponsor's response, the sponsor has provided the radiographic data up to Week 48 (that is the end of the dose-blind treatment period) in Study PsA001 to support the claim of radiographic benefit with CZP in patients with active PsA. The original submission contained X-ray data obtained up to the Week 24 evaluation. A full description of the pre-defined statistical analysis plan and post-hoc imputation methods were provided in the original submission. The sponsor states that in written advice received 9 February 2010, the FDA requested the primary efficacy analysis (including for X-ray endpoints) in Study PsA001 use the Randomized Set (RS) versus the Full Analysis Set (FAS) of subjects. The RS includes all subjects randomised with an intention-to-treat, whether or not valid assessments are available. In contrast, the FAS requires subjects to have at least 1 valid baseline and 1 valid post-baseline assessment. This cohort approach allows for the possibility of applying linear extrapolation when results are missing.

The primary radiographic endpoint of the change from baseline to Week 24 in mTSS was not achieved using the pre-specified analysis plan. The imputation rules applied in the primary analysis resulted in implausibly high Least Square (LS) mean changes from baseline in the mTSS across all treatment groups (ranging from 11.52 to 28.92 points). Hence, post-hoc imputation rules (8 potential cases with different combinations) were applied to the data along with a minimum 8-week window between X-rays. The sponsor states these rules are consistent with those accepted by regulatory authorities for another anti-TNF drug evaluated in patients with PsA (EPAR for golimumab). However, the S31 response did not include this document as a reference and this evaluator was unable to locate the above mentioned statement for review. Using the post-hoc imputation method, less progression of X-ray changes was observed at Week 24 (as measured by the LS mean change from baseline in mTSS) in the combined CZP treatment group compared with the placebo arm (0.06 versus 0.28 points, respectively). The difference between CZP (combined) and placebo was -0.22 points (95% CI -0.38, -0.06; p = 0.007). The LS mean change in mTSS from baseline to Week 24 was smaller (that is , less progression of

radiographic changes) in the CZP 200 mg Q2W group compared with the CZP 400 mg Q4W group (0.01 versus 0.11 points). However, both CZP treatment regimens appeared to be better compared with placebo (treatment difference of -0.27 and -0.17 points, respectively). The difference between CZP 200 mg Q2W and placebo was statistically significant at -0.27 points (95% CI -0.45, -0.08; p = 0.004). However, the difference between CZP 400 mg Q4W and placebo was not statistically significant at -0.17 points (95% CI -0.35, 0.02; p = 0.072). Post-hoc sensitivity analyses (that is with imputation of missing values using mean change or worst change from baseline in the entire study population, and also the same treatment group) showed the same results in that CZP 400 mg Q4W was not statistically superior to placebo but CZP 200 mg Q2W and the combined CZP group were consistently better. This evaluator would not regard this observation as a consistently robust outcome in demonstrating radiographic benefit with CZP as this evaluator would expect both CZP dose regimens (either alone or combined in a dataset) to be statistically significant versus placebo. The LS mean change from baseline to Week 48 in mTSS was 0.13 points (95% CI -0.05, 0.31) in the combined CZP group versus 0.32 points (95% CI 0.10, 0.55) in the placebo arm. Although the data suggested a trend for less progression with CZP, the observation did not reach statistical significance (p = 0.127). For each CZP dose group compared with placebo, the Week 48 data for LS mean change in mTSS did not reach statistical significance. The sponsor opines that this observation may have occurred because there was lower levels of radiographic progression over 48 weeks of observation in Study PsA001 compared with historical progression rates.

In the S31 response, the sponsor has also presented a post-hoc subgroup analysis for the LS mean change from baseline to weeks 24 and 48 on subjects with or without structural damage at baseline. A cut-off mTSS score of 6 was used to define subjects with structural damage at baseline. No supporting literature was provided to justify the choice of this cut-off score, although the sponsor refers to the same methodology being used in the golimumab EPAR assessment. In patients with a baseline mTSS > 6 points, very little radiographic progression was observed, independent of the treatment group. Nonetheless, the comparison between the CZP combined group (and each CZP dose regimen) versus placebo was statistically significant at 24 weeks, but not 48 weeks. In patients with baseline mTSS < 6 points, less than 10% of patients (regardless of treatment allocation) showed any X-ray progression.

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

10.4. Safety

The sponsor has provided 18 tables of data presenting the risk of AE and SAE by subgroups of special interest for PsA and axial SpA.

With respect to Study PsA001, the incidence of AEs (overall and drug related) were similar between CZP and placebo regardless of subgroup factor of interest (gender, age, BMI and concurrent CS use). Female subjects (regardless of treatment allocation) had a higher incidence of AEs and treatment related AEs compared to male patients, but the rates of serious or severe

AEs and discontinuations due to AEs were similar between male and female subjects. The same pattern of relatively increased AE frequency (overall and treatment-related) was observed in those with BMI > 30 kg/m2 compared to non-obese subjects. The dataset also shows the very small number of subjects (22 in total – 7 in the placebo arm and 15 given either dose of CZP) in Study PsA001 who were aged > 65 years.

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

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

11. Second round benefit-risk assessment

11.1. Second round assessment of benefits

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

11.2. Second round assessment of risks

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

11.3. Second round assessment of benefit-risk balance

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

12. Second round recommendation regarding authorisation

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

Should approval of the sponsor's proposed extension of indication be granted the evaluator would recommend 2 conditions of registration: - regular periodic safety update reports; and the

provision by the sponsor to the TGA of the final clinical study reports for Studies PsA001 and AS001.

13. References

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Therapeutic Goods Administration

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