24 October 2013
EMA/CHMP/601513/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cimzia

Procedure no. EMEA/H/C/001037/II/27

Marketing authorisation holder (MAH): UCB Pharma SA

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ACR	American College of Rheumatology
ACR20, ACR50, ACR70	American College of Rheumatology 20%, 50%, and 70% response criteria
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification System
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASDAI50	Bath Ankylosing Spondylitis Disease Activity Index 50% response
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	Crohn's disease
CI	confidence interval
CRP	C-reactive protein
CS	Completer Set
CZP	certolizumab pegol
DAS28	Disease Activity Score-28 joint count
DMARD	disease-modifying antirheumatic drug
ES	Enrolled Set
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
Fab′	fragment antigen binding prime
FAS	Full Analysis Set
FASCA	Fatigue Assessment Scale
FDA	Food and Drug Administration
HAQ-DI	Health Assessment Questionnaire–Disability Index
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
ia	intra-articular
im	intramuscular
ITT	Intent-to-Treat
iv	intravenous
JSN	joint space narrowing
LDI	Leeds Dactylitis Index
LEF	leflunomide
LEI	Leeds Enthesitis Index
LS	least square
MCS	Mental Component Summary
mNAPSI	modified Nail Psoriasis Severity Index
mTSS	modified total Sharp score
MTX	methotrexate
NRI	Nonresponder Imputation
NSAID	nonsteroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PASI50, PASI75, PASI90, PASI100	Psoriasis Area and Severity Index 50%, 75%, 90%, 100% response
PCS	Physical Component Summary
PEG	polyethylene glycol
PhGADA	Physician's Global Assessment of Disease Activity

PhGAP	Physician's Global Assessment of Psoriasis
PK	pharmacokinetic(s)
PPD	purified protein derivative
PPS	Per-Protocol Set
PsA	psoriatic arthritis
PsARC	Psoriatic Arthritis Response Criteria
PsAQoL	Psoriatic Arthritis Quality of Life
PtAAP	Patient's Assessment of Arthritis Pain
PtGADA	Patient's Global Assessment of Disease Activity
Q2W	every 2 weeks
Q4W	every 4 weeks
RA	rheumatoid arthritis
RS	Randomized Set
SAP	statistical analysis plan
sc	subcutaneous(ly)
SD	standard deviation
sDMARD	synthetic disease-modifying antirheumatic drug
SF-36	Short-Form 36-item Health Survey
SOC	System Organ Class
SS	Safety Set
SSZ	sulfasalazine
TB	tuberculosis
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
VAS	visual analog scale
WPS	Work Productivity Survey

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma SA submitted to the European Medicines Agency on 30 November 2012 an application for a variation including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Cimzia	Certolizumab pegol	See Annex A

The following variation was requested:

Variation requested		**Type**
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension of the indication for the treatment of active psoriatic arthritis (PsA) in adults when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.8 and 5.1 of the SmPC. The package leaflet was proposed to be updated in accordance.

The variation proposed amendments to the SmPC and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0208/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0208/2012 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: K Dunder Co-Rapporteur: J Borvendég

Submission date:	30 November 2012
Start of procedure:	21 December 2012
Rapporteur's preliminary assessment report circulated on:	12 February 2013
CoRapporteur's preliminary assessment report circulated on:	11 February 2013
Joint Rapporteur's updated assessment report circulated on:	15 March 2013
PRAC RMP advice and assessment overview adopted by PRAC	18 February 2013
Request for supplementary information and extension of timetable adopted by the CHMP on:	21 March 2013
MAH's responses submitted to the CHMP on:	14 May 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	26 May 2013
PRAC RMP advice and assessment overview adopted by PRAC	02 July 2013
Secondary Request for supplementary information and extension of timetable adopted by the CHMP on:	25 July 2013
MAH's responses submitted to the CHMP on:	21 August 2013
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 September 2013
PRAC RMP advice and assessment overview adopted by PRAC	10 October 2013
CHMP opinion:	24 October 2013

2. Scientific discussion

2.1. Introduction

Cimzia (certolizumab pegol [CZP]) is a humanized fragment antigen binding prime (Fab′) conjugated to polyethylene glycol (PEG). Certolizumab pegol neutralizes human TNFα bioactivity and inhibits the production of inflammatory cytokine by monocytes. In the EU, Cimzia is approved in combination with methotrexate (MTX), for the treatment of moderate to severe, active rheumatoid arthritis (RA) in adult patients. The recommended starting dose of Cimzia for adult RA patients is 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance dose for RA adult patients is 200 mg every 2 weeks. MTX should be continued during treatment with Cimzia where appropriate.

The purpose of this application is to extend the indication of Cimzia for the treatment of adult patients with active psoriatic arthritis**.** The indication applied for was: *Cimzia, alone or in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous disease-modifying antirheumatic drug (DMARD) therapy has been inadequate. Cimzia has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray and to improve physical function*.

Psoriatic arthritis is an inflammatory arthritis that occurs in up to one-third of patients with psoriasis and is usually diagnosed years after, but sometimes before, the skin disease appears. The combination

of joint and skin manifestations of PsA can have a profound impact on patient function, well-being, and health-related quality of life (HRQoL).

Clinical manifestations of PsA include joint inflammation, enthesitis, dactylitis, psoriatic nail involvement, and psoriatic skin lesions. Clinical features that may distinguish PsA from RA include asymmetry of joint involvement, initial oligoarticular involvement, enthesial inflammation, extra-articular manifestations such as iritis, and infrequent presence of rheumatoid factor.

Treatment for PsA traditionally has included non-steroidal anti-inflammatory drugs (NSAIDs). The efficacy of oral or parenteral corticosteroids for peripheral arthritis in PsA has not been examined formally, although they are commonly used in clinical practice. Some data are available to support the use of disease modifying antirheumatic drugs (DMARDs; i.e. sulfasalazine, leflunomide, MTX and cyclosporine) in providing a small to medium degree of improvement in the clinical signs and symptoms of PsA.

Four tumour necrosis factor alpha (TNFα) antagonists (infliximab, etanercept, adalimumab and golimumab) have a marketing authorisation in Europe for the treatment of PsA. For reasons of loss or lack of efficacy or intolerance to currently available TNFα antagonists, the need remains for additional TNFα antagonists as therapeutic options for patients with PsA, as observational data support that failure of an initial TNFα antagonist does not preclude the response to another one.

The PsA clinical development program was discussed with the United States and National European health authorities prior to its initiation. The program is based on one Phase 3 study, PSA001, and was designed to support the effectiveness of CZP in improving signs and symptoms, inhibiting the progression of structural damage, improving physical function and health-related outcomes, and improving skin and nail manifestations of PsA as well as providing safety data in the treatment of adults with active PsA. The doses selected for PsA001 were based on the doses evaluated and shown to be safe and effective for the treatment of subjects with RA.

Supportive data were provided from 2 completed psoriasis phase 2 studies (C87040 and C87044). Efficacy data from this psoriasis studies have not been reviewed by the CHMP in this report as considered not relevant to support this new indication. Safety data has been regarded as supportive (see safety section). In addition to the safety data collected in PsA001, the program was supported by safety data from the large RA program (14 RA studies: 12 completed studies and 2 ongoing studies as of the cutoff date of 30 Nov 2011).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial that supports this submission, PSA001, was performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical study

Study identifier	Obectives of the study	Study design and type of control	Test product / dosage regimen / route of administration	Number of randomized subjects	Duration of treatment	Study status / type of report
PSA001	Efficacy and safety	Randomized, double-blind, parallel-group, PBO-controlled study	PBO or CZP 200mg/mL in prefilled syringe CZP 400mg at W0, 2, and 4 followed by CZP 200mg Q2W or CZP 400mg Q4W sc	409 Subjects Subjects with active PsA	24 weeks	Ongoing/interim

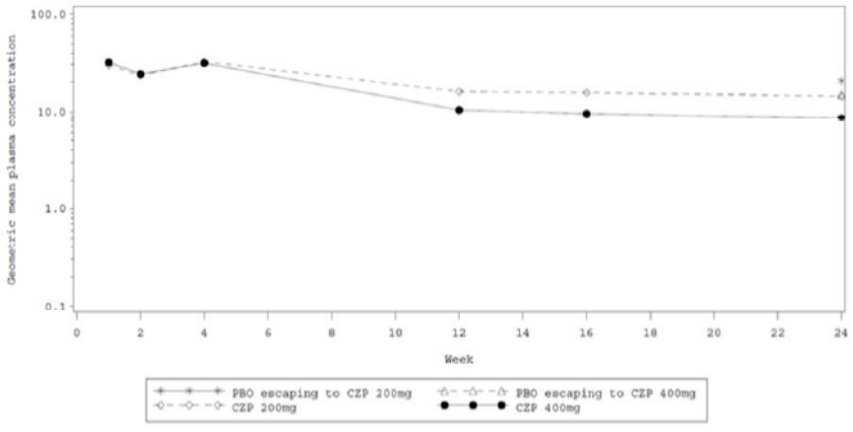
2.3.2. Pharmacokinetics

The pharmacokinetics of CZP in PsA patients was investigated in study PSA001 and the interim results following 24 weeks of treatment with either placebo, 200 mg Q2W or 400 mg Q4W were reported.

Plasma samples for the measurement of CZP concentrations were taken at Baseline; Weeks 1, 2, 4, 12, 16, 24, Early Withdrawal and at the Safety Follow-Up (SFU) Visit 10 weeks after the last dose of study medication.

Mean (geometric) CZP plasma concentrations were consistent with the treatment schedule for the CZP 200mg Q2W and CZP 400mg Q4W groups. Geometric mean plasma concentration of CZP was similar between the two active treatment arms on Week 1, 2 and 4. After completion of the loading dose phase, the CZP trough concentrations at Weeks 12, 16, and 24 were lower than at the early weeks but remained steady over time. At Weeks 12, 16, and 24, plasma CZP trough concentrations were lower in the CZP 400mg Q4W group compared with the CZP 200mg Q2W group, consistent with the difference in dose interval.

Figure 1 Plot of geometric mean plasma concentrations (µg/mL)



BLQ=below the limit of quantification; CZP=certolizumab pegol; LOQ=limit of quantification; OC=Observed Case; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Note: CZP 200mg is Q2W; CZP 400mg is Q4W.
Note: Values of BLQ are replaced by value of LOQ/2 (0.205 µg/mL) in calculation of means. Means are only calculated if at least 2/3 of the concentrations were quantified at the respective time point.

Immunologic measurements

Plasma samples for the measurement of anti-CZP antibodies were taken at Baseline; Weeks 1, 2, 4, 12, 16, 24, Early Withdrawal and at the SFU.

At Baseline (Week 0), 3 subjects (2 in the placebo group and 1 in the CZP 200mg Q2W group) were positive for anti-CZP antibodies (Ab+). During the course of treatment, 16 patients in each dose group (~12%) developed anti CZP antibodies.

At week 12, 16 and 24 the CZP plasma concentration was 30% to 40% lower in the 400 mg Q4W arm compared to the 200 mg Q2W arm for Ab- patients. From week 12 and onwards, the plasma concentration remained relatively stable in each dose group. Plasma concentration of CZP was considerably lower in Ab+ patients compared to Ab- patients. The geometric mean plasma concentration for Ab- and Ab+ patients is shown for each dose group in Table 1.

Table 1 Geometric mean plasma concentration of CZP (µg/mL) by dose group and anti-CZP antibody status in Study PsA001

Dosing regimen	**200 mg Q2W**		**400 mg Q4W**	
Week	Ab- (N=122)	Ab+ (N=16)	Ab- (N=119)	Ab+ (N=16)
0	NA	NA	NA	NA
1*	29.8	27.3	31.5	30.8
2*	23.5	21.8	24.1	23.0
4*	32.9	25.5	31.9	24.6
12	19.1	4.4	13.8	1.7
16	18.9	3.8	12.1	2.1
24	18.2	2.0	12.2	NA

* A loading dose of 400 mg Q2W was given at week 0, 2 and 4 in both dosing regimens

2.3.3. Discussion on clinical pharmacology

The rationale behind the selection of 200 mg Q2W and 400 mg Q4W was partly based on the results from a model based analysis of CZP exposure and ACR20 response in RA patients (Lacroix et al. 2009). Similar ACR20 response for the two regimens at Week 12 was predicted in PsA patients using the model. Based on the observed trough concentration of CZP in study PsA001 in combination with the known PK of CPZ in other indications, the two different dosing regimens seem to achieve a similar exposure in terms of AUC or average concentration at steady state. A model assumption is that the average plasma concentration is directly driving the effect. Thus, the two dosing regimens are expected to perform equally well in terms of efficacy. The two different dosing regimens seemed to achieve comparable ACR20 response at week 12. However, there were tendencies pointing towards a difference between the 2 dosing regimen in favour of 200 mg Q2W when looking at the more sensitive ACR70 response (see clinical efficacy). This was further substantiated when looking at the ACR20/50/70 data longitudinally (per week). Similarly, PASI75 response is comparable between the 2 groups, while for PASI90 there seems to be a difference in favour to the 200mg 2QW dosing (see clinical efficacy).

During the procedure the MAH submitted an analysis of W12 and W24 response rate by trough concentration cut off (above vs. below 3 µg/mL) in order to determine whether the differences observed in ACR response rates between the CZP treatment groups were the result of the lower trough concentrations that occur with the Q4W dose regimen. These analyses have been further categorized by concomitant MTX use. The results suggested that the numerical difference in ACR response rates between the CZP dose groups is driven by the variability in the subjects without concomitant DMARDs and not related to low CZP trough concentrations. The CHMP considered this conclusion as speculative and did not consider that this analysis addressed the potential difference observed between the dosing regimens. Therefore, the potential slightly lower efficacy of the 400 mg Q4W dosing regimen was solved by not recommending using the 400 mg Q4W until the clinical response is confirmed with the

200 mg Q2W which was agreed by the MAH (see clinical efficacy). However in order to further explore this, as requested by the CHMP, the MAH is developing a reliable exposure-response model that will permit further analyses of the numerical differences observed via simulation. The results will be submitted by February 2014.

The plasma concentration of CZP in patients with positive anti-CZP antibody status (11.7%) was markedly lower compared to patients without antibodies towards CZP. No conclusion can be drawn on whether positive anti-CZP antibody status would alter the efficacy of CZP due to the small number of subjects with a positive anti-CZP status.

2.3.4. Conclusions on clinical pharmacology

The pharmacokinetics of CZP in PsA patients receiving 200 mg Q2W or 400 mg Q4W CZP was characterized. The observed concentration was consistent with what has been seen in RA patients. The mean (geometric) plasma CZP concentrations were highest at Weeks 0, 2, and 4 when subjects in both CZP groups were treated with loading doses; plasma concentrations were similar between groups at these time points. The CZP trough concentrations were lower at Weeks 12, 16, and 24 compared with the early weeks but remained steady over time. The CZP trough concentrations at Weeks 12, 16, and 24 were lower in the CZP 400mg Q4W group compared with the CZP 200mg Q2W group because of the longer dose interval.

The recommended starting dose of CZP for adult patients is identical to the RA one i.e. 400 mg (given as 2 subcutaneous injections of 200 mg each) at weeks 0, 2 and 4. After the starting dose, the recommended maintenance is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered (see efficacy section). The CHMP has recommended the development of an exposure-response model that will permit further analyses, via simulation, of the numerical differences observed between the 2 maintenance dosing regimens. The plasma concentration of CZP in patients with positive anti-CZP antibody status was markedly lower compared to patients without antibodies towards CZP. However, no conclusion can be drawn on whether positive anti-CZP antibody status would alter the efficacy of CZP due to the small number of subjects with a positive anti-CZP status.

2.4. Clinical efficacy

2.4.1. Main study

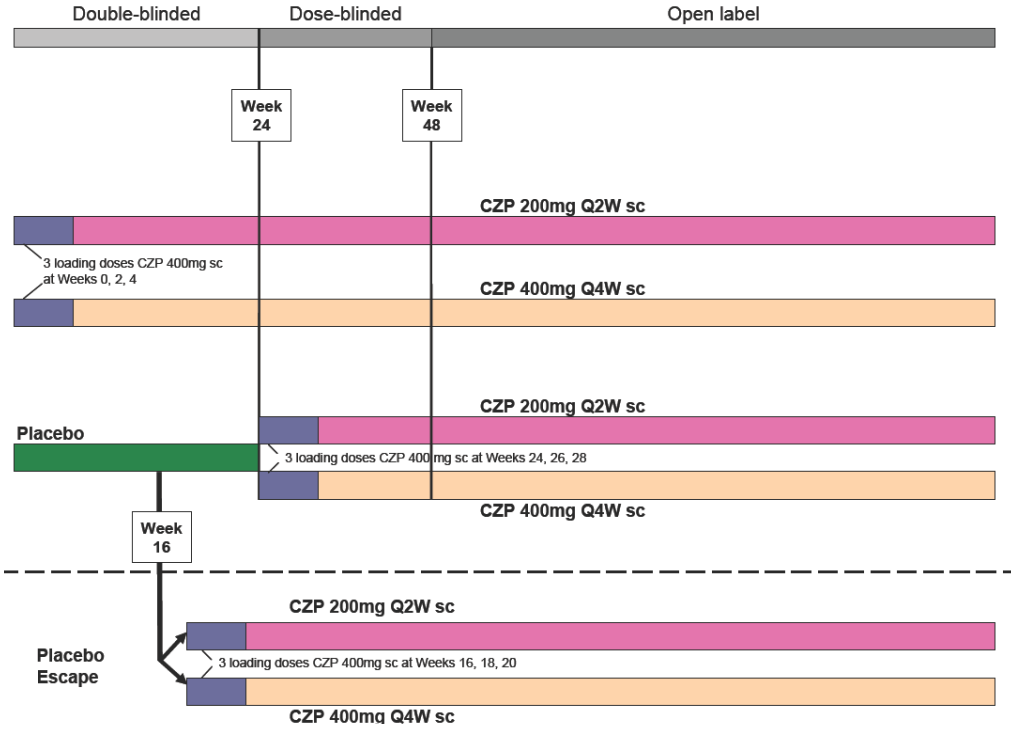
Study PsA001 is a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult-onset active and progressive psoriatic arthritis.

Methods

PsA001 is a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study to evaluate the efficacy and safety of CZP in adult subjects with active and progressive PsA. It is an on-going clinical study conducted across several geographic regions including North America, Latin America, Western Europe, and Central/Eastern Europe. The study is comprised of 5 study periods including a Screening Period (up to 5 weeks), a placebo-controlled Double-Blind Treatment Period (Week 0 to Week 24), a Dose-Blind Treatment Period without a placebo treatment group (Week 24 to Week 48), an Open-Label Treatment Period (Week 48 to Week 216), and a Safety Follow-Up Period (Week 216 to Week 224). Only measurements for assessment of efficacy variables through Week 24 were described in the interim clinical study report in this submission.

A data cut-off of 31 May 2012 was used for this submission. Interim data from this study covering the 24 weeks double blind treatment period form the basis for all efficacy data to support the claimed indication. As of the clinical cut date, the Dose-Blind Treatment Period was complete, and no subject had completed the Open-Label Treatment Period.

Figure 1 PsA001 study design



CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous

Study participants

Main inclusion criteria

- Adult onset PsA of at least 6 months duration as defined by the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria.
- Active psoriatic skin lesions or a history of Psoriasis.
- Active arthritis defined by:
  - ≥3 tender joints at Screening and Baseline
    - ≥3 swollen joints at Screening and Baseline
    - And have fulfilled at least 1 of the following 2 criteria during the Screening Period:
    - Erythrocyte sedimentation rate (ESR) ≥28mm/hour (Westergren)
    - C reactive protein (CRP) > upper limit of normal (ULN)
- Failed 1 or more DMARDs.

The protocol specified that the percentage of subjects at study entry using concomitant DMARDs should be in the range of 30% to 70% of the total subjects and no more than 40% of subjects were to have had previous anti-TNF therapy.

Main exclusion criteria

- The subject had previously received CZP treatment in or outside of another clinical study.
- Subjects must not have had a diagnosis of any other inflammatory arthritis (e.g. RA, sarcoidosis, systemic lupus erythematosus) or a known diagnosis of fibromyalgia.
- Subjects may not have been exposed to more than 1 TNFα antagonist prior to the Baseline Visit and may not have been a primary failure to any TNFα antagonist therapy (defined as no response within the first 12 weeks of treatment with the TNFα antagonist).
- Subjects may not have been exposed to more than 2 previous biological response modifiers for PsA or psoriasis.
- Subjects with a history of chronic or recurrent infections (more than 3 episodes requiring antibiotics/antivirals during the preceding year)
- Known tuberculosis (TB) disease, high risk of acquiring TB infection, or latent TB infection. Exception from exclusion was permitted only if treatment for latent TB infection was initiated or had been initiated at least 4 weeks prior to study medication administration and treatment was still on-going at the time of study entry.

Treatments

Eligible subjects were allocated to the following study treatments in a 1:1:1 ratio:

- CZP administered sc at the dose of CZP 400mg Q2W at Weeks 0, 2, and 4 followed by CZP 200mg Q2W sc (starting at Week 6)
- CZP administered sc at the dose of CZP 400mg Q2W at Weeks 0, 2, and 4 followed by CZP 400mg Q4W sc (starting at Week 8)
- Placebo

Concomitant medication

- NSAIDs/cyclooxygenase-2 inhibitors: doses should have been stable in the 2 weeks prior to an arthritis assessment.
- Analgesics (e.g. acetaminophen or paracetamol, narcotics) were permitted except ad hoc as needed (prn) usage within the 24-hour period prior to any assessments.
- Corticosteroids: Oral maximum ≤10mg daily total prednisone equivalent. No oral dose change, or intra-articular (ia) or IV corticosteroids were allowed during the first 48 weeks of the study.
- SSZ ≤3g daily; MTX ≤25mg weekly; or LEF ≤20mg daily were allowed. No change in dose or dose regimen was allowed during the first 48 weeks of the study except for reasons of intolerance, where the DMARD dose may have been decreased but not discontinued Combinations of 2 or more of the permitted DMARDs were not allowed.
- Phototherapy and/or topical agents for psoriasis were permitted to be used after the first 48 weeks of the study.

Escape treatment

Subjects receiving placebo who did not achieve at least a minimal response (defined as a decrease of at least 10% in the number of tender joints and at least 10% in the number of swollen joints) at both Weeks 14 and 16 were allocated to escape treatment (randomized in a 1:1 ratio to receive CZP 200mg Q2W or CZP 400mg Q4W) from Week 16 onwards. These subjects continued to be treated with the dose regimen for the duration of their participation in the study.

Objectives

The primary objectives of the study were to demonstrate the efficacy of CZP administered sc at the dose of 200mg Q2W or 400mg Q4W after loading with 400mg 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 objectives of the study were to assess the effects on safety and tolerability and to demonstrate the effects of CZP on:

- Health outcomes;
- Psoriatic skin disease in the subgroup of affected subjects (>3% body surface area [BSA]) at Baseline;
- Dactylitis;
- Enthesitis;
- Axial involvement in the subgroup of affected subjects (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4) at Baseline.

The other objectives of the study were to assess the effect of CZP treatment on Psoriatic nail disease, direct medical resources utilization, Subject's health status and Disease Activity Score-28 joint count (DAS28).

Outcomes/endpoints

The 2 primary endpoints were:

- American College of Rheumatology 20% response criteria (ACR20) responder at Week 12
- Change from Baseline in modified total Sharp score (mTSS) at Week 24 (The mTSS Score was modified for psoriatic arthritis by addition of hand distal interphalangeal joints)

The key secondary variables were:

- ACR20 responder at Week 24
- change from Baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) at Week 24
- Psoriasis Area and Severity Index 75% response (PASI75) responder at Week 24

Other secondary efficacy variables included:

- ACR20 responder at Weeks 1, 2, 4, 8, 16, 18, and 20
- ACR 50/70 responders and Change from Baseline in all individual ACR core components at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- Change from Baseline in mTSS at Week 12, and Change from Baseline in the erosion score of mTSS and joint space narrowing (JSN) at Weeks 12 and 24

- Psoriasis Area and Severity Index 90% response (PASI90) responder at Weeks 1, 2, 4, 12,
- and 24 and Physician's Global Assessment of Psoriasis (PhGAP) responder and changes from Baseline in Leeds Dactylitis Index (LDI) and Leeds Enthesitis Index (LEI)at Weeks 12 and 24 at Weeks 12 and 24
- Change from Baseline in the Fatigue Assessment Scale (FASCA) at Weeks 12 and 24
- Change from Baseline in Short Form 36 item Health Survey (SF-36) Physical Component Summary (PCS), Physical Function domain and Mental Component Summary (MCS), Weeks 4, 8, 12, 16, 20, and 24
- Change from Baseline in Psoriatic Arthritis Quality of Life (PsAQoL) at Weeks 12 and 24
- Change from Baseline in BASDAI at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- BASDAI50 responder at Weeks 1, 2, 4, 8, 12, 16, 18, 20, and 24
- Scores of individual questions of the Work Productivity Survey (WPS) at Weeks 4, 12, and 24

Sample size

The sample size was determined by the larger of the 2 sample size estimates for the primary variables. Calculations were based on anticipated differences between the CZP-treated groups and placebo-treated groups in the percentage of subjects with an ACR20 response at Week 12and in the change from Baseline in mTSS at Week 24. The significance level of 5% for ACR20 response at Week 12 was not further adjusted, as testing of the primary endpoint of mTSS at Week 24 was conditional on the ACR20 response at Week 12 being significant for both group comparisons. Based on published data from other TNFα antagonists, it was anticipated that the difference to placebo for the active treatment groups in mean change from Baseline in the mTSS was greater than 1.0. Therefore, a sample size of 130 for each treatment group was sufficient to detect statistically significant differences in the mean change from Baseline in the mTSS between the combined active and placebo group with at least 95% power, assuming an SD of 2.4 points.

The actual number of subjects analysed was 138 subjects in the CZP 200mg Q2W group, 135 subjects in the CZP 400mg Q4W group, and 136 in the placebo group.

Randomisation

Subjects were allocated to treatment in a 1:1:1 ratio (CZP 200mg Q2W: CZP 400mg Q4W: placebo) and randomization was stratified by center and prior TNFα antagonist exposure. An interactive voice response system (IVRS) was used for subject registration as well as randomization and treatment administration. Placebo subjects who were allocated to escape treatment were re-randomized at Week 16 in a 1:1 ratio (CZP 200mg Q2W:CZP 400mg Q4W) stratified by prior TNFα antagonist exposure. Subjects originally randomized to placebo who completed to Week 24 were re-randomized at Week 24 in a 1:1 ratio (CZP 200mg Q2W: CZP 400mg Q4W) stratified by prior TNFα antagonist exposure in a dose-blinded fashion.

Blinding (masking)

Study treatments (including placebo) were administered by dedicated, unblinded, trained study centre personnel. Due to differences in presentation and viscosity between active and placebo, special precautions were taken in order to ensure blinding of the study. Pharmacokinetic data and antibody data were provided only after the study was unblinded for this interim analysis. All study medication

documentation (e.g. shipping receipts, drug accountability logs, IVRS randomization materials) was maintained and accessed by unblinded, trained study centre personnel only. Designated, unblinded study centre personnel were appropriately trained and licensed (per country guidelines) to administer injections. Each study centre was required to have a written blinding plan in place which detailed the study centre's steps for ensuring that the double-blind nature of the study was maintained.

Statistical methods

The Randomized Set (RS) was specified as the primary analysis set for efficacy following the intention-to-treat principle in the narrow sense. In case of subjects not treated at all or subjects not having any data contributing to the efficacy measurements, the RS might have given diluted treatment effect estimators. To cover this issue and provide more reliable effect estimates, the Full Analysis Set (FAS) and Per-Protocol Set (PPS) were also utilized. The FAS consisted of all subjects 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 Week 12 and the mTSS through Week 24. The PPS included subjects with sufficient exposure, efficacy assessments, and no major protocol violations with a potential impact on the primary outcome of the study. The Completer Set (CS) was used to investigate the robustness of the results since no imputation was done; however, the CS provided biased estimates since the placebo group only included subjects who did not meet the protocol definition for escape (i.e. escaped subjects [nonresponders] were not used). For efficacy displays over time, in addition to the RS with imputation, an RS without imputation (Observed Case [OC]) was used.

A hierarchical test procedure was applied to protect the overall significance level for the multiplicity of dose groups and endpoints. The predefined order of hypotheses testing, each at a 2-sided 5% alpha level vs placebo, was performed in the following sequence for the dose regimens and endpoints:

1. ACR20 response at Week 12 for CZP 200mg Q2W
2. ACR20 response at Week 12 for CZP 400mg Q4W
3. ACR20 response at Week 24 for CZP 200mg Q2W
4. ACR20 response at Week 24 for CZP 400mg Q4W
5. Change from Baseline in HAQ-DI at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
6. Change from Baseline in mTSS at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
7. PASI75 response at Week 24 for CZP 200mg Q2W and CZP 400mg Q4W combined
8. Change from Baseline in mTSS at Week 48 for CZP 200mg Q2W and CZP 400mg Q4W combined – not performed for the double-blind analysis

For sensitivity analyses, the FAS (with imputation), PPS (with imputation), and the CS were utilized. Secondary analyses for the primary variables as well as the analyses for the key secondary variables were performed for the same analysis sets. Confirmatory hypothesis testing in a narrow sense was only performed for the primary and key secondary variables in the RS with imputation. Missing data were imputed using Nonresponder Imputation (NRI) for the ACR20 response and linear extrapolation for the change from Baseline in mTSS.

ACR20 response at Week 12

Treatment comparisons vs placebo for the 2 CZP-treated groups (differences in ACR20 responses) was performed using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% confidence intervals (CIs) for the differences were constructed using their asymptotic standard

errors (asymptotic Wald confidence limits). The Wald test and CI calculation were performed without continuity correction. For the primary analysis, subjects who withdrew for any reason before Week 12 or who had missing data at Week 12 were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as nonresponders for the respective visit.

Change from Baseline to Week 24 in mTSS

All enrolled subjects were required to have radiographs taken of both hands and feet at Baseline; Weeks 12 and 24; and Early Withdrawal. Radiographs were read centrally and independently by 2 experienced readers. The mTSS in its modification for PsA (van der Heijde et al, 2005) quantified the extent of bone erosions and JSN for 64 and 52 joints, respectively, with higher scores representing greater damage.

Per the SAP-predefined analyses, for radiograph measurements with assigned Baseline, Week 12, or Week 24 Visit, however outside the time window (Screening to 14 days after Baseline visit,+/-14 days at Week 12, max 14 days before Week 24), linear extrapolation or interpolation was performed to impute a Baseline, Week 12, or Week 24 measurement, if at least 2 measurements were available.

The following imputation rules were defined for subjects with ≤1 available radiograph:

- Missing mTSS Baseline data were set to the lowest Baseline value observed in the entire population randomized into the study; in this case 0.
- Missing mTSS Week 24 data were set to the highest Week 24 value observed in the entire population randomized into the study; in this case 365.5.

Post hoc analysis

The SAP-predefined rules for the across-subject imputation led to physiologically implausible changes in mTSS. To correct for the imputation rules that were applied in the predefined analyses in PsA001, an imputation approach along with sensitivity analyses to ensure reliability of the data, was applied post-hoc along with a specified minimum time interval between radiographs subjected to imputation:

- Missing mTSS values were imputed by using median change from Baseline in the entire study population (in this case 0).
- A minimum time interval of 8 weeks between radiographs was defined to perform a meaningful linear interpolation or extrapolation. If the radiographs were less than 8 weeks apart, the second radiograph was considered missing, and the above imputation rules were used for subjects with 1 remaining radiograph.

All specified analyses for mTSS were repeated in the post-hoc analyses using the median change from Baseline imputation approach. In addition, the following post-hoc sensitivity analyses were performed to ensure the results were consistent across the different imputation methods:

1. Imputation of missing values by using mean change from Baseline in entire study population
2. Imputation of missing values by using worst change from Baseline in entire study population
3. Imputation of missing values by using worst change from Baseline in same treatment group
4. Exclusion of subjects with ≤ 1 available value

PASI75 response at Week 24

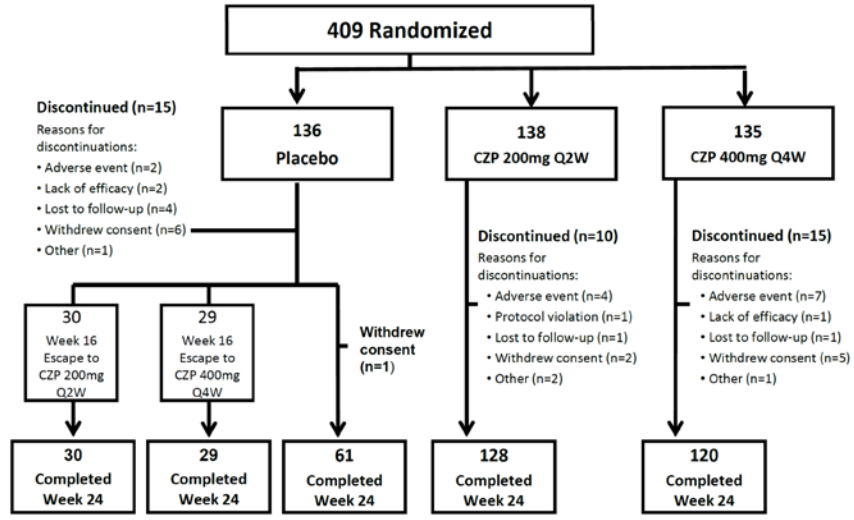
To investigate the effect of treatment on psoriatic skin disease, the PASI75 at Week 24 was used in the subgroup of subjects with at least 3% BSA at Baseline. The PASI is the current gold standard for assessment of extensive psoriasis (i.e. covering more than 3% of the body surface). The PASI75 response at Week 24 used the same statistical approach as for the ACR20. For analysis, subjects who withdrew for any reason before Week 24 were considered as nonresponders.

Results

Participant flow

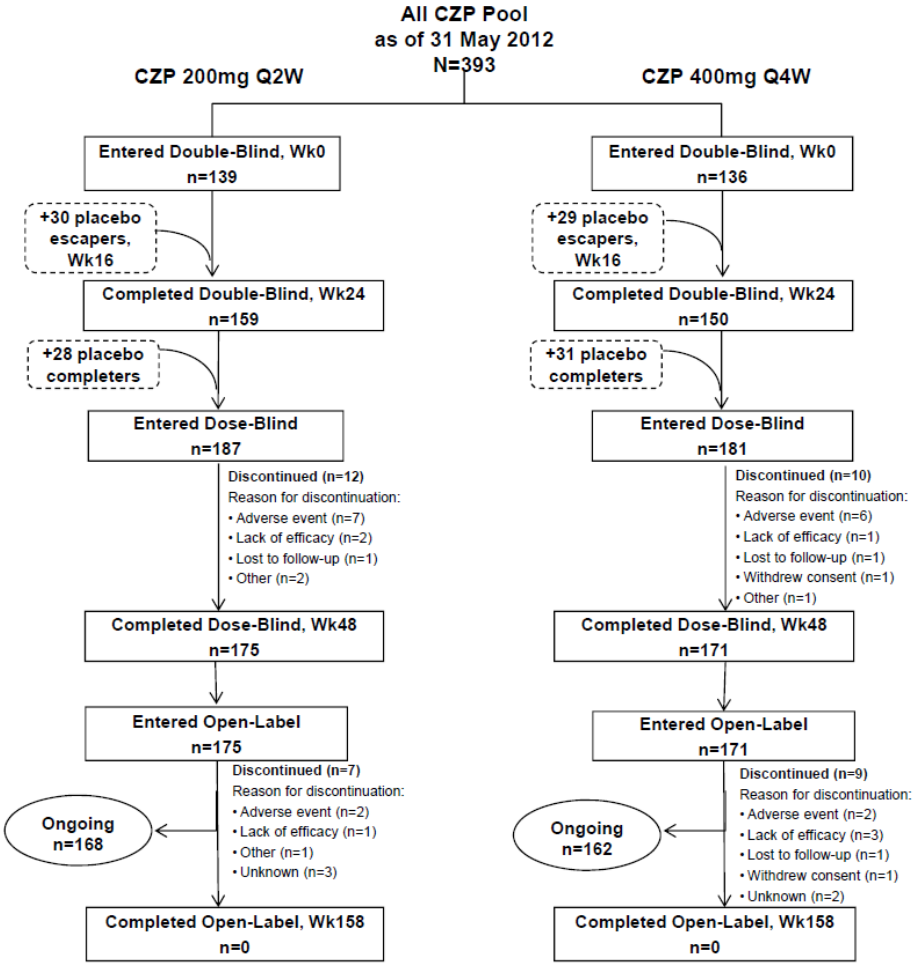
A total of 603 subjects were enrolled in the study, of which 409 subjects were randomized. The most common reason for screen failure was ineligibility. At Week 0, a total of 138 subjects were randomized to receive CZP 200mg Q2W, 135 subjects were randomized to receive CZP 400mg Q4W, and 136 subjects were randomized to receive placebo. At Week 16, a total of 59 placebo-escape subjects were re-randomized to CZP 200mg Q2W (30 subjects) or CZP 400mg Q4W (29 subjects) through to the end of the study.

Figure 2 Flowchart of subject disposition



CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks

Figure 3 Flowchart of subject disposition in PsA001 (data cut-off 31 May 2012)



CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks, Wk=week Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the Double-Blind Safety Pool include subjects escaping from placebo to CZP at Week 16. The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include, in addition, subjects switching from placebo to CZP at Week 24.

Recruitment

PSA001 is a multicenter study involving 92 sites located in North America, Latin America, Western Europe, and Central/Eastern Europe. Total duration for this interim report was 39 weeks, including up to a 5-week Screening Period, a 24-week Double-Blind Treatment Period, and a 10-week Safety Follow-Up Period. The first subject enrolled on 02 March 2010 and the last subject completed date for interim dataset on 03 November 2011.

Conduct of the study

Three global and 2 country-specific amendments were submitted to the final protocol, dated 25 Sep 2009. These amendments do not impact the study results as presented in this submission.

A diagnosis of adult-onset PsA of at least 6 months duration was defined using the CASPAR criteria. However, the protocol included an error in the weighting for the evidence of psoriasis. In this category, psoriasis was weighted by 2 points for current psoriasis, personal history of psoriasis, or family history of psoriasis. However, the weighting in the protocol appendix and the case report form is not correct. According to recent publications, only current psoriasis should be weighted by 2 points; personal history of psoriasis and family history of psoriasis should be weighted by 1 point.

All but 5 subjects fulfilled the CASPAR criteria (score ≥3), as defined in the protocol at Screening (1 in CZP 200mg Q2W, 2 in CZP 400mg Q4W, and 2 in placebo). One subject had a CASPAR score of 2 points and was in violation of both the protocol inclusion/exclusion criteria and the CASPAR criteria defined in the publications. Four subjects did not meet the CASPAR criteria defined in publications. For each of these 4 subjects, the CASPAR score was recorded as 3 points according to the weighting described in the protocol, but the score should have been 2 points according to the correct weighting. These 5 subjects were not included in the PPS.

In compliance with ICH E3 guidelines, protocol deviations important for the conduct, efficacy, and safety of the study were determined during the blinded data review meeting. The occurrence of an important efficacy deviation did not necessarily lead to exclusion a subject from the PPS. Deviations from the protocol that were defined in the Specification of Protocol Deviations were categorized as important, which resulted in a high incidence (75.6% in all subjects) of reported deviations during the 24-week Double-Blind Treatment Period. The incidence was similar between the CZP 200mg Q2W+CZP 400mg Q4W group (76.2%) and the placebo group (71.3%). Of the 409 subjects in the RS, 115 subjects (28.1%) were excluded from the PPS.

Baseline data

Table 2 Demographics summary and Baseline characteristics of PsA (RS)

	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273	All Subjects N=409
DEMOGRAPHICS					
Age in years, mean (SD)	47.3 (11.1)	48.2 (12.3)	47.1 (10.8)	47.7 (11.6)	47.6 (11.4)
Female, n (%)	79 (58.1)	74 (53.6)	73 (54.1)	147 (53.8)	226 (55.3)
DISEASE CHARACTERISTICS					
Disease duration in years, mean (SD)	7.91 (7.67)	9.62 (8.50)	8.11 (8.30)	8.88 (8.42)	8.55 (8.18)
CRP in mg/L, median (min, max)	9.00 (0.2, 131.0)	7.00 (0.2, 238.0)	8.70 (0.1, 87.0)	8.00 (0.1, 238.0)	8.00 (0.1, 238.0)
ESR in mm/h, median (min, max)	34.0 (6, 125) [(1)]	35.0 (5, 125)	33.0 (4, 120)	34.0 (4, 125)	34.0 (4, 125)[(2)]
Psoriasis BSA ≥3%, n (%)	86 (63.2)	90 (65.2)	76 (56.3)	166 (60.8)	252 (61.6)
Nail psoriasis, n (%)	103 (75.7)	92 (66.7)	105 (77.8)	197 (72.2)	300 (73.3)
Enthesitis, n (%)	91 (66.9)	88 (63.8)	84 (62.2)	172 (63.0)	263 (64.3)
Dactylitis, n (%)	45 (33.1)	47 (34.1)	47 (34.8)	94 (34.4)	139 (34.0)
BASDAI ≥4 (suspected axial involvement), n (%)	114 (83.8)	119 (86.2)	114 (84.4)	233 (85.3)	347 (84.8)
Tender joint count, mean	19.90	21.51	19.55	20.54	20.33
Swollen joint count, mean	10.43	11.04	10.48	10.76	10.65
HAQ-DI, mean	1.30	1.33	1.29	1.31	1.31
PtAAP, mean	60.0	59.7	61.1	60.4	-
PtGADA-VAS, mean	57.0	60.2	60.2	60.2	-
PhGADA-VAS, mean	58.7	56.8	58.2	57.5	-

	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W + CZP 400mg Q4W N=273	All Subjects N=409
DAS28(CRP), mean	4.99	5.04	4.99	5.02	5.01
mTSS, mean (SD)[3]	24.46 (49.68)	18.03 (30.58)	23.18 (46.57)	20.58 (39.32)	-
Erosion score, mean (SD)[3]	14.05 (27.01)	10.30 (17.26)	13.57 (25.16)	11.92 (21.56)	-
JSN score, mean (SD)[3]	10.40 (23.31)	7.74 (14.48)	9.61 (22.15)	8.66 (18.66)	-
PRIOR AND CONCOMITANT MEDICATION USE					
Prior TNFα-antagonist exposure[4], n (%)	26 (19.1)	31 (22.5)	23 (17.0)	54 (19.8)	80 (19.6)
Prior use of ≥1 sDMARDs[5], n (%)	134 (98.5)	134 (97.1)	132 (97.8)	266 (97.4)	400 (97.8)
Taking 1 or 2 allowed concomitant DMARDs at Baseline[5], n (%)	84 (61.7)	94 (68.1)	91 (67.4)	185 (67.8)	269 (65.7)

BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BSA=body surface area; CRP=C-reactive protein; CZP=certolizumab pegol; DAS28=Disease Activity Score 28-joint count; DMARD=disease-modifying antirheumatic drug; ESR=erythrocyte sedimentation rate; HAQ-DI=Health Assessment Questionnaire-Disability Index; JSN=joint space narrowing; max=maximum; min=minimum; mTSS=modified total Sharp score; PBO=placebo; PhGADA=Physician's Global Assessment of Disease Activity; PsA=psoriatic arthritis; PtAAP=Patient's Assessment of Arthritis Pain; PtGADA=Patient's Global Assessment of Disease Activity; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; sDMARD=synthetic disease-modifying antirheumatic drug; TNFα=tumor necrosis factor alpha; VAS=visual analog scale; "-"=not available

[1]The number of placebo subjects contributing data to the ESR value is 135.

[2]The number of subjects in the All Subjects group contributing data to the ESR value is 408.

[3]For the mTSS, erosion score, and JSN score the RS using imputation was used.

[4]Prior TNFα antagonist use is equivalent to past TNFα antagonist use as these medications were required to be stopped prior to study entry.

[5]The values presented were manually combined from the source table.

Numbers analysed

A total of 409 subjects were included in the RS and SS. Of these, 27 subjects were excluded from the FAS, 115 were excluded from the PPS, and 55 subjects were excluded from the CS. The percentage of subjects excluded from the PPS was higher in the CZP 400mg Q4W group (32.6%, 44 subjects) compared with the CZP 200mg Q2W (25.4%, 35 subjects) and placebo (26.4%, 36 subjects) groups.

Outcomes and estimation

The primary analyses of the efficacy variables were performed for the RS with imputation of missing values. For supportive and sensitivity analyses, the FAS (with imputation), PPS (with imputation), and CS were used. Some of the predefined imputation methods led to physiologically implausible changes in mTSS, which do not accurately portrayed subject response. To correct for the predefined imputation rules, post-hoc analyses were performed. A summary of the results from the hierarchical testing procedure of the primary and key secondary efficacy variables is presented below.

Table 3 Summary of hierarchical testing procedure of primary and key secondary efficacy variables (RS, with imputation)

Efficacy variables presented in order of hierarchical testing	p-value	Significant[1]
ACR20 response at Week 12: CZP 200mg Q2W vs PBO	<0.001[2]	Yes
ACR20 response at Week 12: CZP 400mg Q4W vs PBO	<0.001[b]	Yes
ACR20 response at Week 24: CZP 200mg Q2W vs PBO	<0.001[b]	Yes
ACR20 response at Week 24: CZP 400mg Q4W vs PBO	<0.001[b]	Yes
Change from Baseline in HAQ-DI at Week 24: CZP 200mg Q2W+CZP 400mg Q4W vs PBO	<0.001[b]	Yes
Change from Baseline in mTSS at Week 24: CZP 200mg Q2W+CZP 400mg Q4W vs PBO		
SAP-predefined analysis	0.203[c]	No
Post-hoc analysis	0.007[c,d]	Yes
PASI75 response at Week 24: CZP 200mg Q2W+CZP 400mg Q4W vs PBO		
SAP-predefined analysis	<0.001[b]	No
Post-hoc analysis	<0.001[b,d]	Yes
Change from Baseline in mTSS at Week 48: CZP 200mg Q2W+CZP 400mg Q4W vs PBO (to be tested in the Week 48 interim CSR)	NA	NA

ACR20=American College of Rheumatology 20% response criteria; ANCOVA=analysis of covariance; CSR=clinical study report; CZP=certolizumab pegol; HAQ-DI=Health Assessment Questionnaire-Disability Index; mTSS=modified total Sharp score; NA=not applicable; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SAP=statistical analysis plan; TNFα=tumor necrosis factor alpha

[a] Statistical significance was assessed in the context of hierarchical testing procedure as defined in the SAP. Each step tested at 0.05 two-sided. If the result was not significant at any step, then all steps after that were considered not statistically significant.

[b] P-value was estimated from standard 2-sided Wald asymptotic test with a 5% alpha level.

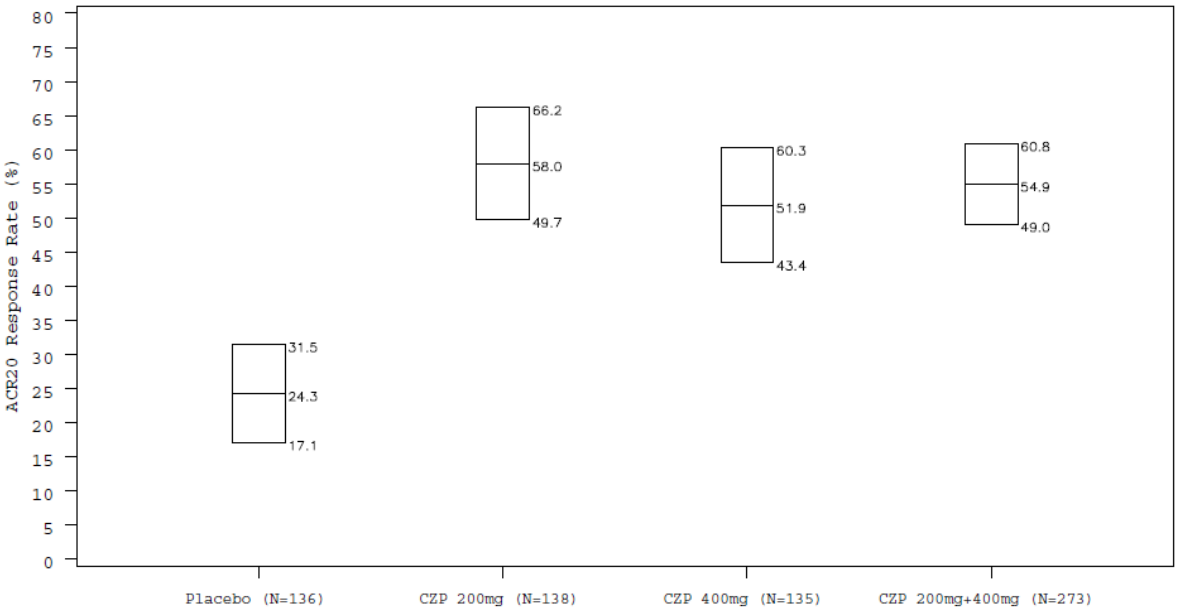
[c] P-value was estimated from the ANCOVA model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and Baseline score as a covariate.

[d] Post-hoc analysis using median change from Baseline in the entire study population (in this case 0) for imputation would have provided a statistically significant result (p=0.007) for mTSS. With the post-hoc analysis results for change from Baseline in mTSS at Week 24, the PASI75 response could have been considered statistically significant.

Treatment of signs and symptoms

For the primary endpoint of ACR20 responders at Week 12, a statistically significant difference between the CZP groups and placebo was demonstrated. The percentage of ACR20 responders at Week 12 was statistically significantly greater (p<0.001) in both active groups (CZP 200mg Q2W and CZP 400mg Q4W) compared with the placebo group.

Figure 4 ACR20 responders at Week 12 (RS, with imputation)



ACR20=American College of Rheumatology 20% response criteria; CI=confidence interval; CZP=certolizumab pegol; RS=Randomized Set
Note: Nonresponder Imputation (NRI) was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.
Note: The percentage of responders and 95% CI are shown.

Table 4 Responders for ACR and ACR components at Weeks 12 and 24 (RS, with imputation)

	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273
ACR20 responders				
Week 12 (%), 95% CI	24.3 (17.1, 31.5)	58.0 (49.7, 66.2)	51.9 (43.4, 60.3)	54.9 (49.0, 60.8)
Difference to PBO, % (95% CI)	–	33.7 (22.8, 44.6)	27.6 (16.5, 38.7)	30.7 (21.4, 40.0)
p-value	–	<0.001	<0.001	<0.001
Week 24, % (95% CI)	23.5 (16.4, 30.7)	63.8 (55.7, 71.8)	56.3 (47.9, 64.7)	60.1 (54.3, 65.9)
Difference to PBO, % (95% CI)	–	40.2 (29.5, 51.0)	32.8 (21.8, 43.8)	36.5 (27.3, 45.7)
p-value	–	<0.001	<0.001	<0.001
HAQ-DI responders				
Week 12, n (%)	29 (21.3)	63 (45.7)	66 (48.9)	129 (47.3)
Difference to PBO, % (95% CI)	–	24.3 (13.5, 35.1)	27.6 (16.7, 38.5)	25.9 (16.8, 35.0)
p-value	–	<0.001	<0.001	<0.001
Week 24, n (%)	21 (15.4)	68 (49.3)	65 (48.1)	133 (48.7)
Difference to PBO, % (95% CI)	–	33.8 (23.5, 44.2)	32.7 (22.3, 43.1)	33.3 (24.8, 41.8)
p-value	–	<0.001	<0.001	<0.001

	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273
PtAAP-VAS responders				
Week 12, n (%)	62 (45.6)	97 (70.3)	88 (65.2)	185 (67.8)
Difference to PBO, % (95% CI)	–	24.7 (13.4, 36.0)	19.6 (8.0, 31.2)	22.2 (12.1, 32.2)
p-value	–	<0.001	<0.001	<0.001
Week 24, n (%)	40 (29.4)	96 (69.6)	93 (68.9)	189 (69.2)
Difference to PBO, % (95% CI)	–	40.2 (29.3, 51.0)	39.5 (28.5, 50.4)	39.8 (30.4, 49.2)
p-value	–	<0.001	<0.001	<0.001
PtGADA VAS responders				
Week 12, n (%)	54 (39.7)	99 (71.7)	76 (56.3)	175 (64.1)
Difference to PBO, % (95% CI)	–	32.0 (20.9, 43.2)	16.6 (4.9, 28.3)	24.4 (14.4, 34.4)
p-value	–	<0.001	<0.006	<0.001
Week 24, n (%)	38 (27.9)	97 (70.3)	91 (67.4)	188 (68.9)
Difference to PBO, % (95% CI)	–	42.3 (31.6, 53.1)	39.5 (28.5, 50.4)	40.9 (31.6, 50.3)
p-value	–	<0.001	<0.001	<0.001

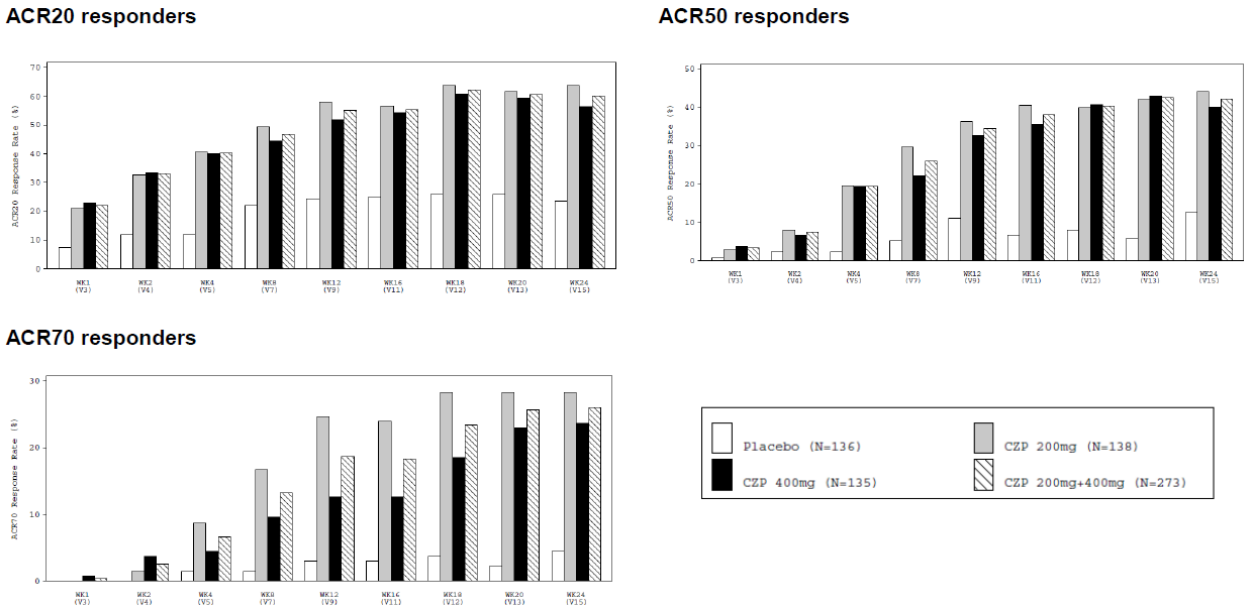
ACR20=American College of Rheumatology 20% response criteria; CI=confidence interval; CZP=certolizumab pegol; HAQ-DI=Health Assessment Questionnaire–Disability Index; PtAAP=Patient's Assessment of Arthritis Pain; PtGADA=Patient's Global Assessment of Disease Activity; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; VAS=visual analog scale; "–"=not applicable

Note: Nonresponder imputation was used: subjects who withdrew for any reason or PBO subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit. For the HAQ-DI, the PtAAP-VAS, and PtGADA-VAS, nonresponder imputation was used in the entire PBO group.

Note: Treatment difference calculations were CZP 200mg Q2W–PBO, CZP 400mg Q4W–PBO and CZP 200mg Q2W+CZP 400mg Q4W–PBO (and corresponding 95% CI and p-value) and were estimated using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

The percentage of ACR20 responders at Week 24 was significantly ($p<0.001$) greater in both CZP treatment groups compared with the placebo group. The percentage of HAQ-DI responders was greater in the CZP 200mg Q2W+CZP 400mg Q4W group compared with placebo beginning at Week 4 (39.2% vs 21.3%, a difference of 17.9% [$p<0.001$]. The percentage of HAQ-DI responders showed a trend towards increasing over time in the combined CZP group but remained fairly stable in the placebo group. By Week 24, 48.7% of subjects in the CZP 200mg Q2W+CZP 400mg Q4W group were HAQ-DI responders; the difference to placebo was 33.3% ($p<0.001$). The percentage of HAQ-DI responders and the trends over time were similar between the CZP 200mg Q2W and CZP 400mg Q4W groups.

Figure 5 ACR20, ACR50, and ACR70 responders by visit (RS, with imputation)



ACR20(50)(70)=American College of Rheumatology 20%(50%)(70%) response criteria; CZP=certolizumab pegol; RS=Randomized Set; V=visit; Wk=week Note: Nonresponder Imputation was used: subjects who withdrew for any reason were considered as nonresponders from the time that they dropped out. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit. Note: The y-axis scale differs across the 3 graphs. The times across the x-axis in each graph are Weeks 1, 2, 4, 8, 12, 18, 20 and 24.

The percentage of ACR 20 responders in the CZP 200mg Q2W+CZP 400mg Q4W group increased steadily over time to Week 12 (54.9%) and remained stable through Week 24 (60.1%). The percentage of ACR50 responders was greater in the CZP 200mg Q2W+CZP 400mg Q4W group compared with the placebo group starting at Week 1 through Week 24; at each visit from Week 2 through Week 24, the p-value for the difference to placebo was p≤0.012. The percentage of responders increased steadily over time to Week 16 (38.1%) and remained stable through Week 24 (42.1%). The percentage of ACR70 responders was greater in the CZP 200mg Q2W+CZP 400mg Q4W group compared with the placebo group starting at Week 2 through Week 24; at each visit from Week 4 through Week 24, the p-value for the difference to placebo was ≤0.005. The percentage of responders increased steadily over time through Week 24 (26.0%).

The mean changes from Baseline in all ACR components (swollen joint count, tender joint count, HAQ-DI, PtAAP, PtGADA, PhGADA, and CRP) in the CZP 200mg Q2W+CZP 400mg Q4W group were improved compared with placebo at all visits. These improvements were observed as early as Weeks 1 and 2 and were maintained through Week 24. Mean changes from Baseline in ACR components at Weeks 12 and 24 are summarized below.

Table 5 Change from Baseline in ACR components at Weeks 12 and 24 (RS, with imputation)

Mean change from Baseline (SD)	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273
Swollen joint count				
Week 12	-1.73 (8.75)	-6.96 (7.94)	-5.73 (6.10)	-6.35 (7.10)
Week 24	-0.53 (9.17)	-7.93 (8.68)	-7.44 (6.53)	-7.69 (7.68)
Tender joint count				
Week 12	-3.45 (11.60)	-10.35 (13.74)	-8.33 (14.06)	-9.35 (13.91)
Week 24	-2.86 (11.52)	-12.98 (14.59)	-10.18 (12.62)	-11.60 (13.70)
HAQ-DI				
Week 12	-0.16 (0.36)	-0.45 (0.56)	-0.39 (0.47)	-0.42 (0.52)
Week 24	-0.17 (0.43)	-0.52 (0.66)	-0.43 (0.54)	-0.48 (0.60)
PtAAP-VAS				
Week 12	-9.9 (21.0)	-26.9 (28.7)	-22.5 (23.4)	-24.7 (26.3)
Week 24	-11.2 (21.8)	-28.6 (28.8)	-28.4 (25.5)	-28.5 (27.2)
PtGADA-VAS				
Week 12	-6.8 (22.3)	-27.6 (28.3)	-20.7 (25.1)	-24.2 (26.9)
Week 24	-8.0 (24.0)	-29.2 (28.4)	-27.8 (25.3)	-28.5 (26.9)
PhGADA-VAS				
Week 12	-14.6 (20.8)	-32.0 (22.2)	-29.5 (21.1)	-30.8 (21.7)
Week 24	-16.5 (24.6)	-37.2 (21.1)	-37.1 (23.7)	-37.2 (22.4)
CRP (mg/L)				
Week 12	-3.81 (13.91)	-9.70 (28.26)	-7.37 (15.69)	-8.55 (22.91)
Week 24	-3.90 (17.42)	-10.78 (27.15)	-6.34 (17.15)	-8.59 (22.83)

ACR=American College of Rheumatology; CRP=C-reactive protein; CZP=certolizumab pegol; HAQ-DI=Health Assessment Questionnaire–Disability Index; PBO=placebo; PhGADA=Physician's Global Assessment of Disease Activity; PtAAP=Patient's Assessment of Arthritis Pain; PtGADA=Patient's Global Assessment of Disease Activity; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; VAS=visual analog scale

Note: Last Observation Carried Forward was used: for subjects who withdraw for any reason, subjects with a missing measurement, or PBO subjects who used escape medication, last observation prior to the early withdrawal or the missing measurement or before receiving CZP was carried forward.

Note: All p-values for differences to placebo were <0.001.

Subjects treated with CZP had greater improvement from Baseline in enthesitis (as measured by LEI) than observed in the placebo group (-1.9 vs -1.1 points at Week 24, respectively). In the original analysis, the mean change from Baseline in dactylitis (as assessed by LDI) was minimal at all time points indicating little or no progression of dactylitis, with no difference across groups. However, upon further review of the data, it was found that the method used to calculate the LDI did not fully reflect the original intention of the SAP and methods used to validate the index. As part of the responses, the MAH submitted a revised analysis correcting the analysis method showing that subjects treated with CZP had greater improvement from Baseline in dactylitis (as measured by LDI) than observed in the placebo group. The majority of CZP-treated subjects (77.7%) achieved the PsA response criteria (as

measured by PsARC) at Week 24, which quantifies improvements in PtGADA, PhGADA, swollen joint count, and tender joint count, compared with 33.1% of placebo subjects. The percentage of PsARC responders increased over time for CZP-treated subjects and was consistently greater than in placebo-treated subjects. Disease activity (as measured by DAS28[CRP]) was markedly reduced over time in CZP-treated subjects and was consistently improved compared with placebo-treated subjects. At Week 24, the percentage of subjects with a EULAR response of good was 52.4% in the CZP 200mg Q2W+CZP 400mg Q4W group compared with 13.2% of subjects in the placebo group. Subjects treated with CZP had a greater improvement in BASDAI from Baseline and a greater percentage of BASDAI50 responders compared with placebo-treated subjects suggesting a possible decrease in axial involvement.

Inhibition of the progression of structural damage

For the primary endpoint of change from Baseline in mTSS at Week 24 using the PsA001 SAP-predefined imputation rules, the difference between CZP and placebo could not be shown to be statistically significant. These imputation rules led to physiologically implausible LS mean changes from Baseline in mTSS (All CZP was 18.28 and placebo was 28.92), which do not accurately portray subject response. When the data were analysed post-hoc, missing mTSS values were imputed by using median change from Baseline in the entire study population (in this case 0). This imputation method and the rule to specify the minimum 8-week window between radiographs led to results that were realistic and also trended with the results from a placebo-controlled study in PsA with another TNFα inhibitor (Kavanaugh et al, 2012). There was less progression of radiographic changes in the CZP 200mg Q2W+CZP 400mg Q4W group compared with the placebo group (0.06 vs 0.28 points); the difference to placebo was -0.22 points (p=0.007).

Table 6 Change from Baseline in mTSS at Week 24 with the post-hoc imputation of median change from Baseline in the entire PsA001 study population and a specified minimum of 8 weeks between radiographs (RS, with imputation)

	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mgQ2W+ CZP 400mg Q4W N=273
Post-hoc primary analysis with ANCOVA				
Change from Baseline				
LS mean (SE)	0.28 (0.07)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)
95% CI	(0.13, 0.42)	(-0.14, 0.15)	(-0.04, 0.26)	(-0.06, 0.17)
Difference to PBO				
LS mean (SE)	–	-0.27 (0.09)	-0.17 (0.09)	-0.22 (0.08)
95% CI	–	(-0.45, -0.08)	(-0.35, 0.02)	(-0.38, -0.06)
p-value	–	0.004	0.072	0.007
Analysis with ANCOVA utilizing CZP data for PBO-escape subjects				
Change from Baseline				
LS mean (SE)	0.18 (0.07)	-0.01 (0.06)	0.08 (0.07)	0.04 (0.05)
95% CI	(0.05, 0.31)	(-0.14, 0.11)	(-0.05, 0.22)	(-0.07, 0.14)
Difference to PBO				
LS mean (SE)	–	-0.20 (0.08)	-0.10 (0.08)	-0.15 (0.07)
95% CI	–	(-0.36, -0.04)	(-0.26, 0.06)	(-0.29, -0.01)
p-value	–	0.016	0.228	0.037

ANCOVA=analysis of covariance; CI=confidence interval; CZP=certolizumab pegol; LS=least square; mTSS=modified total Sharp score; PBO=placebo; RS=Randomized Set; SE=standard error; TNFα=tumor necrosis factor alpha; "–"=not applicable

Note: Linear extrapolation was used: subjects who withdrew for any reason, subjects with a missing Week 24 measurement, or PBO subjects who used escape medication, the scores were linearly extrapolated from the last 2 radiographs before Week 24, from the Early Withdrawal Visit, or before receiving CZP.
Note: For the entire PBO group, linear extrapolations were used for subjects escaping to CZP.
Note: The change from Baseline data represent an ANCOVA model with treatment, region, and prior TNFα-antagonist exposure (yes/no) as factors and Baseline score as covariate.

Table 7 Post-hoc sensitivity analyses for the change from Baseline in mTSS at Week 24 in PsA001 (RS, with imputation)

	Placebo[1] N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mgQ2W+ CZP 400mg Q4W N=273
Imputation of missing values by using mean change from Baseline in entire study population For subjects with <2 radiographs, mean change from Baseline to Week 24 in mTSS was utilized.				
Change from Baseline				
LS mean (SE)	0.28 (0.07)	0.01 (0.07)	0.11 (0.08)	0.06 (0.06)
95% CI	(0.13, 0.43)	(-0.13, 0.16)	(-0.04, 0.26)	(-0.06, 0.18)
Difference to placebo				
LS mean (SE)	–	-0.27 (0.09)	-0.17 (0.09)	-0.22 (0.08)
95% CI	–	(-0.45, -0.09)	(-0.35, 0.02)	(-0.38, -0.06)
p-value	–	0.004	0.072	0.007
Imputation of missing values by using worst change from Baseline in entire study population For subjects with <2 radiographs, worst change from Baseline to Week 24 in mTSS was utilized.				
Change from Baseline				
LS mean (SE)	0.66 (0.13)	0.18 (0.13)	0.52 (0.13)	0.35 (0.10)
95% CI	(0.40, 0.92)	(-0.07, 0.43)	(0.25, 0.78)	(0.15, 0.55)
Difference to placebo				
LS mean (SE)	–	-0.48 (0.16)	-0.14 (0.16)	-0.31 (0.14)
95% CI	–	(-0.80, -0.16)	(-0.47, 0.18)	(-0.59, -0.03)
p-value	–	0.003	0.380	0.028
Imputation of missing values by using worst change from Baseline in same treatment group For subjects with <2 radiographs, worst change from Baseline to Week 24 in mTSS by treatment was utilized.				
Change from Baseline				
LS mean (SE)	0.39 (0.11)	0.14 (0.11)	0.49 (0.12)	0.31 (0.09)
95% CI	(0.16, 0.61)	(-0.08, 0.35)	(0.26, 0.71)	(0.14, 0.49)
Difference to placebo				
LS mean (SE)	–	-0.25 (0.14)	0.10 (0.14)	-0.08 (0.12)
95% CI	–	(-0.53, 0.03)	(-0.18, 0.38)	(-0.32, 0.16)
p-value	–	0.077	0.483	0.538

Exclusion of subjects with <2 available values The RS was restricted to subjects with at least 2 radiograph visit values, which were at least 8 weeks apart.				
Change from Baseline	n=127	n=133	n=123	n=256
LS mean (SE)	0.29 (0.08)	0.01 (0.08)	0.12 (0.08)	0.06 (0.06)
95% CI	(0.14, 0.45)	(-0.15, 0.16)	(-0.04, 0.28)	(-0.06, 0.19)
Difference to placebo				
LS mean (SE)	–	-0.29 (0.10)	-0.17 (0.10)	-0.23 (0.09)
95% CI	–	(-0.48, -0.09)	(-0.37, 0.02)	(-0.40, -0.06)
p-value	–	0.004	0.083	0.008

ANCOVA=analysis of covariance; CI=confidence interval; CZP=certolizumab pegol; LS=least square; mTSS=modified total Sharp score; NA=not applicable; RS=Randomized Set; SE=standard error; "–"=not applicable Note: The change from Baseline data represent an ANCOVA model with treatment, region, and prior TNF antagonist exposure (yes/no) as factors and Baseline score as covariate. [1] For the entire placebo group, linear extrapolations were used for subjects escaping to CZP.

The mTSS response at Week 24 was analysed using the post-hoc imputation rules. A subject was considered an mTSS responder if the subject had a change from Baseline to Week 24 in mTSS of ≤0 (a subject was considered a nonresponder if there was a progression [change from Baseline to Week 24 in mTSS>0]; in accordance with advice from the Food and Drug Administration (FDA), escapers were treated as if they had a change >0).

Table 8 mTSS responders at Week 24 (RS, with imputation)

Week 24	**PBO** **N=136**	**CZP 200mg Q2W** **N=138**	**CZP 400mg Q4W** **N=135**	**CZP 200mg Q2W+ CZP 400mg Q4W** **N=273**
Responders, % (95% CI)(1)	34.6 (26.6, 42.6)	83.3 (77.1, 89.6)	76.3 (69.1, 83.5)	79.9 (75.1, 84.6)
Difference to PBO(2), % (95% CI)	–	48.8 (38.6, 58.9)	41.7 (31.0, 52.5)	45.3 (36.0, 54.6)
p-value	–	<0.001	<0.001	<0.001

CI=confidence interval; CZP=certolizumab pegol; mTSS=modified total Sharp score; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; "–"=not applicable

Note: Nonresponder Imputation was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

Note: For subjects with less than 2 radiographs, median change from Baseline to Week 24 in mTSS was utilized.

[1]Asymptotic Wald confidence limits.

[2]Treatment difference: CZP 200mg Q2W–PBO, CZP 400mg Q4W–PBO and CZP 200mg Q2W+CZP 400mg Q4W–PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

Improvement in physical function and health-related outcomes

Irrespective of the dose regimen, CZP-treated subjects had significant improvements in physical function (HAQ-DI, relief of pain (PtAAP) and tiredness/fatigue (Fatigue Assessment Scale [FASCA]), and reduction in their disease activity (PhGADA and PtGADA) compared with placebo-treated subjects. These improvements were clinically meaningful with rapid (occurring as early as Weeks 1 and 2) and sustained results through Week 24. These improvements were sustained up to Week 48.

Health-related quality of life was notably improved in CZP-treated subjects compared with placebo-treated subjects, as measured by both PsA-specific and psoriasis-specific measures (Psoriatic Arthritis Quality of Life) and by generic measures (SF-36 PCS, Mental Component Summary, and all domains). Productivity within and outside the home (Work Productivity Survey) was improved in the CZP

treatment groups relative to placebo as early as Week 4 (first assessment) and sustained through Week 24. These improvements were sustained up to Week 48.

Change from Baseline in BASDAI

At Baseline, the majority of all subjects (84.8%) had a BASDAI ≥4, which was used in this study for suspected axial involvement; the distribution was similar across groups. The mean change from Baseline in BASDAI (for subjects with BASDAI ≥4 at Baseline) was improved in all treatment groups, although subjects treated with CZP had greater improvement compared with placebo-treated subjects.

The mean change from Baseline in BASDAI at visit 12 in the 200mg Q2W group was -2.42 in the 200mg Q2W group, and -2.11 in the 400 4QW group.

BASDAI50 responders

The percentage of BASDAI50 responders (for subjects with BASDAI ≥4 at Baseline) increased over time in all groups, although the CZP groups had greater percentages of BASDAI50 responders compared with the placebo-treated subjects at all time points. The trend was similar when using the entire RS. The number of BASDAI50 responders at visit 12 in the 200mg Q2W group was 45 (37.8%), and in the 400 4QW group 39 (34.2%).

Skin effects

Table 9 PASI75 and PASI90 responders at Weeks 12 and 24 for subjects with at least 3% psoriasis BSA at Baseline (RS, with imputation)

	PBO[1] N=86	CZP 200mg Q2W N=90	CZP 400mg Q4W N=76	CZP 200mg Q2W+ CZP 400mg Q4W N=166
PASI75				
Week 12				
Responders, n (%)	12 (14.0)	42 (46.7)	36 (47.4)	78 (47.0)
Difference to PBO[2], % (95% CI)	–	32.7 (20.1, 45.4)	33.4 (20.0, 46.8)	33.0 (22.5, 43.6)
p-value	–	<0.001	<0.001	<0.001
Week 24				
Responders, n (%)	13 (15.1)	56 (62.2)	46 (60.5)	102 (61.4)
Difference to PBO[2], % (95% CI)	–	47.1 (34.6, 59.7)	45.4 (32.1, 58.8)	46.3 (35.7, 56.9)
p-value	–	<0.001	<0.001	<0.001
PASI90				
Week 12				
Responders, n (%)	4 (4.7)	20 (22.2)	15 (19.7)	35 (21.1)
Difference to PBO[2], % (95% CI)	–	17.6 (7.9, 27.2)	15.1 (5.1, 25.1)	16.4 (8.8, 24.1)
p-value	–	<0.001	0.004	<0.001
Week 24				
Responders, n (%)	5 (5.8)	42 (46.7)	27 (35.5)	69 (41.6)

Difference to PBO[(2)], % (95% CI)	–	40.9 (29.4, 52.3)	29.7 (17.9, 41.6)	35.8 (26.8, 44.7)
p-value	–	<0.001	<0.001	<0.001

BSA=body surface area; CI=confidence interval; CZP=certolizumab pegol; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; "–"=not applicable

Note: Nonresponder Imputation (NRI) was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

[1]For the entire placebo group, NRI was used for subjects escaping to CZP.

[2]Treatment difference: CZP 200mg Q2W–PBO, CZP 400mg Q4W–PBO and CZP 200mg Q2W+CZP 400mg Q4W–PBO (and corresponding 95% CI and p-value) were estimated using a standard 2-sided Wald asymptotic test with a 5% alpha level. The corresponding 95% CI for the differences were constructed using their asymptotic standard errors (asymptotic Wald confidence limits).

These results indicate that treatment with CZP provides efficacy with regard to skin effects of psoriasis for the subgroup of PsA subjects with psoriasis involving at least 3% BSA at Baseline.

The mean change from Baseline in PASI at Weeks 1, 2, 4, 8, 12, 16, 20, and 24 for subjects with at least 3% psoriasis BSA at Baseline was defined as another efficacy variable.

The mean change from Baseline in PASI in the CZP 200mg Q2W+CZP 400mg Q4W group decreased over time, with a greater decrease from Baseline (i.e. improvement) compared with placebo at all visits. The mean change from Baseline at Week 24 was -9.31 points in the CZP 200mg Q2W+CZP 400mg Q4W group (-10.89 in the CZP 200mg Q2W and -7.45 in the CZP 400mg Q4W groups respectively) compared with -1.31 points in the placebo group.

Efficacy results in PsA001 subgroups

Regardless of age, gender, geographic region, concomitant use of allowed DMARDs at Baseline, and prior use of sDMARDs, CZP treatment provided a significant and robust clinical response to treatment of signs and symptoms (ACR20) at 12 and 24 weeks with 1 exception. In Latin America, there was a smaller difference in ACR20 responders between the CZP groups and placebo (12.5% difference for the CZP 200mg Q2W+CZP 400mg Q4W group) primarily due to an unexplainable larger placebo response than in other regions, while all other regions had approximately 30% differences in responders between the CZP groups and placebo.

As observed with the ACR20 response at Weeks 12 and 24, similar results were obtained in CZP-treated subjects with and without prior anti-TNFα therapy for the change from Baseline in mTSS at Week 24

Table 10 ACR20 responders at Weeks 12 and 24 by prior anti-TNFα therapy (RS, with imputation)

Percentage of responders by prior anti-TNFα therapy	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273
Week 12				
No, n (%)	29/110 (26.4)	66/107 (61.7)	55/112 (49.1)	121/219 (55.3)
Difference to PBO, % (95% CI)[(1)]	–	35.3 (23.0, 47.7)	22.7 (10.4, 35.1)	28.9 (18.3, 39.4)
p-value	–	<0.001	<0.001	<0.001
Yes, n (%)	4/26 (15.4)	14/31 (45.2)	15/23 (65.2)	29/54 (53.7)
Difference to PBO, % (95% CI)[(1)]	–	29.8 (7.4, 52.1)	49.8 (25.9, 73.7)	38.3 (19.1, 57.5)

p-value	–	0.012	<0.001	<0.001
Week 24				
No, n (%)	29/110 (26.4)	69/107 (64.5)	63/112 (56.3)	132/219 (60.3)
Difference to PBO, % (95% CI)[(1)]	–	38.1 (25.9, 50.4)	29.9 (17.5, 42.2)	33.9 (23.4, 44.4)
p-value	–	<0.001	<0.001	<0.001
Yes, n (%)	3/26 (11.5)	19/31 (61.3)	13/23 (56.5)	32/54 (59.3)
Difference to PBO, % (95% CI)[(1)]	–	49.8 (28.7, 70.8)	45.0 (21.3, 68.7)	47.7 (29.8, 65.7)
p-value	–	<0.001	<0.001	<0.001

ACR20=American College of Rheumatology 20% response criteria; CI=confidence interval; CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha; "–"=not applicable

Note: Nonresponder Imputation was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

Table 11 Concomitant DMARD medications (RS)

Preferred term	PBO[a] N=136 n (%)	CZP 200mg Q2W N=138 n (%)	CZP 400mg Q4W N=135 n (%)	CZP 200mg Q2W+ CZP 400mg Q4W N=273 n (%)	All CZP[b] N=332 n (%)
Any concomitant DMARD medication used	88 (64.7)	100 (72.5)	101 (74.8)	201 (73.6)	238 (71.7)
Methotrexate	80 (58.8)	86 (62.3)	86 (63.7)	172 (63.0)	207 (62.3)
Leflunomide	2 (1.5)	4 (2.9)	8 (5.9)	12 (4.4)	12 (3.6)
Suflasalazine	3 (2.2)	8 (5.8)	4 (3.0)	12 (4.4)	12 (3.6)
Methotrexate sodium	4 (2.9)	2 (1.4)	2 (1.5)	4 (1.5)	6 (1.8)
Hydroxychloroquine	0	0	1 (0.7)	1 (0.4)	1 (0.3)

CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

[a] For the entire placebo group, CZP data from placebo subjects were not utilized.

[b] The All CZP column includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.

Table 12 ACR20 responders at Week 12 by subgroups (RS, with imputation)

Percentage of responders	PBO N=136	CZP 200mg Q2W N=138	CZP 400mg Q4W N=135	CZP 200mg Q2W+ CZP 400mg Q4W N=273
Concomitant use of allowed DMARDs at Baseline				
No, n (%)	8/52 (15.4)	26/44 (59.1)	17/44 (38.6)	43/88 (48.9)
Difference to PBO, % (95% CI)[(1)]	–	43.7 (26.2, 61.2)	23.3 (5.8, 40.7)	33.5 (19.2, 47.8)
p-value	–	<0.001	0.011	<0.001
Yes, n (%)	25/84 (29.8)	54/94 (57.4)	53/91 (58.2)	107/185 (57.8)
Difference to PBO, % (95% CI)[(1)]	–	27.7 (13.7, 41.7)	28.5 (14.4, 42.6)	28.1 (16.0, 40.2)

p-value	–	<0.001	<0.001	<0.001
Prior use of sDMARDs				
1, n (%)	22/74 (29.7)	42/61 (68.9)	42/72 (58.3)	84/133 (63.2)
Difference to PBO, % (95% CI)[(1)]	–	39.1 (23.5, 54.7)	28.6 (13.2, 44.0)	33..4 (20.2, 46.7)
p-value	–	<0.001	<0.001	<0.001
≥2, n (%)	11/60 (18.3)	38/73 (52.1)	28/60 (46.7)	66/133 (49.6)
Difference to PBO, % (95% CI)[(1)]	–	33.7 (18.6, 48.8)	28.3 (12.4, 44.3)	31.3 (18.3, 44.3)
p-value	–	<0.001	<0.001	<0.001

ACR20=American College of Rheumatology 20% response criteria; CI=confidence interval; CZP=certolizumab pegol; (s)DMARD=(synthetic) disease-modifying rheumatic drug; NC=not calculated; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha; "–"=not applicable

Note: Nonresponder Imputation was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

Tolerance effects

Anti-CZP antibody-positive status (defined by a level of >2.4 units/mL in at least 1 visit, excluding the Safety Follow-Up Visit in case of subjects early terminating) is associated with lower plasma concentration of CZP, and, therefore, raises the possibility of reduced efficacy in those subjects. In PsA001, the effect of anti-CZP antibody status on efficacy was evaluated for the 2 primary variables and the key secondary variables, with exception of the PASI75. No conclusions can be drawn due to the small number of subjects with a positive anti-CZP status.

Table 13 ACR20 responders at Week 12 by anti-CZP antibody status (RS, with imputation)

Percentage of responders	**PBO N=136**	**CZP 200mg Q2W N=138**	**CZP 400mg Q4W N=135**	**CZP 200mg Q2W+ CZP 400mg Q4W N=273**
Anti-CZP antibody status[b]				
Negative, n (%)	32/129 (24.8)	71/122 (58.2)	61/119 (51.3)	132/241 (54.8)
Difference to PBO, % (95% CI)[(1)]	–	33.4 (21.9, 44.9)	26.5 (14.8, 38.1)	30.0 (20.2, 39.7)
p-value	–	<0.001	<0.001	<0.001
Positive, n (%)	1/7 (14.3)	9/16 (56.3)	9/16 (56.3)	18/32 (56.3)
Difference to PBO, % (95% CI)[(1)]	–	42.0 (6.4, 77.5)	42.0 (6.4, 77.5)	42.0 (10.9, 73.1)
p-value	–	0.048	0.048	0.040

ACR20=American College of Rheumatology 20% response criteria; CI=confidence interval; CZP=certolizumab pegol; (s)DMARD=(synthetic) disease-modifying rheumatic drug; NC=not calculated; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha; "–"=not applicable

Note: Nonresponder Imputation was used: subjects who withdrew for any reason or placebo subjects who used escape medication were considered as nonresponders from the time that they dropped out or when escape therapy was initiated. Subjects who had missing data at a visit were counted as a nonresponder for the respective visit.

2.4.2. Discussion on clinical efficacy

Design and conduct of the clinical study

The MAH has conducted one pivotal study, PsA001, to support the addition of the PsA indication. PsA001 was designed to demonstrate the efficacy of CZP administered sc at the dose of 200mg Q2W or 400mg Q4W after loading with 400mg 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; as well as provided safety data in the treatment of adults with active PsA. This is an on-going, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study. It is conducted in 92 sites located in North America, Latin America, Western Europe, and Central/Eastern Europe and randomized 409 subjects into 3 treatment arms, one placebo and 2 different dosing regimens, 200mgQ2W or 400mg Q4w. A data cut-off of 31 May 2012 was used for this submission. Interim data from this study covering the 24 weeks double blind treatment period form the basis for all efficacy data to support the claimed indication. As of the clinical cut date, the Dose-Blind Treatment Period was complete, and no subject had completed the Open-Label Treatment Period.

The current guideline (CHMP/EWP/438/04) on investigation of medicinal products for the treatment of PsA recommends a placebo-controlled add-on design, where all patients receive established standard therapy. The PsA001 study included subjects with or without DMARD in all arms. However, as appropriate subgroup analyses were made, this has not impacted the interpretation of the results. Inclusion and exclusion criteria were acceptable and the allowed concomitant medication was endorsed. The efficacy endpoints are consistent with current guidelines. Since all subjects receiving active treatment were administered both placebo and study drug, differences in presentation such as viscosity and colour, may have made it possible to determine what dosing regimen were used. During the procedure the MAH clarified that sufficient measures and monitoring were implemented during the study to prevent potential unblinding. This was accepted by the CHMP.

Upon request of the CHMP, the MAH provided clarifications on the number of subjects that were excluded from the per protocol set. These cases were limited and the efficacy results based on the PPS were consistent with those observed for the RS indicating the limited impact on the outcome of the study primary analysis.

Efficacy data and additional analyses

There were 2 primary efficacy variables in PsA001 including the ACR20 response at Week 12 and the change from Baseline in mTSS at Week 24. The key secondary efficacy variables were ACR20 response at Week 24, change from Baseline in HAQ-DI at Week 24, change from Baseline in mTSS at Week 48, and PASI 75% response (PASI75) at Week 24 in the subgroup of subjects with psoriasis involving at least 3% BSA at Baseline.

For the ACR20 responders at Week 12, a statistically significant difference between the CZP groups and placebo was demonstrated. The percentage of ACR20 responders at Week 12 was statistically significantly greater ($p<0.001$) in both active groups (CZP 200mg Q2W and CZP 400mg Q4W) compared with the placebo group, and the differences were clinically relevant. The percentages of ACR20 responders at Week 12 were greater in the CZP 200mg Q2W (58.0%) and CZP 400mg Q4W (51.9%) groups compared with placebo (24.3%), and the differences to placebo were statistically significant for both comparisons (differences of 33.7% and 27.6%, respectively; $p<0.001$ for each). The results of the key secondary endpoint for ACR20 responders at Week 24 were clinically meaningful and statistically significant. The percentages of ACR20 responders at Week 24 were greater in the CZP 200mg Q2W (63.8%) and CZP 400mg Q4W (56.3%) groups compared with placebo (23.5%); the differences to placebo were statistically significant for both comparisons (differences of 40.2% and

32.8%, respectively; p<0.001 for each). For ACR20, the difference to placebo was 30.7% in the pooled CZP group after 12 weeks, and 36.5% after 24 weeks of treatment. Once reached, the ACR20 response was maintained over time; 60.1% of subjects in the CZP 200mg Q2W+CZP 400mg Q4W group at Week 24 compared with only 23.5% in the placebo group. Similar time courses for ACR50 and ACR70 responses were observed.

Although ACR20 response was similar between the 2 dosing groups, there was a trend toward a lower rate of ACR70 response in the 400mg Q4W dosing group from Week 12. Further, there was a tendency to lower improvement in tender joint count, HAQ-DI and CRP for the 400mg dosing Q4W. Improvement of PtAAP and PtGADA as well as PhGADA was lower at W12 for the 400mg dosing Q4W, but catches up at W24. Regarding skin improvement it was noted that efficacy has been shown for both 200mg 2QW and 400mg 4QW and that the PASI75 related endpoint has been met in both dose regimens. However, there was a difference in the proportion of subjects achieving PASI90, indicating a better result for the 200mg Q2W dosing. It is also noted that the mean change from baseline in PASI was greater in the 200mg Q2W group than in the 400mg Q4W group. In general, the differences between the 2 dosing regimens were considered fairly small and diminished over time. However, the initial difference in ACR70 response was more pronounced and the differences between the two dose groups persisted for a longer time period. Thus the CHMP considered justified that the 400mg Q4W dosing regimen can be considered as an alternative maintenance dosing regimen once a clinical response with the 200mg Q2W dosing regimen is established. This was accepted by the MAH and reflected in section 4.2 of the SmPC accordingly.

During the procedure data were provided suggesting that a clinical response with respect to signs and symptoms was usually achieved within 12 weeks of treatment. Data as of week 48 showed that the majority of subject that achieved ACR20 response did so by week 12. Continued therapy should therefore be carefully reconsidered in subjects who show no evidence of therapeutic benefit within the first 12 weeks of treatment. This recommendation is reflected in the SmPC.

Two thirds of the subjects were on concomitant DMARD medication in all 3 treatment arms. The primary end point (ACR 20) was met both for those on DMARDs and for those on monotherapy. The initial claim made by the MAH, that Cimzia could be used without MTX required therefore to be further supported by analyses of all relevant endpoints and comparisons of patients with and without concomitant MTX, and for the two dose regimens. The MAH provided analyses showing that both dosing regimens are effective compared to placebo with or without MTX, however the results favoured the combination treatment. The difference to placebo for ACR 20 responders at 24 weeks was approximately 30% in the monotherapy group and 40% in the combination group. For ACR70 responders, the differences to placebo were approximately 15% and 25% respectively. It is acknowledged that since subjects were not randomised to receive MTX, the two groups are not completely comparable. However, the differences in baseline characteristics are not significant, and not considered sufficient to fully explain the differences in response rates between the monotherapy and combination therapy groups. Overall, based on the data presented, the CHMP considered justified aligning the PsA indication wording with the current wording for the RA indication stating that CZP should be used in combination with MTX. This was accepted by the MAH and reflected in section 4.1 of the SmPC accordingly (see section 2.7).

The CHMP noted that for patients not on concomitant DMARD, i.e. receiving CZP as monotherapy, a difference in ACR20 response between 200mg Q2W and 400mg Q4W was seen (43.7% vs 23.3% respectively). The MAH was asked to discuss this difference within the submission of additional analyses of monotherapy *vs* combination with MTX, and for the different dose groups. The MAH has investigated whether this difference is due to differences in incidence of anti-CZP antibodies or to lower trough plasma concentrations, but no evidence was identified. The 400 mg Q4W dose as monotherapy may be slightly less effective than the 200 mg Q2W monotherapy, early after treatment initiation.

However the number of subjects in the CZP monotherapy subgroup for the 2 dose regimens is relatively small (35 and 39 respectively), which makes it difficult to properly assess the clinical relevance of the numerical differences observed.

For the primary endpoint of change from Baseline in mTSS at Week 24 using the predefined imputation rules, the difference between CZP and placebo could not be shown to be statistically significant. Therefore, the study failed to show reduced progression of structural changes when analysed in accordance with the SAP. The CHMP agreed that the result using the predefined rules led to implausible changes and that the post hoc analysis used can be accepted. This post hoc analysis showed a statistically significant difference in the mTSS values (i.e. quantified radiographic structural changes) in favour of CZP 200mg Q2W over placebo. The change from baseline for mTSS was greater in the CZP 400mg Q4W group but the difference to placebo was not statistically significance. This tendency was seen even more clearly in the sensitivity analyses.

During the procedure, the MAH has provided 48 weeks data on structural changes in order to further substantiate the claim of reduced rate of progression of structural damage. There was low or no progression as measured by mTSS change from Baseline at Week 48 in both the CZP 200mg Q2W and CZP 400mg Q4W groups. These results were not statistically significant compared with the linearly extrapolated placebo group. Progression was inhibited in subjects switching from placebo to CZP treatment at Week 16 or Week 24 and was maintained until Week 48. The progression of structural damage at Week 48 in the combined CZP-treated subjects was lower than the Week 48 extrapolated progression in subjects randomized to placebo. The 24 week difference between CZP 200mg Q2W or 400mg Q4W and the placebo treated patients was slightly increased in the 48 week analysis, however, the result was not statistically significant. The 24 week tendency of a lesser effect in the CZP 400mg Q4W could not be seen in the 48 week analysis. In a 24 week subgroup analysis of patients with structural damage at baseline (patients with a Baseline mTSS score of > 6), statistically significant differences were shown for both CZP 200mgQ2W and CZP 400mg Q4W treatment. For subjects with >6 in mTSS at Baseline, the change in mTSS was greater in placebo treated subjects than for CZP treated subjects after 48 weeks. The difference was statistically significant for the combined 200mg and 400mg groups. Thus, there is a clear trend towards protection by CZP treatment.

Overall, the effect of 200mg Q2W and 400mg Q4W appeared to be similar up to Week 48. Inhibition of progression of structural damage by CZP treatment for up to 48 weeks has not been formally established in the overall population, however, in a subset of patients at higher risk of radiographic progression inhibition of radiographic progression was maintained with CZP treatment up to Week 48.The MAH agreed to remove the claim of reduced rate of progression of peripheral joint damage in section 4.1 of the SmPC and reflected the above results in section 5.1 of the SmPC.

An assessment of current presence of sacroiliitis or spondyloarthritis on imaging was not performed in PSA001 study, therefore subjects with active axial involvement could not be identified. It is therefore unknown whether a given patient with PsA and with relatively mild peripheral arthritis and skin symptoms, but with predominant axial involvement may have benefit from CZP treatment or not. This has been reflected in section 5.1 of the SmPC.

No difference in ACR20 responders at Weeks 12 and 24 was observed based on prior anti-TNFα therapy. Notably, in subjects with prior anti-TNFα therapy, a greater percentage of ACR20 responders at Weeks 12 and 24 was observed with CZP treatment compared with placebo, demonstrating that subjects with prior anti-TNFα therapy use (approximately 20% of subjects) can achieve a comparable response to CZP as those without prior anti-TNFα therapy. Some variability in response between the CZP 200mg Q2W and CZP 400mg Q4W groups was present. Subgroups for anti-CZP antibody status, race, and duration of disease were also analysed for the endpoints; however, no conclusions can be drawn due to the small number of subjects with a positive anti-CZP status.

2.4.3. Conclusions on the clinical efficacy

The submission is based on a Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled clinical study, investigating the effect of 2 different dose regimens compared to placebo in subjects with active PsA who had failed at least 1 DMARD. Subjects received either placebo or one of two dosing regimens, 200mgQ2W or 400mg Q4W. The 2 primary endpoints were proportions of ACR20 responder at Week 12 and change from Baseline in mTSS at Week 24. Among key secondary endpoints was proportion of PASI75 responders at Week 24. The design and conduct of the study were acceptable.

The results showed efficacy of CZP on signs and symptoms from both joints and skin. For the ACR20 response, the difference to placebo was 30.7% in the pooled CZP group after 12 weeks, and 36.5% after 24 weeks of treatment. PASI 75 at week 24, which was a key secondary variable used to capture the effect on the psoriasis symptoms in patients with >3% body surface area involved, showed 46.3% difference to placebo in the pooled CZP group. Most of the improvement in signs and symptoms was achieved by week 12. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment (as described in the SmPC). The results from this study demonstrated that both dosing regimens effectively reduced signs and symptoms in subjects with active PsA with a sustained response through Week 24 as measured by the ACR20, ACR50, and ACR70 responses. These data were supported by the percentages of responders for the HAQ-DI, PtAAP-VAS and PtGADA-VAS. The mean changes from Baseline in all ACR components (swollen joint count, tender joint count, HAQ-DI, PtAAP, PtGADA, PhGADA and CRP) in the pooled CZP group were improved compared with placebo at all visits; all p-values for differences to placebo were <0.001. These improvements were observed as early as Weeks 1 and 2 and were maintained through Week 24.

During the procedure the CHMP questioned the claim that CZP could be used without MTX. Additional analyses showed that CZP has an effect both when used as monotherapy and in combination with MTX, however the results favour the combination treatment. Therefore CZP can be given as monotherapy in case only of intolerance to MTX or when continued treatment with MTX is inappropriate. This is reflected in the wording of the indication.

Although ACR20 responses were similar between the 2 dosing groups, there was a tendency to lower improvement of symptoms for the 400mg dosing. Similar trends of a higher response rate for 200 mg Q2W versus 400 mg Q4W were also seen for secondary endpoints. Further, the reduced rate of progression of structural changes in the 400mg Q4W dosing group after 24 weeks was not convincing, and the difference to placebo did not reach statistically significance. Data up to 48 weeks showed that the differences between the dosing regimens diminished over time for effect on symptoms. However, the difference in ACR70 response was more pronounced than for other variables and the differences between the two doses groups persisted for a longer time period. Thus, the CHMP considered justified that after the starting dose, the recommended maintenance dose of CZP for adult patients with PsA is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered as described in the SmPC. MTX should be continued during treatment with CZP where appropriate.

The results also showed an effect on reduced rate of progression of structural damage for the 200mg Q2W dosing group, compared with placebo. At Week 24 there was less progression of radiographic changes in the CZP 200mg Q2W+CZP 400mg Q4W group compared to the placebo group (0.06 vs 0.28 points); the difference to placebo was -0.22 points (p=0.007). To support the claim of reduced rate of progression of structural damage, 48 weeks data was submitted. The 24 week difference between CZP treated patients and the placebo treated patients was slightly increased in the 48 week analysis, however this was a not statistically significant. The 24 week tendency of a lesser effect in the

CZP 400mg Q4W group was not seen in the 48 week analysis. Overall, the effect of 200mg Q2W and 400mg Q4W appeared to be similar. Inhibition of progression of structural damage by CZP treatment for up to 48 weeks has not been formally established in the overall population, however, in a subset of patients at higher risk of radiographic progression (patients with a Baseline mTSS score of > 6), inhibition of radiographic progression was maintained with CZP treatment up to Week 48. Based on these data the claim on reduced rate of progression of structural damage was removed from section 4.1 while the above results were reflected in section 5.1 of the SmPC.

In PsA001, CZP-treated patients reported significant improvements in physical function as assessed by the HAQ-DI, in pain as assessed by the PtAAP and in tiredness (fatigue) as reported by the FASCA as compared to placebo. CZP-treated patients reported significant improvements in health-related quality of life as measured by the psoriatic arthritis QoL (PsAQoL), Dermatology Life Quality Index (DLQI) and the SF-36 Physical and Mental Components and in psoriatic arthritis-related productivity at work and within household, as reported by the Work Productivity Survey compared to placebo. These improvements were sustained up to Week 48. In line with the Guideline on Summary of Product Characteristics, the results on physical function were reflected in section 5.1.

As described in the RMP the MAH will submit the final results of Study PSA001 by Q2 2016 which will bring additional data to further characterize the long term benefit of CZP treatment in PSA patients up to 216 weeks of treatment.

2.5. Clinical safety

2.5.1. Introduction

Safety data were evaluated from the ongoing PsA001 study, which includes data from the completed Double-Blind Treatment Period, as well as pooled data from completed visits in the other study periods through a data cutoff date of 31 May 2012.

The following 3 safety sets were used for the pooled analyses in the PsA001 clinical cut:

- The Double-Blind Safety Pool (Pool S1) consisted of subjects who received at least 1 dose of CZP in the completed Double-Blind Treatment Period of PsA001. Data for the placebo-escape subjects were included in the CZP 200mg Q2W or CZP 400mg Q4W groups. This is in contrast to the Week 24 PsA001 CSR, where the CZP data for placebo-escape subjects was presented separately and not included in the individual CZP groups but rather in the All CZP group.
- The All CZP Safety Pool (Pool S2) consisted of subjects who received at least 1 dose of CZP in PsA001. Data up to the last completed visit before or on the day of 31 May 2012 was utilized and includes data from the Double-Blind, Dose-Blind, and Open-Label Treatment Periods.
- The SS consisted of all randomized subjects who received at least 1 dose of study medication (CZP or placebo), which is the same definition used in the PsA001 Week 24 SAP for the Week 24 PsA001 CSR. This analysis set was used to rerun select tables and listings for updates obtained after the database lock for the Week 24 Double-Blind Treatment Period (ie, AEs that were not included in the CSR) and for updates for the placebo-escape subjects.

In addition to the safety data collected in PsA001, the PsA program is primarily supported by safety data from the large RA program (14 RA studies: 12 completed studies and 2 ongoing studies as of the cutoff date of 30 Nov 2011) that includes 4049 subjects and 9277 pt-yrs. Supportive safety data are also provided from 2 completed psoriasis phase 2 studies (C87040 and C87044) that includes 117 subjects with at least 1 exposure, 105 subjects exposed for a total of 12 weeks of double-blind

treatment, and 62 subjects exposed for an additional 12 weeks of open-label treatment. In addition, a brief summary of the CZP safety profile in 2518 CD subjects was provided.

Patient exposure

A total of 393 subjects have been exposed to at least 1 dose of CZP in the ongoing PsA001 study. In the Week 24 data, the exposure was 132.7 pt-yrs for subjects while on CZP and 51.1 pt-yrs for subjects while on placebo. The exposure while on CZP treatment in the All CZP Safety Pool was 458.7 pt-yrs compared with 131.6 pt-yrs in the Double-Blind Safety Pool (as treated). The All CZP Safety Pool included subjects treated with CZP 200mg Q2W, CZP 400mg Q4W, and the escaped or incorrectly treated placebo subjects with their CZP data.

The median number of doses received was 12.0 for the CZP 200mg Q2W group and 7.0 for the CZP 400mg Q4W group, as expected per the injection schedule, and per the study design, the number of injections was identical in both groups. 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% of placebo subjects escaped to CZP at Week 16

As of the 31 May 2012 clinical data cutoff date, a total of 79 subjects (20.1%) had received CZP for ≥6 to <12 months, 204 subjects (51.9%) had received CZP for ≥12 to <18 months, and 70 subjects (17.8%) had received CZP for ≥18 to <24 months. A total of 279 subjects (71.0%) of subjects were treated with CZP for at least 12 months, which equaled 373 pt-yrs of exposure. Few subjects were treated for ≥24 months (1.3%); however, the study is ongoing, and safety data continues to be collected. During the ongoing Safety Follow-Up Period, subjects have a visit 10 weeks after their last dose of study medication. As of the data cutoff date of 31 May 2012, no subject had completed the Open-Label Treatment Period.

Table 14 Duration of exposure in the All CZP Safety Pool (SS as treated)

	CZP 200mg Q2W N=197	**CZP 400mg Q4W N=196**	**All CZP N=393**
Patient-years of exposure	**232.4**	**226.3**	**458.7**
Total study drug duration of exposure(1)	**n (%) [patient-years]**	**n (%) [patient-years]**	**n (%) [patient-years]**
>0 months	197 (100.0) [224]	196 (100.0) [219]	393 (100.0) [443]
>6 months	182 (92.4) [220]	176 (89.8) [214]	358 (91.1) [434]
>12 months	139 (70.6) [186]	140 (71.4) [187]	279 (71.0) [373]
>24 months	1 (0.5) [2]	4 (2.0) [8]	5 (1.3) [10]
Duration of exposure(2)	**n (%)**	**n (%)**	**n (%)**
<3 months	8 (4.1)	12 (6.1)	20 (5.1)
≥3 to <6 months	7 (3.6)	8 (4.1)	15 (3.8)
≥6 to <12 months	43 (21.8)	36 (18.4)	79 (20.1)
≥12 to <18 months	95 (48.2)	109 (55.6)	204 (51.9)
≥18 to <24 months	43 (21.8)	27 (13.8)	70 (17.8)

	CZP 200mg Q2W N=197	CZP 400mg Q4W N=196	All CZP N=393
Patient-years of exposure	**232.4**	**226.3**	**458.7**
≥24 months	1 (0.5)	4 (2.0)	5 (1.3)

CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set
Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include subjects escaping from placebo to CZP at Week 16 and subjects switching from placebo to CZP at Week 24.
(1) Total study drug duration is the sum of each subject's study drug duration within a treatment group.
(2) A subject's study drug duration=(date of last dose–date of first dose)+1 maintenance dosing interval (either 14 or 28 days) except where a change of treatment occurred prior to the completion of this period.

Concomitant medications

Any medication that had been taken for at least 1 day during the Double-Blind Treatment Period was considered as concomitant. In the PsA001 Week 24 CSR data, 71.7% of subjects used concomitant DMARDs see table below.

Table 15 Concomitant DMARD medications during the 24-week Double-Blind Treatment Period (RS)

Preferred term	PBO[a] N=136 n (%)	CZP 200mg Q2W N=138 n (%)	CZP 400mg Q4W N=135 n (%)	CZP 200mg Q2W+ CZP 400mg Q4W N=273 n (%)	All CZP[b] N=332 n (%)
Any concomitant DMARD medication used	88 (64.7)	100 (72.5)	101 (74.8)	201 (73.6)	238 (71.7)
Methotrexate	80 (58.8)	86 (62.3)	86 (63.7)	172 (63.0)	207 (62.3)
Leflunomide	2 (1.5)	4 (2.9)	8 (5.9)	12 (4.4)	12 (3.6)
Suflasalazine	3 (2.2)	8 (5.8)	4 (3.0)	12 (4.4)	12 (3.6)
Methotrexate sodium	4 (2.9)	2 (1.4)	2 (1.5)	4 (1.5)	6 (1.8)
Hydroxychloroquine	0	0	1 (0.7)	1 (0.4)	1 (0.3)

CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
a For the entire placebo group, CZP data from placebo subjects were not utilized.
b The All CZP column includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.

Subjects were allowed to decrease the dose of DMARDs but were not allowed to change the type of DMARD or use more than 1 DMARD during the study. The majority of subjects (72.6%) reported concomitant NSAID use, and use was similar across treatment groups.

Adverse events

The incidence of treatment-emergent adverse events (TEAEs) was 62.3% in the All CZP group and 67.6% in the placebo group; the incidence was similar between the CZP 200mg Q2W and CZP 400mg Q4W groups. The incidence of drug-related TEAEs, TEAEs severe in intensity, and discontinuation due to TEAEs was also similar across groups. The overall incidence of serious adverse events (SAEs) was similar between the All CZP group and the placebo group (6.6% and 4.4%, respectively); the incidence of SAEs was slightly lower in the CZP 200mg Q2W group compared with the CZP 400mg Q4W group (5.8% vs 9.6%). Two deaths were reported during the Double-Blind Treatment Period; both were receiving CZP treatment.

Table 16 Overall summary of TEAEs during the 24-week Double-Blind Treatment Period (SS)

	PBO[1] N=136 n (%)	CZP 200mg Q2W N=138 n (%)	CZP 400mg Q4W N=135 n (%)	All CZP[2] N=332 n (%)
Any TEAEs	92 (67.6)	94 (68.1)	96 (71.1)	207 (62.3)
TEAEs by intensity:				
Mild	74 (54.4)	78 (56.5)	77 (57.0)	168 (50.6)
Moderate	49 (36.0)	47 (34.1)	45 (33.3)	99 (29.8)
Severe	2 (1.5)	7 (5.1)	7 (5.2)	15 (4.5)
Drug-related[3] TEAEs	37 (27.2)	39 (28.3)	41 (30.4)	86 (25.9)
Serious TEAEs	6 (4.4)	8 (5.8)	13 (9.6)	22 (6.6)
Discontinuation due to TEAEs:				
Permanent discontinuation	2 (1.5)	4 (2.9)	6 (4.4)	10 (3.0)
Temporary discontinuation	19 (14.0)	30 (21.7)	25 (18.5)	56 (16.9)
Death	0	1 (0.7)	1 (0.7)	2 (0.6)

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event

a For the entire placebo group, CZP data from placebo subjects were not utilized.

b The All CZP column includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.

c Drug-related TEAEs are those with a relationship of "related," "possibly related," or those with missing responders.

The increased number of TEAEs, drug-related TEAEs, severe TEAEs, SAEs, discontinuation due to TEAEs, and deaths in the All CZP Safety Pool compared with the Double-Blind Safety Pool was not unexpected given the approximately 3.5-fold increase in exposure; therefore, the increased numbers do not indicate an increase of TEAE risk with longer exposure to CZP.

Table 17 Overall summary of TEAEs during PsA001 (data cutoff 31 May 2012) (SS as treated)

	Double-Blind Safety Pool			All CZP Safety Pool		
	CZP 200mg Q2W N=169	CZP 400mg Q4W N=165	All CZP N=334	CZP 200mg Q2W N=197	CZP 400mg Q4W N=196	All CZP N=393
Patient exposure years	**66.9**	**64.6**	**131.6**	**232.4**	**226.3**	**458.7**
	n (%)					
Any TEAEs	104 (61.5)	106 (64.2)	210 (62.9)	165 (83.8)	167 (85.2)	332 (84.5)
Severe TEAEs	7 (4.1)	8 (4.8)	15 (4.5)	22 (11.2)	19 (9.7)	41 (10.4)
Drug-related[1] TEAEs	42 (24.9)	46 (27.9)	88 (26.3)	77 (39.1)	83 (42.3)	160 (40.7)
Serious TEAEs	8 (4.7)	14 (8.5)	22 (6.6)	24 (12.2)	28 (14.3)	52 (13.2)
Permanent discontinuation due to TEAEs	3 (1.8)	6 (3.6)	9 (2.7)	15 (7.6)	15 (7.7)	30 (7.6)
Death	1 (0.6)	1 (0.6)	2 (0.6)	3 (1.5)	3 (1.5)	6 (1.5)

CZP=certolizumab pegol; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event

	Double-Blind Safety Pool			All CZP Safety Pool		
	CZP 200mg Q2W N=169	CZP 400mg Q4W N=165	All CZP N=334	CZP 200mg Q2W N=197	CZP 400mg Q4W N=196	All CZP N=393

Note: The CZP 200mg Q2W and CZP 400mg Q4W groups in the Double-Blind Safety Pool include subjects escaping from placebo to CZP at Week 16. The CZP 200mg Q2W and CZP 400mg Q4W groups in the All CZP Safety Pool include, in addition, subjects switching from placebo to CZP at Week 24. [(1)]Drug-related TEAEs are those with a relationship of "related," "possibly related," or those with missing responses.

Of the most common TEAEs (≥2% in the All CZP group), those that occurred in a higher percentage of subjects in the All CZP group compared with the placebo group (difference of ≥2%) were upper respiratory tract infection (7.8% vs 5.1%), ALT increased (3.6% vs 1.5%), headache (3.6% vs 1.5%), AST increased (3.0% vs 0.7%), and sinusitis (2.7% vs 0.7%). In the PsA001 clinical cut data, there was no increase in TEAE risk overall with longer exposure to CZP (i.e. 3.5-fold increase in exposure).

In the CZP RA studies, the AE profile of CZP was as expected for an anti-TNFα therapy and was consistent with previous experience for CZP. No new safety signal was identified. There was generally no increase in incidence rates with long-term exposure. The AE profile of the PsA001 population and the CZP RA studies were generally similar. In the PsA population, events related to liver function analyses were among the most common TEAEs; these were not identified as common in the RA studies.

Serious adverse event / deaths / other significant events

Deaths

Two deaths (cardiac arrest, sudden death) were reported during the 24-week Double-Blind Treatment Period. Four additional deaths (breast cancer, sepsis, lymphoma, cardiac infarction) occurred after the subjects completed the 24-week Double-Blind Treatment Period (during the Dose-Blind or Open-Label Treatment Periods).

A review of the 6 fatal cases revealed the presence of confounding factors that contributed in part or wholly to the deaths. Examples of confounding factors in the deceased include hypertension, prior history of myocardial infarction, smoking, hyperlipidemia, hypercholesterolemia, concomitant drug use, and underlying medical conditions. Both the MAH and Investigator agreed that 3 cases (cardiac arrest, breast cancer, and myocardial infarction) were unrelated (not related or unlikely related) and 3 cases (sepsis, lymphoma, and sudden death) were considered related (possibly or probably related).

The standardized mortality ratios are similar across the general population and PsA population referent groups, ranging from 0.9 to 1.3. Based on standardized mortality ratio analyses, there was no evidence of excess mortality for CZP in PsA001 compared to general populations and PsA populations from epidemiological studies.

Serious adverse events

In the PsA001 Week 24 CSR data, the overall incidence of SAEs was similar between the All CZP group and the placebo group (6.6% and 4.4%, respectively). In the All CZP group, SAEs were reported most often in the SOC of Infections and infestations (1.2% vs 0.7% for placebo); for all other SOCs, the incidence was <1%. No individual SAE (by PT) was reported by more than 1 subject.

In the All CZP Safety Pool, SAEs were also reported most often in the SOC of Infections and infestations (2.8% for the All CZP group); however, the incidence rate of serious infections did not increase with long-term exposure (2.43/100 pt-yrs in the All CZP Safety Pool vs 3.06/100 pt-yrs in the Double-Blind Safety Pool). There was no increase in SAE risk with long-term exposure to CZP (data cutoff 31 May 2012).

The overall incidence of SAEs was slightly lower in the CZP 200mg Q2W group compared with the CZP 400mg Q4W group (5.8% vs 9.6%), although there were no notable differences in incidences for SOCs and PTs between the groups.

The types of SAEs were generally similar between the All CZP Safety Pool and the Double-Blind Safety Pool. As expected, a higher percentage of subjects in the All CZP group in the All CZP Safety Pool (13.5%) reported SAEs compared with the Double-Blind Safety Pool (6.6%); however, the incidence rate of SAEs did not increase with long-term CZP exposure (12.05/100 pt-yrs in the All CZP Safety Pool vs 17.27/100 pt-yrs in the Double-Blind Safety Pool). Furthermore, the individual SOCs were generally not increased with long-term exposure to CZP.

Table 18 Summary of SAEs in all SOCs, including HLTs with an incidence of at least 0.5% in the All CZP group in the All CZP Safety Pool during PsA001 (data cutoff 31 May 2012) (SS as treated)

System Organ Class High level term	Double-Blind Safety Pool						All CZP Safety Pool					
	CZP 200mg Q2W N=169		CZP 400mg Q4W N=165		All CZP N=334		CZP 200mg Q2W N=197		CZP 400mg Q4W N=196		All CZP N=393	
Patient exposure years	66.9		64.6		131.6		232.4		226.3		458.7	
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Any Serious TEAEs	8 (4.7)	12.26	14 (8.5)	22.53	22 (6.6)	17.27	24 (12.2)	10.89	28 (14.3)	13.27	52 (13.2)	12.05
Blood and lymphatic system disorders	0	0	0	0	0	0	0	0	0	0	0	0
Cardiac disorders	2 (1.2)	3.01	1 (0.6)	1.56	3 (0.9)	2.29	5 (2.5)	2.17	1 (0.5)	0.44	6 (1.5)	1.32
Ischaemic coronary artery disorders	1 (0.6)	1.50	1 (0.6)	1.56	2 (0.6)	1.53	3 (1.5)	1.30	1 (0.5)	0.44	4 (1.0)	0.88
Congenital, familial, and genetic disorders	0	0	0	0	0	0	0	0	0	0	0	0
Ear and labyrinth disorders	0	0	1 (0.6)	1.55	1 (0.3)	0.76	0	0	1 (0.5)	0.44	1 (0.3)	0.22
Eye disorders	0	0	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	1 (0.6)	1.50	0	0	1 (0.3)	0.76	2 (1.0) [1]	0.87	0	0	2 (0.5) [1]	0.44
General disorders and administration site conditions	0	0	1 (0.6)	1.55	1 (0.3)	0.76	1 (0.5)	0.43	2 (1.0)	0.89	3 (0.8)	0.66
Hepatobiliary disorders	0	0	0	0	0	0	0	0	1 (0.5)	0.44	1 (0.3)	0.22
Immune system disorders	0	0	0	0	0	0	0	0	0	0	0	0
Infections and infestations	2 (1.2)	3.01	2 (1.2)	3.11	4 (1.2)	3.06	4 (2.0)	1.74	7 (3.6)	3.14	11 (2.8)	2.43
Bacterial infections NEC	0	0	0	0	0	0	1 (0.5)	0.43	1 (0.5)	0.44	2 (0.5)	0.44
Lower respiratory tract and lung infections	1 (0.6)	1.50	2 (1.2)	3.11	3 (0.9)	2.29	1 (0.5)	0.43	3 (1.5)	1.33	4 (1.0)	0.88
Retroviral infections	0	0	0	0	0	0	1 (0.5)	0.43	1 (0.5)	0.44	2 (0.5)	0.44
Injury, poisoning, and procedural complications	0	0	2 (1.2)	3.11	2 (0.6)	1.52	3 (1.5)	1.30	4 (2.0)	1.80	7 (1.8)	1.54
Limb injuries NEC (incl. traumatic amputation)	0	0	0	0	0	0	1 (0.5)	0.43	1 (0.5)	0.44	2 (0.5)	0.44

System Organ Class High level term	Double-Blind Safety Pool						All CZP Safety Pool					
	CZP 200mg Q2W N=169		CZP 400mg Q4W N=165		All CZP N=334		CZP 200mg Q2W N=197		CZP 400mg Q4W N=196		All CZP N=393	
Patient exposure years	**66.9**		**64.6**		**131.6**		**232.4**		**226.3**		**458.7**	
	n (%)	**IR**	**n (%)**	**IR**	**n (%)**	**IR**	**n (%)**	**IR**	**n (%)**	**IR**	**n (%)**	**IR**
Muscle, tendon, and ligament injuries	0	0	1 (0.6)	1.55	1 (0.3)	0.76	0	0	2 (1.0)	0.89	2 (0.5)	0.44
Non-site specific injuries NEC	0	0	0	0	0	0	2 (1.0)	0.87	0	0	2 (0.5)	0.44
Investigations	1 (0.6)	1.50	0	0	1 (0.3)	0.76	1 (0.5)	0.43	0	0	1 (0.3)	0.22
Metabolism and nutrition disorders	0	0	2 (1.2)	3.11	2 (0.6)	1.52	1 (0.5)	0.43	2 (1.0)	0.89	3 (0.8)	0.66
Musculoskeletal and connective tissue disorders	0	0	2 (1.2)	3.12	2 (0.6)	1.53	2 (1.0)	0.86	5 (2.6)	2.24	7 (1.8)	1.54
Psoriatic arthropathies[2]	0	0	1 (0.6)	1.55	1 (0.3)	0.76	2 (1.0)	0.86	3 (1.5)	1.33	5 (1.3)	1.10
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	0	0	0	0	0	0	1 (0.5)	0.43	2 (1.0)	0.88	3 (0.8)	0.65
Breast and nipple neoplasms malignant	0	0	0	0	0	0	1 (0.5)	0.43	1 (0.5)	0.44	2 (0.5)	0.44
Nervous system disorders	0	0	1 (0.6)	1.55	1 (0.3)	0.76	1 (0.5)	0.43	3 (1.5)	1.33	4 (1.0)	0.87
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.6)	1.55	1 (0.3)	0.76	0	0	1 (0.5)	0.44	1 (0.3)	0.22
Psychiatric disorders	0	0	0	0	0	0	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	0	0	0	0	0	0	0	0
Reproductive system and breast disorders	1 (0.6)	1.50	0	0	1 (0.3)	0.76	2 (1.0)	0.87	2 (1.0)	0.89	4 (1.0)	0.88
Respiratory, thoracic, and mediastinal disorders	1 (0.6)	1.50	0	0	1 (0.3)	0.76	3 (1.5)	1.29	0	0	3 (0.8)	0.65
Skin and subcutaneous tissue disorders	1 (0.6)	1.50	0	0	1 (0.3)	0.76	1 (0.5)	0.43	0	0	1 (0.3)	0.22
Social circumstances	0	0	1 (0.6)	1.55	1 (0.3)	0.76	0	0	1 (0.5)	0.44	1 (0.3)	0.22
Surgical and medical procedures	0	0	0	0	0	0	0	0	1 (0.5)	0.44	1 (0.3)	0.22
Uncoded[3]	0	0	0	0	0	0	0	0	1 (0.5)	0.44	1 (0.3)	0.22
Vascular disorders	0	0	0	0	0	0	2 (1.0)	0.86	0	0	2 (0.5)	0.44

[1]An event of umbilical hernia was incorrectly coded as serious. Per the case report form, this event was nonserious.
[2]The events of psoriatic arthropathy were a worsening of psoriatic arthritis.
[3]One subjects (Subject 975/00219) had an uncoded event with a reported term of " lap band erosion". An additional subject (Subject 306/00579 in the CZP 200mg Q2W group) had an uncoded event with a reported term of "erysipelas – leg ulcer of left les" that is not captured in PsA001 (data cutoff 31 May 2012) Table 8.11:2, but can be found in PsA001 (data cutoff 31 May 2012).

In the RA studies, the most common SAEs were infections, as expected for this class of drug. Overall, the pattern and incidence of SAEs were in line with those expected for this patient population treated with anti-TNFα therapies. The SAE profile did not change with long-term exposure to CZP. The SAE profile of the PsA001 population and the CZP RA studies were generally similar, and no new safety signals were identified.

Significant adverse events

Infections

The incidence of infection TEAEs in PsA001 was similar between CZP-treated and placebo-treated subjects (35.8% and 38.2%, respectively) for the 24-week Double-Blind Treatment Period. The most common Infection and infestation TEAEs were in the HLT Upper respiratory tract infection, which were reported at a higher incidence in the All CZP group compared with the placebo group (23.8% vs 15.4%). The most common infection TEAEs (by PT) were nasopharyngitis (8.7% in the All CZP group and 7.4% in the placebo group) and upper respiratory tract infection (7.8% in the All CZP group and 5.1% in the placebo group). In the All CZP group, a total of 12 subjects (3.6% vs 2.2% in the placebo group) reported herpes viral infections, including 2 subjects (0.6%) reporting herpes zoster.

Evaluation of both the incidence rate and event rate of infections indicated that long term exposure to CZP did not result in increasing recurrence of infections.

In the PsA001 Week 24 data, serious infections were reported by 4 subjects (1.2%) in the All CZP group (2 subjects in the CZP 200mg Q2W group and 2 subjects in the CZP 400mg Q4W group) and 1 subject (0.7%) in the placebo group. The SAEs in the CZP 200mg Q2W group were bronchopneumonia with pleuritis and herpes zoster, and in the 400mg Q4W pneumonia and bronchitis. In the placebo group 1 patient experienced pyelonephritis.

In the All CZP Safety Pool in the clinical cut data (data cutoff 31 May 2012), 14 serious infections were reported by 11 subjects (2.8%) in the All CZP group (4 subjects in the CZP 200mg Q2W group and 7 subjects in the CZP 400mg Q4W group). The most common serious infection by HLT was lower respiratory tract and lung infections that included 5 events reported by 4 subjects (1.0%) in the All CZP Safety Pool; there was no increased SAE risk of infections with longer exposure to CZP (0.88/100 vs 2.29/100 pt-yrs in the All CZP group in the All CZP Safety Pool and Double-Blind Safety Pool, respectively.

The incidence rate of Infections and infestations TEAEs leading to withdrawal increased over time (2.19/100 pt-yrs in the All CZP Safety Pool vs 0.76/100 pt-yrs in the Double-Blind Safety Pool). This was due, in part, to an increase in tuberculous infections.

There were no events of TB reported during the 24-week Double-Blind Treatment Period. Subjects with negative TB test (PPD or Elispot/Quantiferon) results at Screening/Baseline had to be retested for TB at Weeks 48 and 96. Overall, 8 subjects had either a positive PPD test or latent or active TB recorded as a TEAE at the time of the data cutoff (31 May 2012). None of the PPD conversions led to the diagnosis of active TB (up to the point of the data cutoff); however, all the subjects with suspected latent or active TB were withdrawn from the study, in accordance with the protocol.

No rare or opportunistic infections were reported in the PsA001 Week 24 CSR data or the reanalysis data. Three opportunistic infections were reported after the 24-week Double-Blind Treatment Period, 2 SAEs of HIV infection and 1 nonserious TEAE of herpes ophthalmic

In the RA studies, there was an increase in the overall incidence of infections, serious infections, and infections leading to withdrawal with CZP therapy compared with placebo; however, there was no increase in risk with increased duration of exposure. Most infections were not serious and were those that commonly occur in the general RA population, such as upper respiratory tract infections and urinary tract infections. The incidence rates of opportunistic infections were low and are consistent with recent reviews of rare infections observed with anti-TNFα therapy use.

The profile of infections associated with CZP treatment was generally similar between the PsA001 study and the RA studies and is consistent with other anti-TNFα therapies. No new safety signals were identified.

Malignancies

One malignancy (cervix carcinoma) was reported during the 24-week Double-Blind Treatment Period in the PsA001 in the CZP 400mg Q4W group. There was 1 premalignant condition reported, an SAE of vulvar dysplasia, in the CZP 200mg Q2W group. One subject in the placebo group reported after database lock an AE of breast cancer that occurred during the Double-Blind Treatment Period.

During the Dose-Blind and Open-Label Treatment Periods, 4 malignancies were reported, including breast cancer (2 events), lymphoma, and thyroid neoplasm. The lymphoma and 1 event of breast cancer were fatal. The thyroid neoplasm was reported as thyroid nodules and was considered to be mild in intensity, and did not lead to a change in study medication. A computerized axial tomography scan confirmed that no intervention or additional assessments were necessary. This is interpreted as a non-malignant neoplasm.

In the RA studies, the overall incidence of malignancies was similar between CZP-treated and placebo-treated subjects. There was no evidence of an increased risk of malignancies with longer exposure to CZP. The profile of malignancies associated with CZP treatment was generally similar between the PsA001 population and the RA studies and is consistent with other anti-TNFα therapies. No new safety signals were identified.

Cardiovascular system

A total of 8.3% of all subjects reported a variety of past or concomitant cardiac disorders and 40.1% of all subjects reported a variety of past or concomitant vascular disorders

The incidence of cardiac events in the PsA001 Week 24 data were similar between the CZP 200mg Q2W (2.2%) and CZP 400mg Q4W (1.5%) groups. No individual cardiac event (by PT) was reported by more than 1 subject. There were no events of or related to congestive heart failure. Serious CV events included acute myocardial infarction, angina unstable, cardiac arrest, and cerebrovascular accident. The profile of CV events did not change and there was no increased TEAE risk of CV events with longer exposure to CZP. There was no evidence of a cardiac signal and no event of or related to congestive heart failure.

In the RA studies, the overall incidence of CV TEAEs was greater with CZP treatment compared with placebo, but there appeared to be no increased risk overall for cardiovascular TEAEs with increased duration of exposure. Hypertension was the most common cardiovascular event. Heart failures, including congestive heart failure, were only reported in CZP-treated subjects, but the risk did not increase with increased exposure. Overall, no new safety concerns for CV events were identified.

Neurological system

There were no TEAEs suggestive of demyelinating disorders or notable neurological SAEs reported during the 24-week Double-Blind Treatment Period. Similarly, in the RA studies, no AEs suggesting demyelination were reported.

Hematology

Reports of leukopenia, neutropenia, and thrombocytopenia were rare throughout the study. All of these events were non serious and mild or moderate in intensity. There were no serious events of bone marrow aplasia/dysplasia reported during the study. In the RA studies, 4 serious blood dyscrasias were reported; however, the number of serious dyscrasias is too small to draw conclusions on the potential effect of CZP on such events. The profile of hematological events was generally similar between the PsA001 population and the RA studies and is consistent with other anti-TNFα therapies. No new safety signals were identified.

Hepatic system

In the PsA001 Week 24 data, the incidence of TEAEs in the SOC of Hepatobiliary disorders was similar between the All CZP and placebo groups (2.4% and 2.2%, respectively; however, in the SOC of investigations, TEAEs related to liver function parameters were reported at a greater incidence in CZP-treated subjects compared with placebo-treated subjects. In the HLT of liver function analyses the incidence of TEAEs was 7.5% in the All CZP group compared with 3.7% in the placebo group, and included TEAEs of ALT increased (3.6% vs 1.5%), AST increased (3.0% vs 0.7%), hepatic enzyme increased (2.7% vs 1.5%), GGT increased (1.2% vs 0.7%), liver function test abnormal (0.9% vs 0.7%), and blood bilirubin increased (0.3% vs 0). Other TEAEs related to liver function parameters included hyperbilirubinemia (0.3% vs 0) and hypertransaminasemia (0.3% vs 0.7%). All TEAEs but 1 event of hepatic enzyme increased were mild or moderate in intensity. Most events were considered to be at least possibly related to study medication.

Concomitant use of DMARDs (e.g. MTX) resulted in a higher incidence of hepatic TEAEs with CZP treatment compared with placebo (8.5% in the CZP 200mg Q2W+CZP 400mg Q4W group vs 4.7% in the placebo group). There was no increased risk in hepatic TEAEs (overall or by Baseline use of DMARDs) with long-term CZP exposure. Differences between the All CZP and placebo groups were largely due to differences in nonsignificant shifts (from normal at Baseline to a post-Baseline value of >1 to <2xULN). Very high elevations (≥10xULN) of ALT and AST did not occur in any subject. Three subjects (all in the CZP 400mg Q4W group) had both elevations of bilirubin ≥1xULN and AST or ALT ≥3xULN. No subjects fulfilled the Hy's law criteria (ALT or AST ≥3xULN and total bilirubin ≥2xULN).

In the RA studies, the majority of hepatic events involved the liver function analyses HLT, with the most common event being ALT increased. There were slightly more hepatic events in CZP-treated subjects compared with placebo-treated subjects; however, there was no overall increased risk for hepatic events with longer CZP exposure. Markedly abnormal elevations in liver function parameters were low and similar between CZP-treated and placebo-treated subjects.

Injection reactions (including hypersensitivity)

There was no acute systemic hypersensitivity injection reaction reported in CZP-treated subjects. The incidence of delayed systemic hypersensitivity injection reactions was low (≤1.5% in the All CZP group and placebo group). Injection site reaction was the most common injection reaction, and the incidence was 1.8% in the All CZP group compared with 0.7% in the placebo group. There was no increased TEAE risk of any type of injection/hypersensitivity reaction with longer exposure to CZP.

In the RA studies, as expected, more injection site reactions and hypersensitivity events occurred in subjects treated with CZP compared with placebo; however, the incidence of these events did not increase with increased exposure to CZP. The profile of injection and hypersensitivity reactions associated with CZP treatment was generally similar between the PsA001 population and the RA studies.

Autoimmune disorders

There have been no reports of autoimmune disorders, no TEAEs suggestive of demyelinating disorders or notable neurological SAEs, and the occurrence of serious skin disorders was rare. One case of cutaneous lupus erythematosus was reported in the 200mg 2QW group. In RA studies, reports of autoimmune disorders (e.g. lupus-like illness, autoantibodies, and sarcoidosis) were rare and consistent to that observed with other anti-TNFα therapies

Adverse events by anti-CZP antibody status

In the PsA001 Week 24 CSR data, a total of 36 of 332 subjects (10.8%) were positive for anti-CZP antibodies. The overall incidence of TEAEs was 75.0% in subjects who were anti-CZP positive

compared with 60.8% in subjects who were anti-CZP negative. The incidences of TEAEs severe in intensity, and discontinuation due to TEAEs were similar regardless of anti-CZP antibody status. The incidences of drug-related TEAEs and SAEs were higher in anti-CZP positive subjects compared with anti-CZP negative subjects (33.3% vs 25.0% and 11.1% vs 6.1%, respectively).

Table 19 Overall summary of TEAEs by anti-CZP antibody status for subjects with CZP exposure during the 24-week Double-Blind Treatment Period (SS)

	Anti-CZP antibody status			
	Any N=332 n (%)	Negative N=296 n (%)	Positive N=36 n (%)	After the onset of positive antibody status N=36 n (%)
Any TEAEs	207 (62.3)	180 (60.8)	27 (75.0)	15 (41.7)
Severe TEAEs	15 (4.5)	13 (4.4)	2 (5.6)	1 (2.8)
Drug-related(1) TEAEs	86 (25.9)	74 (25.0)	12 (33.3)	7 (19.4)
Serious TEAEs	22 (6.6)	18 (6.1)	4 (11.1)	3 (8.3)
Discontinuation due to TEAEs	10 (3.0)	9 (3.0)	1 (2.8)	1 (2.8)
Death	2 (0.6)	2 (0.7)	0	0

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: Only data from subjects treated with CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data were included.
(1)Drug-related TEAEs are those with a relationship of "related," "possibly related," or those with missing responses.

In PsA001, the incidences of TEAEs reported after the onset of positive antibody status were generally similar to those reported by subjects who were always anti-CZP antibody negative; however, there were too few antibody-positive subjects to draw meaningful conclusions.

Laboratory findings

No clinically meaningful adverse changes in haematology values and serum biochemistry values, other than changes in liver function parameters, were observed. Markedly abnormal hematology and biochemistry values were low and similar between CZP- and placebo-treated subjects. No clinically significant vital signs or physical findings were noted in the Double-Blind Treatment Period.

Results for PsA001 are consistent with the RA studies; no clinically relevant effects of CZP were observed on markedly abnormal (Grade 3 or 4) haematology or biochemistry values.

Discontinuation due to adverse events

In the PsA001 Week 24 CSR data, the overall incidence of TEAEs leading to permanent study medication discontinuation was low (3.0% in the All CZP group and 1.5% in the placebo group. No individual TEAEs leading to withdrawal was reported by more than 1 subject.

The types of TEAEs leading to withdrawal were generally similar in the All CZP Safety Pool and the Double-Blind Safety Pool. As expected, a higher percentage of subjects in the All CZP group in the All CZP Safety Pool (7.6%) reported TEAEs leading to withdrawal compared with the Double-Blind Safety Pool (2.7%).The incidence rate of TEAEs leading to withdrawal did not increase with long-term exposure (6.6/100 pt-yrs in the All CZP Safety Pool vs 6.9/100 pt-yrs in the Double-Blind Safety Pool), suggesting that there was no increased risk of TEAEs leading to withdrawal with long-term exposure

The most common TEAEs that led to withdrawal in the All CZP Safety Pool were in the SOCs of Infections and infestations (2.5%); Investigations (1.3%); and Skin and subcutaneous tissue disorders (1.0%). The incidence rate of Infections and infestations TEAEs leading to withdrawal increased over time (2.19/100 pt-yrs in the All CZP Safety Pool vs 0.76/100 pt-yrs in the Double-Blind Safety Pool). This was due, in part, to an increase in tuberculous infections; however, a comparison between the long-term and 24-week data is not valid as no TB retests were performed until Week 48

An imbalance in the incidence rate of TEAEs leading to withdrawal overall between the CZP 200mg Q2W and CZP 400mg Q4W groups was observed in the Double-Blind Safety Pool (4.51/100 vs 9.37/100 pt-yrs); however, this difference was not apparent with longer CZP exposure (6.53/100 vs 6.68/100 pt-yrs.

Table 20 Summary of TEAEs leading to permanent study medication discontinuation during the 24-week Double-Blind Treatment Period (SS)

System Organ Class Preferred term	PBO(1) N=136 n (%)	CZP 200mg Q2W N=138 n (%)	CZP 400mg Q4W N=135 n (%)	All CZP(2) N=332 n (%)
Any TEAE leading to permanent study medication discontinuation	2 (1.5)	4 (2.9)	6 (4.4)	10 (3.0)
Cardiac disorders	0	1 (0.7)	0	1 (0.3)
Cardiac arrest	0	1 (0.7)	0	1 (0.3)
General disorders and administration site conditions	0	0	1 (0.7)	1 (0.3)
Sudden death	0	0	1 (0.7)	1 (0.3)
Immune system disorders	1 (0.7)	0	0	0
Allergic oedema	1 (0.7)	0	0	0
Infection and infestations	0	0	1 (0.7)	1 (0.3)
Sinusitis	0	0	1 (0.7)	1 (0.3)
Investigations	0	2 (1.4)	0	2 (0.6)
Alanine aminotransferase increased	0	1 (0.7)	0	1 (0.3)
Aspartate aminotransferase increased	0	1 (0.7)	0	1 (0.3)
Hepatic enzyme increased	0	1 (0.7)	0	1 (0.3)
Musculoskeletal and connective tissue disorders	0	0	1 (0.7)	1 (0.3)
Psoriatic arthropathy(3)	0	0	1 (0.7)	1 (0.3)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	0	0	1 (0.7)	1 (0.3)
Cervix carcinoma stage 0	0	0	1 (0.7)	1 (0.3)
Nervous system disorders	0	0	1 (0.7)	1 (0.3)
Cerebrovascular accident	0	0	1 (0.7)	1 (0.3)
Pregnancy, puerperium, and perinatal conditions	0	0	1 (0.7)	1 (0.3)
Pregnancy	0	0	1 (0.7)	1 (0.3)

System Organ Class Preferred term	PBO(1) N=136 n (%)	CZP 200mg Q2W N=138 n (%)	CZP 400mg Q4W N=135 n (%)	All CZP(2) N=332 n (%)
Respiratory, thoracic, and mediastinal disorders	1 (0.7)	1 (0.7)	0	1 (0.3)
Dyspnoea	1 (0.7)	0	0	0
Pleurisy	0	1 (0.7)	0	1 (0.3)

CZP=certolizumab pegol; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SS=Safety Set; TEAE=treatment-emergent adverse event
(1)For the entire placebo group, CZP data from placebo subjects were not utilized.
(2)The All CZP column includes CZP 200mg Q2W, CZP 400mg Q4W, and the escaped placebo subjects with their CZP data.
(3)The event of psoriatic arthropathy was a worsening of psoriatic arthritis.

2.5.2. Discussion on clinical safety

In PsA001, the AE profile of CZP was as expected for an anti-TNFα therapy and was consistent with previous experience for CZP. The incidences of TEAEs, including severe and drug-related TEAEs, reported during the Double-Blind Treatment Period were similar between the All CZP and placebo groups. The most common TEAEs in the All CZP group compared with the placebo were upper respiratory tract infection (7.8% vs 5.1%), ALT increased (3.6% vs 1.5%), headache (3.6% vs 1.5%), AST increased (3.0% vs 0.7%), and sinusitis (2.7% vs 0.7%).

The AE profile of the PsA001 population and the CZP RA studies were generally similar. In the PsA population, events related to liver function analyses were among the most common TEAEs and seemed to be more common in the PsA population than in RA cohorts earlier studied. Hepatic TEAEs were reported by more often in subjects with Baseline DMARDs compared with subjects without Baseline DMARD use. It is acknowledged that it is difficult to make meaningful comparisons between the subgroups due to the small number of subjects with hepatic events in each subgroup. In future PSURS, the potential effect of combination therapy with Cimzia and DMARD should be presented in separate analyses, including per indication and dosing regimen separately. Further, when presenting elevation of liver enzymes, the actual levels should be presented, to facilitate evaluation of the clinical significance.

During the procedure the MAH provided narratives for 4 subjects that experienced a combination of elevated bilirubin and ALT ≥3xULN. Overall, 2 of the cases were on concomitant isoniazid medication. The remaining 2 cases did not experience an increased bilirubin. All patients had normalized values during unchanged or reintroduced CZP treatment. It is noted that all 4 patients received 400mg Q4W, however, these cases are too few to allow for conclusions regarding a different safety profile for this dosing regimen.

The types of SAEs were generally similar between the All CZP Safety Pool and the Double-Blind Safety Pool. As expected, a higher percentage of subjects in the All CZP group in the All CZP Safety Pool (13.5%) reported SAEs compared with the Double-Blind Safety Pool (6.6%); however, the incidence rate of SAEs did not increase with long-term CZP exposure (12.05/100 pt-yrs in the All CZP Safety Pool vs 17.27/100 pt-yrs in the Double-Blind Safety Pool). Furthermore, the individual SOCs were generally not increased with long-term exposure to CZP.

The SAE profile of the PsA001 population and the CZP RA studies were generally similar, and no new safety signals were identified. The most common SAEs in the Double-Blind Treatment Period were Infections and infestations (1.2% for the All CZP group vs 0.7% for placebo). In the All CZP Safety Pool, SAEs most often reported were infections and infestations (2.8% for the All CZP group).

Six fatal events were reported, whereof 2 in the double-blind phase of the study. The types of events leading to death in PsA001 (cardiac disorders, infections, and malignancies) are consistent with the types of fatal events reported in the RA studies and are known risks with anti-TNFα medications, and therefore, do not present a new safety signal.

In the PsA001 Week 24 data, the most common infection and infestation TEAEs were in the HLT upper respiratory tract infection, which were reported at a higher incidence in the All CZP group compared with the placebo group (23.8% vs 15.4%). The 200mg Q2W group had an incidence of 27.5%, and the 400mg Q4W group 28.1%. The All CZP group included the escaped placebo subjects with their CZP data, which is due to the lower figure (23.8%) for this group.

In the All CZP Safety Pool in the clinical cut data (data cutoff 31 May 2012), 14 serious infections were reported by 11 subjects (2.8%) in the All CZP group (4 subjects in the CZP 200mg Q2W group and 7 subjects in the CZP 400mg Q4W group). The most common serious infection by HLT was lower respiratory tract and lung infections that included 5 events reported by 4 subjects (1.0%) in the All CZP Safety Pool; there was no increased SAE risk of infections with longer exposure to CZP (0.88/100 vs 2.29/100 pt-yrs in the All CZP group in the All CZP Safety Pool and Double-Blind Safety Pool, respectively; PsA001.

In order to ensure that the higher Cmax for patients treated with 400mg Q4W did not entail any safety risks, data from the 2 dosing groups was presented separately by the MAH. Nearly 6 months of additional data through a cutoff date of 16 Nov 2012 were provided for the CZP 200mg Q2W, CZP 400mg Q4W, and All CZP groups and represented 611.7 patient-years (pt-yrs) of CZP exposure (compared with 458.7 pt-yrs in the original filing). When comparing between the CZP 200mg Q2W (N=198) and CZP 400mg Q4W (N=195) dosing regimens, which had similar patient-years of exposure, the incidences of TEAEs, drug-related TEAEs, severe TEAEs, serious adverse events, and discontinuation due to TEAEs were similar in the safety update, which is consistent with the initial data submitted with cutoff date of 31 May 2012 . There were no additional deaths reported.

Specifically related to the concern that the CZP 400mg Q4W group has a higher maximum concentration, potential effects on the liver were evaluated. The incidence rate for hepatobiliary disorders was 3.07 pt-yrs in the CZP 400mg Q4W group and 3.02 pt-yrs in the CZP 200mg Q2W group. The incidence rate for liver function analyses was 7.64 pt-yrs in the CZP 400mg Q4W group and was 9.22 pt-yrs in the CZP 200mg Q2W group. The incidence of subjects with elevations in total bilirubin ≥1.5x upper limit of normal (ULN) was low in both groups (1.5% in the CZP 200mg Q2W group and 2.6% in the CZP 400mg Q4W group). There were no differences between the dosing regimens with regard to subjects with elevations in AST and ALT. Elevations in ALT or AST were generally transient and returned to normal or nonclinically significant values while the subjects remained on CZP treatment. One subject reported a hepatic TEAE (asthenia) associated with elevated AST or ALT (≥3xULN). A total of 4 subjects each in the CZP 400mg Q4W group had simultaneous post-Baseline liver function test elevations of bilirubin ≥1x upper limit of normal (ULN) and ALT or AST ≥3xULN. These subjects presented with different combinations of risk factors at Baseline including current and former alcohol and tobacco use (3 subjects); in addition, 1 subject had a history of liver steatosis. Transient high levels of transaminase values were observed in each subject. Taken together, these data suggest that factors other than CZP treatment contributed to the elevated values and further suggest that the maximum concentration of CZP 400mg Q4W did not play a role in the elevations. Overall, the safety profile of both CZP dose regimens in subjects with psoriatic arthritis as described in the safety update is consistent with the data submitted in the original dataset submitted with cutoff date of 31 May 2012. No new safety signals were identified with longer exposure to CZP.

Throughout PsA001, malignancies were reported by a total of 5 CZP-treated subjects (cervix carcinoma, breast cancer [2 events], lymphoma, and thyroid neoplasm) and 1 placebo-treated subject

(breast cancer). The profile of malignancies associated with CZP treatment was generally similar between the PsA001 population and the RA studies and is consistent with other anti-TNFα therapies. No new safety signals were identified.

During the procedure the MAH provided a safety update of the PSA001 study. The safety update provided an additional 153 patient-years of CZP exposure, 56 additional subjects with ≥12 months of exposure, and 62 additional subjects with ≥24 months of exposure. The safety data update was consistent with the initial data provided. There were no treatment-emergent adverse events, that increased in incidence rate with increased exposure to CZP and in general no new safety signals were identified. When comparing between the 2 dosing regimens, which had similar patient-years of exposure, the incidences of TEAEs, drug-related TEAEs, severe TEAEs, SAEs, discontinuation due to TEAEs, and deaths were similar between the CZP 200mg Q2W and CZP 400mg Q4W groups in this Safety Update, which is consistent with the original data submitted. Overall the number of patients with PsA who received CZP treatment for ≥ 24 months remain limited. Further information concerning the long term safety of CZP in the treatment of PsA will become available in the post marketing setting and through the submission of the final results of Study PSA001 by Q2 2016 as described in the RMP. This is considered sufficient to address long-term safety in PsA. In addition extrapolation from long term safety follow up within on-going RA registries, and some data from patients with PsA from at least the ARTIS registry will also become available.

Supportive safety data were provided from 2 completed psoriasis studies (C87040 and C87044) that includes 117 subjects with at least 1 exposure, 105 subjects exposed for a total of 12 weeks of double-blind treatment, and 62 subjects exposed for an additional 12 weeks of open-label treatment. No unexpected safety signals were observed with CZP in C87040 or C87044. The studies did not reveal any major concerns regarding safety for the treatment or retreatment of subjects with moderate to severe chronic plaque psoriasis who relapsed after a positive response to initial treatment with CZP.

A brief summary of the CZP safety profile in 2518 CD subjects with an estimated total of 2837.0 pt-yrs exposure to CZP treatment was provided. Overall, the AE profile for CZP described in subjects with CD is typical of a TNFα antagonist. None of the data suggest any new safety signals following longer-term treatment with CZP in subjects with CD.

2.5.3. Conclusions on clinical safety

CZP was generally well tolerated during in study PSA001. The most common AE was non-serious infections, such as nasopharyngitis. No new safety signal has been identified in the psoriatic arthritic population studied in PSA001. Comparisons were made to the RA safety databases. The safety profile for PsA patients was consistent with the safety profile in RA and previous experience with Cimzia, with the exception of hepatic TEAEs which were generally higher in patients with PsA as compared to the RA population. Hepatic events are known risks for CZP, already addressed as part of the RMP and the product information. The MAH will continue to closely monitor these events in future PSURs.

As described in the RMP the MAH will submit the final results of Study PSA001 by Q2 2016 which will bring additional data to further characterize the long term safety profile of CZP treatment in psoriatic arthritic patients up to 216 weeks of treatment.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

2.6.1. PRAC advice

The CHMP received the following PRAC advice on the submitted Risk Management Plan.

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 9.3 the PRAC considers by consensus that the risk management system for certolizumab pegol (Cimzia) for the treatment of active PsA either alone or in combination with MTX in adults when the response to previous DMARD therapy has been inadequate.

Advice on conditions of the marketing authorisation

The PRAC do not advise any changes to the current conditions of the Marketing Authorisation.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

Table 21 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	• Infections including TB and serious opportunistic infections • Moderate to severe congestive heart failure (NYHA class III/IV) • Hypersensitivity reactions • Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma • Demyelinating-like disorders • Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia • Lupus and lupus-like illness • Immunogenicity including sarcoidosis • New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions • Hepatobiliary events including hepatitis, hepatic enzymes increased, and cholestasis
Important potential risks	• Ischemic cardiac events • Serious bleeding events • Hepatitis B virus reactivation
Important missing information	• Pregnancy and lactation • Children and adolescents • Elderly • Patients with renal or hepatic impairment • Potential for overdose • Potential for medication errors • Off-label use • Concomitant use with DMARDs other than MTX • Use by patients with prior anti-TNF use • Vaccination • Long-term use in axial spondyloarthritis

DMARD=disease modifying antirheumatic drug, MTX=methotrexate, NYHA=New York Heart Association, TB=tuberculosis, TNFα=tumor necrosis factor α

Pharmacovigilance plans

Table 22 Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Registries • ARTIS (RA0021) • RABBIT (RA0020) • NDB (RA0005) • BSRBR (RA0022) (Category 3)	Details of the objectives for each registry are described in Module SV of the RMP	In general, registries capture events related to important identified and potential risks.	Ongoing	Ongoing, final reports to be provided by 31 Jul 2018, except for BSRBR anticipated by 31 May 2019
Pregnancy • Ongoing studies • Post marketing reports • Registries (ARTIS, RABBIT) (Category 3)	To gather pregnancy data in a proactive and systematic way	Missing information Pregnancy and lactation Children and adolescents	Ongoing	Data will be provided concomitantly with the PSURs
AS001 Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with active axial spondyloarthritis (axial SpA) (Category 3)	Provide data on long-term use of CZP in axial spondyloarthritis subjects up to 204 weeks of treatment and a Safety Follow-Up Visit 10 weeks after their last dose of study medication	Missing information Long-term use in axial spondyloarthritis	Ongoing	The Week 48 interim report is in preparation, and the final complete report is planned for Q2 2016
PsA001 Phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of certolizumab pegol in subjects with adult-onset active and progressive psoriatic arthritis (PsA) Category 3	Provide data on long-term use of CZP in psoriatic arthritis subjects up to 216 weeks of treatment and a Safety Follow-Up Visit 10 weeks after their last dose of study medication	Important missing information Long-term use in psoriatic arthritis	Ongoing	The Week 48 interim report is in preparation, and the final complete report is planned for Q2 2016

Risk minimisation measures

Table 23 Summary table of risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Infections including TB and serious opportunistic infections	• SmPC Section 4.8: addresses the risk of infections and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.4: includes a warning statement to perform screening tests for TB prior to initiating therapy, as well as appropriate anti-TB treatment in cases of latent TB infection. • SmPC Section 4.3: includes active TB and other severe infections as Contraindications	Educational program including HCP and patient surveys to assess the educational materials
Moderate to severe congestive heart failure (NYHA class III/IV)	• SmPC Section 4.8: addresses the risks of CHF and cardiac ischemic events and their characteristics • SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.3: includes moderate to severe heart failure under Contraindications	Educational program including HCP and patient surveys to assess the educational materials
Hypersensitivity reactions	• SmPC Section 4.4 : includes Special warnings and precautions for use • SmPC Section 4.3: includes hypersensitivity reactions as Contraindications	Educational program including HCP and patient surveys to assess the educational materials
Malignancies including lymphoma, leukemia, Merkel cell carcinoma, Hepatosplenic T-cell lymphoma, and melanoma	• SmPC Section 4.8: addresses the risk of malignancies, including lymphoma, leukemia, Merkel cell carcinoma, and melanoma, and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use	Educational program including HCP and patient surveys to assess the educational materials
Demyelinating-like disorders	• SmPC Section 4.4: includes Special warnings and precautions for use	None
Aplastic anemia, neutropenia, thrombocytopenia, pancytopenia, and leukopenia	• SmPC Section 4.8: addresses the risks of anemia, neutropenia, thrombocytopenia, leukopenia, and pancytopenia, and their characteristics • SmPC Section 4.4: includes Special warnings and precautions for use	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Lupus and lupus-like illness	• SmPC Section 4.8: addresses the risk of autoimmune disorders and its characteristics • SmPC Section 4.4: includes Special warnings and precautions for use	None
Immunogenicity including sarcoidosis	• SmPC Section 5.1: addresses the risk of immunogenicity and its characteristics • SmPC Section 4.8: includes sarcoidosis in the table of adverse drug reactions	None
New onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions	• SmPC Section 4.8: includes the risk of new onset or worsening of psoriasis (including palmoplantar pustular psoriasis) and related conditions in the table of adverse drug reactions	None
Hepatobiliary events including hepatitis, hepatic enzyme increased, and cholestasis	• SmPC Section 4.8: includes the risk of hepatobiliary events including hepatitis, hepatic enzyme increased, and cholestasis in the table of adverse drug reaction • SmPC Section 4.2: includes information on risk of use in patients with hepatic impairment	None
Important potential risks		
Ischemic cardiac events	• SmPC Section 4.8: addresses the risks of cardiac ischemic events	None
Serious bleeding events	• SmPC Section 4.4: includes Special warnings and precautions for use, and describes the aPTT assay interaction and explains the use of caution in the interpretation of abnormal coagulation test results	Educational program including HCP and patient surveys to assess the educational materials
Hepatitis B virus reactivation	• SmPC Section 4.4: includes Special warnings and precautions for use to perform screening tests for HBV prior to initiating therapy, and monitoring during treatment and for several months following termination of therapy	Educational program including HCP and patient surveys to assess the educational materials
Missing information		
Pregnancy and lactation	• SmPC Section 4.6: addresses the risk of use during pregnancy and lactation • SmPC Section 4.6: addresses the increased risk for infection in an infant whose mother was treated with CZP during pregnancy • SmPC Section 4.8: addresses pregnancy outcome risk (spontaneous abortion)	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Children and adolescents	• SmPC Section 4.2: includes information on risk of use in children and adolescents • SmPC Section 4.6: addresses the increased risk for infection in an infant whose mother was treated with CZP during pregnancy	None
Elderly	• SmPC Section 4.2 and Section 4.4: includes information on the risk of use in elderly patients	None
Patients with renal or hepatic impairment	• SmPC Section 5.2: includes PK properties • SmPC Section 4.2: describes the absence of data on Patients with renal or hepatic impairment	None
Potential for overdose	• SmPC Section 4.9: includes a description on the risk of overdose	None. The risk of overdose has been extremely minimal to date.
Potential for medication errors	• SmPC Section 4.2: the text is proposed to be separated into 2 parts: loading dose and maintenance dose in order to enhance clarity and ensure that the loading dose is correctly administrated. The review of the proposed text is ongoing as part of the PSUR6 assessment	An educational program serves to minimize the risks of erroneous administration by clearly describing the method of administration and the amount to be administered. The program includes HCP and patient surveys to assess the educational materials.
Off label use	• SmPC Section 4.1: includes therapeutic indications	None
Concomitant use with DMARDs other than MTX	• SmPC Section 4.5: includes information on risk of use with DMARDs other than MTX	None
Previous use of anti TNF therapy	• SmPC Section 4.4 includes the following text: There are limited data on the use of Cimzia in patients who have experienced a severe hypersensitivity reaction towards another TNF antagonist; in these patients caution is needed	None
Vaccination	• SmPC Section 4.4: includes Special warnings and precautions for use • SmPC Section 4.6: addresses the increased risk for infection in an infant whose mother was treated with CZP during pregnancy	Educational program including patient surveys to assess the educational materials
Long-term use in axial spondyloarthritis	• The safety risk of CZP in long-term use in axial spondyloarthritis is yet to be elucidated (per proposed EU SmPC).	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures

aPTT=activated partial thromboplastin time, CHF=congestive heart failure, DMARDs=disease modifying antirheumatic drugs, HBV=hepatitis B virus, HCP=health care professional, MTX=methotrexate, NYHA=New York Heart Association, PK=pharmacokinetic, SmPC=Summary of product characteristics, TB=tuberculosis, TNF=tumor necrosis factor

The CHMP endorsed this advice without changes.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1of the SmPC have been updated (**addition**; ~~deletion~~).

The Package Leaflet has been updated accordingly.

4.1 Therapeutic indications

[…]

Psoriatic arthritis

Cimzia, in combination with MTX, is indicated for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

4.2 Posology and method of administration

[…]

Posology

Loading dose

The recommended starting dose of Cimzia for adult patients is 400 mg (given as 2 subcutaneous injections of 200 mg each on one day) at weeks 0, 2 and 4. For rheumatoid arthritis **and psoriatic arthritis**, MTX should be continued during treatment with Cimzia where appropriate.

Maintenance dose

[…]

Psoriatic arthritis

After the starting dose, the recommended maintenance dose of Cimzia for adult patients with psoriatic arthritis is 200 mg every 2 weeks. Once clinical response is confirmed, an alternative maintenance dosing of 400 mg every 4 weeks can be considered. MTX should be continued during treatment with Cimzia where appropriate.

4.8 Undesirable effects

[…]

Psoriatic arthritis

Cimzia was studied in 409 patients with psoriatic arthritis in a placebo-controlled clinical trial (PsA001) for up to 30 months. The safety profile for psoriatic arthritis patients treated with Cimzia was consistent with the safety profile in rheumatoid arthritis and previous experience with Cimzia.

[…]

Malignancies and lymphoproliferative disorders

Excluding non-melanoma of the skin, 121 malignancies including 5 cases of lymphoma were observed in the Cimzia RA clinical trials in which a total of 4,049 patients were treated, representing 9,277 patient-years. Cases of lymphoma occurred at an incidence rate of 0.05 per 100 patient-years and melanoma at an incidence rate of 0.08 per 100 patient-years with Cimzia in rheumatoid arthritis clinical trials (see section 4.4). **One case of lymphoma was also observed in the Phase III psoriatic arthritis clinical trial.**

5.1 Pharmacodynamic properties

See SmPC for details.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Cimzia 200 mg solution for injection. The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

In study PSA001, 200mg Q2W and 400mg Q4W was tested in comparison to placebo during a 24 week period. For the primary endpoint, the percentage of ACR20 responders at Week 12 was statistically significantly greater ($p<0.001$) in both active groups (CZP 200mg Q2W and CZP 400mg Q4W) compared with the placebo group. The percentage of ACR20 responders at Week 24 was significantly ($p<0.001$) greater in both CZP treatment groups compared with the placebo group. The difference to placebo was 30.7% in the pooled CZP group after 12 weeks, and 36.5% after 24 weeks of treatment and is considered as clinically relevant. Cimzia treated patients also had significant improvements in ACR50 and 70 response rates. PASI 75 at week 24, which was a key secondary variable used to capture the effect on the psoriasis symptoms in patients with >3% body surface area involved, showed 46.3% difference to placebo in the pooled certolizumab group.

At Week 24 there was less progression of radiographic changes in the CZP 200mg Q2W+CZP 400mg Q4W group compared to the placebo group (0.06 vs 0.28 points); the difference to placebo was -0.22 points ($p=0.007$). Inhibition of radiographic progression was maintained with Cimzia treatment up to Week 48 in the subset of patients at higher risk of radiographic progression (patients with a Baseline mTSS score of > 6).

Cimzia-treated patients reported significant improvements in physical function as assessed by the HAQ-DI, in pain as assessed by the PtAAP and in tiredness (fatigue) as reported by the FASCA as compared to placebo. Cimzia-treated patients reported significant improvements in health-related quality of life as measured by the psoriatic arthritis QoL (PsAQoL), Dermatology Life Quality Index

(DLQI) and the SF-36 Physical and Mental Components and in psoriatic arthritis-related productivity at work and within household, as reported by the Work Productivity Survey compared to placebo. These improvements were sustained up to Week 48.

Uncertainty in the knowledge about the beneficial effects

During the procedure the CHMP questioned the claim that CZP could be used without MTX. Additional analyses showed that CZP has an effect both when used as monotherapy and in combination with MTX; however the results favour the combination treatment. Therefore CZP can be given as monotherapy in case only of intolerance to MTX or when continued treatment with MTX is inappropriate. This is reflected in the wording of the indication.

Although ACR20 response was similar between the 2 dosing groups, there was a trend toward a lower rate of ACR70 response in the 400mg Q4W dosing group. Across the various endpoints studied, the differences between the 2 dosing regimens were considered fairly small and diminished over time (48 weeks data). However, the initial difference in ACR70 response was more pronounced and the differences between the two dose groups persisted for a longer time period. Thus, the CHMP considered justified that the 400mg Q4W dosing regimen can be considered as an alternative maintenance dosing regimen once a clinical response with the 200mg Q2W dosing regimen has been established. This was accepted by the MAH and reflected in section 4.2 of the SmPC accordingly.

The results showed an effect on reduced rate of progression of structural damage for the 200mg Q2W dosing group, compared with placebo. The 24 week difference between CZP treated patients and the placebo treated patients was slightly increased in the 48 week analysis, however this was a not statistically significant. The 24 week tendency of a lesser effect in the CZP 400mg Q4W group was not seen in the 48 week analysis. Overall, the effect of 200mg Q2W and 400mg Q4W appeared to be similar. Inhibition of progression of structural damage by CZP treatment for up to 48 weeks has not been formally established in the overall population, however, in a subset of patients at higher risk of radiographic progression (patients with a Baseline mTSS score of > 6), inhibition of radiographic progression was maintained with CZP treatment up to Week 48. Based on these data the claim on reduced rate of progression of structural damage was reflected in section 5.1 of the SmPC.

Risks

Unfavourable effects

No new safety signal has emerged in study PSA001. Comparisons were made to the RA safety databases. The safety profile for PsA patients was consistent with the safety profile in RA and previous experience with CZP, with the exception of hepatic TEAEs which were generally higher in patients with PsA as compared to the RA population. Hepatic events are known risks for CZP, already addressed as part of the RMP and the product information. The MAH will continue to closely monitor these events in future PSURs.

Uncertainty in the knowledge about the unfavourable effects

The safety profile of CZP is well established and is characterised by several potentially serious risks, including but not limited to infections and potential risks of malignancies, congestive heart failure and demyelinating disorders. As described in the RMP, these risks are monitored through extensive ongoing follow up programs (including registries) in rheumatologic diseases with focus on RA, in which long term safety data is collected and reported annually for several years. As described in the RMP the MAH

will submit the final study report of study PSA001 by Q2 2016 which will bring additional data on the long term safety of CZP in the treatment of psoriatic arthritic patients.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Psoriatic arthritis is a disease affecting the joints and the skin that in its more severe forms entails a considerable amount of pain, working disability, and hampered quality of life. When the initial treatment, NSAID, is insufficient DMARDs may be tried, but often with limited effect. There is therefore a need for alternatives, and others TNF-blockers have shown to have a significant effect on this disease.

The safety profile of CZP is well established. Treatment with CZP is connected with several potentially serious risks. In Study PSA001 the most common AE was non serious infections, such as nasopharyngitis. No new safety signal has been identified in the PsA clinical development program submitted. The safety profile of CZP in the treatment of PsA appeared to be similar with the one known for the RA indication.

Benefit-risk balance

The MAH showed a robust effect of CZP treatment in the studied PsA patient population and this is of clinical relevance in terms of symptomatic treatment. The efficacy results presented support a positive effect of CZP on the symptoms from joints and skin in PsA. There was a tendency to a slightly lower effect with the 400mg Q4W dosing compared to the 200mg Q2W dosing at week 24. These differences diminishes over time, however the initial difference in ACR70 response was more pronounced and the differences between the two dose groups persisted for a longer time period. Thus, the 400mgQ4W dosing regimen should not be used until a clinically relevant effect of the 200mg Q2W dosing regimen has been established as reflected in the SmPC. An effect on reduced rate of progression of structural damage CZP after 24 weeks was observed. This effect reached significance in a post hoc analysis, where patients with a certain amount of joint destruction (cut off limit mTSS 6) at baseline were included. The 48 weeks data showed a sustained reduction of progression of structural changes. Cimzia-treated patients reported significant improvements in physical function and significant improvements in health-related quality of life. These improvements were sustained up to Week 48. In line with the Guideline on Summary of Product Characteristics, the results on physical function were reflected in section 5.1.

The safety profile of CZP in the studied population did not differ from the established safety profile of CZP in the RA indication. PsA patients who are candidates for CZP treatment must have an active disease and inadequate response to previous DMARD therapy.

In conclusion, based on the available efficacy and safety data presented, the benefit risk balance of Cimzia, in combination with methotrexate, is considered positive for the treatment of active psoriatic arthritis in adults when the response to previous DMARD therapy has been inadequate. Cimzia can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.1.6 a)	Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include the treatment of active psoriatic arthritis in adults patients when the response to previous DMARD therapy has been inadequate. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP shall be submitted anually until renewal.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that, prior to launch, all physicians who are expected to prescribe/use Cimzia are provided with a physician information pack containing the following:

- The Summary of Product Characteristics

- Physician information
- Patient Alert Card

The physician information should contain the following key messages:

- The risk of serious infections, including opportunistic bacterial, viral and fungal infections in patients treated with Cimzia,
- The need to evaluate patients for both active and inactive tuberculosis prior to starting the treatment, including use of appropriate screening tests,
- The contraindication of Cimzia in patients with history of moderate to severe heart failure (NYHA III/IV), and potential risk of congestive heart failure being worsened by Cimzia,
- The risk of acute injection-related reactions and delayed serious systemic hypersensitivity reactions, the need for instructing patients on techniques for administration, and guidance for Health Care Professionals on how to report administration errors,
- The role and use of patient alert card.