C87027 / CDP 870-027, 2004-002993-49

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB, Inc.

1950 Lake Park Drive

Smyrna, GA 30080

USA

Official study title:

A Phase III multicenter, double-blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lyophilized CDP870 given subcutaneously as additional medication to methotrexate in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate

2. SYNOPSIS

Name of Sponsor/Company: UCB Inc	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product: Cimzia™	Volume:	
Name of Active Ingredient: Certolizumab pegol (CZP or CDP870)	Page:	
Title of Study: A Phase III multicenter, double blind, placebo-controlled, parallel group 52-week study to assess the efficacy and safety of 2 dose regimens of lyophilized CDP870 given subcutaneously as additional medication to methotrexate in the treatment of signs and symptoms and preventing structural damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate		
Investigator(s): [redacted]		
Study Center(s): There were 147 centers in 22 countries.[1]		
Publication: None		
Studied Period (years): Feb 2005 to Sep 2006	**Phase of Development:** Phase III	
Objectives: Primary Objectives: To assess the efficacy of 2 dose regimens of CZP in combination with methotrexate (MTX) compared to MTX alone in the: • Treatment of signs and symptoms in patients with active rheumatoid arthritis (RA) • Prevention (inhibition of progression) of structural damage in patients with RA. Secondary Objectives: To assess the 2 dose regimens of CZP in combination with MTX compared to MTX alone in: • Safety and tolerability in patients with active RA • Major clinical response in patients with active RA • Physical function in patients with active RA • Health Outcome Measures (Health-Related Quality of Life [HRQoL], tiredness [fatigue], productivity) in patients with active RA • Pharmacokinetic (PK) profile and immunogenicity (anti-CZP antibodies profile) of 2 dose regimens of CZP in combination with MTX.		
Methodology: This double-blind, randomized, multicenter, placebo-controlled, parallel-group study assessed the efficacy and safety of 2 dose regimens of lyophilized CZP administered subcutaneously (sc) in combination with MTX compared to MTX alone in the treatment of signs and symptoms and inhibition of the progression of structural damage in patients with active RA. The study consisted of a Screening visit, a 52-week Treatment period, and a 12-week Follow-up visit. Eligible patients were randomized to 1 of the following 3 study treatments in a 2:2:1 ratio: 1. CZP 200 mg 2. CZP 400 mg 3. Placebo (0.9% preservative free saline solution). All patients continued their treatment on MTX with or without folic acid at the same dose as at entry (unless there was a need to reduce the dose for reasons of toxicity).		

1: Comment has been added on page three of this document because of shortage of space on this page.

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Patients were assessed for safety and efficacy, including physical function and disability, rheumatoid arthritis pain, disease activity, HRQoL, tiredness (fatigue), productivity within and outside the home, and PK/ immunogenicity variables throughout the study. Patients who failed to achieve an American College of Rheumatology (ACR) 20 response at Week 12 (confirmed at the Week 14 visit) were designated as treatment failures and withdrawn. These patients and patients who completed the study at Week 52 were offered the choice of entering CDP870-028, an open-label follow-up study. All patients had a Follow-up visit 12 weeks after their last dose of investigational product unless they continued into the open-label study.

Sample Size: Screening allowed for an approximate screen failure rate of 25% between Screening and Baseline. The sample size was determined on the basis of anticipated differences between active CZP and placebo with regard to the 2 co-primary efficacy endpoints. For the sample size calculation for the percentage of patients with an ACR-20 response at Week 24, in order to detect a clinically relevant difference of 20% (i.e., 30% placebo [assumed], 50% active CZP), at a 2-sided significance level of 2.5% for a 1:2:2 ratio with 90% power, a total of 590 patients were required (118 on placebo and 236 on each active arm). For modified total sharp score (mTSS), a sample size of 190 for placebo, and 380 for each active CZP group was sufficient to detect differences larger than 2.2 in the mean change from Baseline in the mTSS between an active and control group with at least 90% power (and assuming a standard deviation of 7 points). The sample size was based on the larger of the 2 estimates so as to control the Type II error. A total of 950 patients were to be randomized.

Diagnosis and Main Criteria for Inclusion: Patients had to have a diagnosis of adult-onset RA (of at least 6 months' duration but not longer than 15 years prior to Screening) as defined by the 1987 ACR classification criteria. Main inclusion criteria included the following:

- Had active RA disease at Screening and Baseline, defined as ≥9 tender joints, ≥9 swollen joints and either ≥30 mm/h erythrocyte sedimentation rate (ESR) (Westergren) or C-reactive protein (CRP) >15 mg/L
- Received treatment with MTX (with or without folic acid) for at least 6 months prior to Baseline. The dose of MTX had to be stable for at least 2 months prior to Baseline. The minimum dose of MTX had to be equivalent to 10 mg weekly.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
Certolizumab pegol (CZP)	• CZP 200 mg (given as 2 sc injections: 1 injection of CZP 200 mg and 1 injection of placebo) given every 2 weeks following an initial regimen of CZP 400 mg (of 2 sc injections of CZP 200 mg) at Baseline, Week 2 and Week 4 • CZP 400 mg every 2 weeks (given as 2 sc injections of CZP 200 mg).	[redacted]

Duration of Treatment: 52 weeks

1: This note was added for correction purpose afterwards on 19-Aug-2015:
The original text contains the wrong number of Sites by error. The correct information is as following:
The below attached Investigator list refers to all Sites that enrolled Subjects, which is a total of 133 Sites in 22 Countries. The inconsistencies noted do not have an impact on the overall assessment regarding the safety and tolerability profile and clinical benefit of certolizumab pegol as assessed in this study and described in the Clinical Study Report (CSR), and hence are not considered substantial. Therefore, a revision or amendment of the CSR of study C87027 is not considered necessary.

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Reference Therapy: Placebo, 0.9% saline (preservative free) solution	**Dose and Mode of Administration:** Given as 2 sc injections at Baseline and every 2 weeks thereafter	**Batch Number:** [redacted]

Criteria for Evaluation
Efficacy/Pharmacokinetics/ Immunogenicity /Safety:
Efficacy

Treatment of Signs and Symptoms:

- ACR-20/50/70 response
- Major clinical response, defined as ACR-70 response at any 2 time-points 24 weeks apart during the study and at all assessments in between
- Sustained response, defined as ACR-20 responders at both Weeks 24 and 52
- Number of tender joints
- Number of swollen joints
- Health Assessment Questionnaire – Disability Index (HAQ–DI)
- Patient's Assessment of Arthritis Pain - Visual Analogue Scale (VAS)
- Patient's Global Assessment of Disease Activity – VAS
- Physician's Global Assessment of Disease Activity – VAS
- CRP
- Duration of morning stiffness

ACR-20 response at Week 24 was a co-primary efficacy variable.

Inhibition of Progression of Structural Damage:

- mTSS
- Joint erosion score
- Joint–space narrowing score

mTSS at Week 52 was a co-primary efficacy variable.

Physical Function and Disability:

- HAQ-DI
- Short Form 36-item Health Survey (SF-36), Physical Component Summary (PCS)
- SF-36 Physical Functioning domain

Health-Related Quality of Life:

- SF-36 Physical and Mental Component Summaries (PCS and MCS) and domains

Tiredness:

- Fatigue Assessment Scale (FAS)
- SF-36 Vitality domain

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Productivity:

- Work Productivity Survey (WPS)

Additional Efficacy Measures:

- Disease Activity Score (28) Erythrocyte Sedimentation Rate (DAS28(ESR))
- DAS remission, defined as a DAS28(ESR) score <2.6
- European League Against Rheumatism (EULAR)
- ESR
- Changes in RA concomitant medication
- Time to withdrawal due to lack of efficacy or adverse events (AEs) reflecting significant worsening of RA
- EuroQol-5D (EQ–5D) Health State Evaluation (Europe only)
- Healthcare Resource Utilization (HCRU) Questionnaire

Pharmacokinetic/ Immunogenicity Variables

- Plasma concentrations of CZP
- Plasma concentrations of anti-CZP antibodies

Safety

Safety variables included AEs, extent of exposure, laboratory values (hematology, biochemistry, urinalysis and autoantibodies), vital signs, urine pregnancy testing, physical examination, body mass index, concomitant medications, and chest X-ray.

Other

Magnetic resonance imaging (MRI) assessments of the hands and feet were conducted on a subset of patients (approximately 50); however, these imaging readings have not yet been completed, and will be reported upon separately.

Statistical Methods: For the primary analysis of ACR-20 response at Week 24, treatment comparisons versus placebo for the 2 CZP dose groups were performed using logistic regression, with factors for treatment and region. The treatment effect was estimated using the odds ratio and corresponding 97.5% confidence interval (CI) obtained by fitting this model. Several sensitivity analyses were also performed. For change from Baseline in the mTSS, treatment comparisons versus placebo for the 2 CZP dose groups were performed using an analysis of covariance (ANCOVA) model on the ranks, with treatment and region as factors and rank Baseline mTSS as covariate. The treatment effect was estimated by Hodges-Lehmann point estimate of shift and 97.5% exact CI. The study was considered successful for the treatment of signs and symptoms objective if at least 1 of the 2 dose comparisons was statistically significant for the ACR-20 endpoint. It was also declared successful for the inhibition of progression of structural damage objective if, given that the ACR-20 endpoint was significant, the mTSS primary endpoint was also statistically significant for the same dose comparison. Analyses of the secondary and exploratory efficacy parameters were generally similar to those employed for the primary efficacy analyses.

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Adverse events (AEs) were classified according to the Medical Dictionary for Regulatory Activities (MedDRA, Version 9.0). Incidence tables were used to summarize AEs. Descriptive statistics and shift tables were used to summarize laboratory findings; incidences of markedly abnormal values were listed. Descriptive statistics were used to summarize changes from Baseline in vital signs and weight; changes in vital signs from pre-injection to 30 minutes post-injection were also summarized. Abnormal physical examination findings were listed by patient. The number of patients with "Normal," "Abnormal, Clinically Insignificant," and "Abnormal, Clinically Significant" chest X-rays was summarized by visit.
CPD870 plasma concentrations were summarized and listed for each active treatment at each scheduled visit. CPD870 plasma concentrations were also summarized. The proportion of patients with antibodies to CZP was summarized by each active treatment for all patients, and separately for those withdrawn patients with a 12-week follow-up sample. Shifts from Baseline in autoantibody presence (anti-double stranded DNA [anti-dsDNA] and antinuclear antibodies [ANA]) were presented by visit and treatment.

SUBJECT DISPOSITION AND DEMOGRAPHICS:
A total of 992 patients were randomized but 10 were excluded from the analysis. The remaining 982 patients (199 in the placebo + MTX, 393 in the CZP 200 mg + MTX, and 390 in the CZP 400 mg + MTX) were all included in the ITT Population for analysis of efficacy. A total of 572 patients completed the study to Week 52 (43, 255, and 274, respectively). Since patients who failed to achieve an ACR-20 response at Weeks 12 and 14 were withdrawn from the study at Week 16, the largest drop in patient numbers occurred at Week 16. Discontinuation due to lack of efficacy at Week 16 occurred in 62.8% of patients (n=125) in the placebo + MTX group, 21.1% of patients (n=83) in the CZP 200 mg + MTX group and 17.4% of patients (n=68) in the CZP 400 mg + MTX group.

The mean age of patients in the ITT Population was 52.0 years (52.2 in the placebo + MTX, 51.4 in the CZP 200 mg + MTX and 52.4 in the CZP 400 mg + MTX group). As expected for an RA study, there were more females (83.2%, 817 of 982 patients) than males. The majority of patients were Caucasians (90.7%, 891 of 982 patients), with Hispanic/Latin American (7.1%, 70 of 982 patients) and other races accounting for the remainder (2.2%, 21 of 982 patients). Overall, the treatment groups were comparable with regard to measures of disease activity at Baseline.

EFFICACY RESULTS:
Both co-primary objectives of this study were achieved successfully. The study demonstrated that CZP is effective in the treatment of signs and symptoms as well as the inhibition of the progression of structural damage in patients with active RA despite ≥6 months' treatment with MTX when administered in a lyophilized formulation every 2 weeks. The ACR-20 response rate at Week 24 was statistically significantly greater ($p<0.001$) in both doses tested, CZP 200 mg + MTX and CZP 400 mg + MTX, compared with placebo + MTX. Similarly, changes in mTSS from Baseline at Week 52 were statistically significantly less ($p<0.001$) for the CZP 200 mg + MTX and CZP 400 mg + MTX doses compared with placebo + MTX.

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	Placebo + MTX (N=199)	CZP 200 mg + MTX (N=393)	CZP 400 mg + MTX (N=390)
ACR-20 Week 24			
n	198	388	388
Responder	27 (13.6%)	228 (58.8%)	236 (60.8%)
Non-Responder	171 (86.4%)	160 (41.2%)	152 (39.2%)
Odds Ratio vs. PBO+ MTX		9.2	10.1
97.5% CI for Odds Ratio		[5.5, 15.6]	[6.0, 17.0]
p-value		<0.001	<0.001
mTSS Week 52 Change from Baseline			
n	181	364	363
Mean (SD)	2.8 (7.8)	0.4 (5.7)	0.2 (4.8)
Median [Q1, Q3]	0.0 [0.0, 4.4]	0.0 [-0.5, 0.5]	0.0 [-0.5, 0.5]
Min, Max	-16, 46	-24, 62	-20, 62
Difference vs. PBO+ MTX		-0.5	-0.6
97.5% CI for Difference		[-1.5, 0.0]	[-1.5, 0.0]
p-value		<0.001	<0.001
% Inhibition vs. Placebo + MTX		85	92

The odds ratio for achieving ACR-20 response at Week 24 versus placebo + MTX was significantly higher than 1.0 ($p<0.001$) in both active groups (9.2 for CZP 200 mg + MTX; 10.1 for CZP 400 mg + MTX). Similar significant ($p<0.001$) results favoring each active dose over the control were demonstrated for ACR50 and ACR70 responses at Week 24. The clinical benefit of each active treatment over placebo was maintained at Week 52 for ACR-20, ACR50, and ACR70 response rates with significant ($p<0.001$) odds ratios versus control. The small differences between the 200 mg and 400 mg doses for any of the ACR responses were not significant ($p>0.05$) and not clinically relevant.

The improvements in the ACR response components (number of tender and swollen joints, Patient's and Physician's Global Assessment of Disease Activity - VAS, Patient's Assessment of Arthritis Pain - VAS, HAQ-DI, and CRP) were statistically significantly greater in both CZP + MTX groups compared to the placebo + MTX group ($p<0.001$).

Analysis of the radiographic change as measured by mTSS change from Baseline at Week 52 demonstrated a significantly smaller ($p<0.001$) change in the active doses (CZP 200 mg + MTX, CZP 400 mg + MTX) compared to placebo + MTX, indicating inhibition of the progression of structural damage. The changes in mTSS from Baseline at Week 24 were also significantly smaller ($p<0.001$) in the 2 active doses compared to control. Percent inhibition over control was 85% or above in both active groups at Week 52.

Both erosion and joint space narrowing scores demonstrated statistically significant improvement in both CZP + MTX groups compared to placebo + MTX ($p<0.001$) at Weeks 24 and 52.

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The significant improvements from Baseline reported in physical function and disability in the CZP + MTX groups were greater than in the placebo + MTX group as early as the first assessment (Week 1) through to the end of the study (Week 52) as assessed by the HAQ-DI score, the SF-36 Physical Component Summary (PCS) and the Physical Functioning (PF) domain. These improvements were statistically significantly ($p<0.001$) greater in both CZP + MTX groups compared to the placebo + MTX group and the differences between the active groups were not significant ($p>0.05$).

The significant improvements from Baseline reported in HRQoL in the CZP + MTX groups were greater than in the placebo + MTX group as assessed by the SF-36 Physical and Mental Component Summaries scores. These improvements in CZP-treated patients were further confirmed by greater mean changes at each assessment in all SF-36 domains over control-treated patients ($p<0.001$, except Role Emotional at Week 12 $p<0.002$). All scores were significantly improved ($p<0.001$) following CZP treatment at Week 24 and Week 52 irrespective of dose regimen.

Significantly greater reduction in tiredness was reported in both CZP + MTX groups at all time-points as measured by the FAS and the SF-36 Vitality domain compared to placebo + MTX ($p<0.001$).

Productivity within and outside the home as assessed by the WPS was improved in both CZP + MTX groups as early as Week 4 and maintained until end-of-treatment compared to the placebo-treated group.

Improvement in health state from Baseline to Week 52 as assessed by the mean EQ-5D VAS score was greater in the CZP + MTX groups compared to the placebo group.

The EULAR response criteria were statistically significantly different in favor of the CZP + MTX groups compared to the placebo group at all time-points from Week 4 onwards. The CZP + MTX groups demonstrated a statistically significant ($p<0.001$) greater improvement compared to placebo at all time-points in the change from Baseline in duration of morning stiffness. The CZP + MTX groups also demonstrated a statistically significant greater improvement at all time-points in the change from Baseline in the DAS28 (ESR) compared to placebo + MTX ($p<0.001$). In the comparison of the ratio to Baseline in ESR by visit, the CZP + MTX groups demonstrated a statistically significant improvement compared to placebo + MTX group ($p<0.001$) at all time-points.

Statistically significantly fewer patients in the CZP + MTX groups withdrew due to lack of efficacy or AEs of worsening of RA disease than did patients in the placebo + MTX group ($p<0.001$).

Based on the health care resource utilization (HCRU) questionnaire the number of hospitalizations, the number of outpatient visits, and the number of medical procedures were higher in the CZP + MTX-treated groups compared to the placebo-treated group. The proportion of patients with length of hospitalizations of at least 14 days was lowest in the CZP 400 mg + MTX group. Most of the patients had no home care visits. It should be noted that these results are based on observed data during the whole treatment period. When reporting the resource utilizations, the overall exposure to CZP should be considered. A total of 125 patients (62.8%) in the placebo + MTX group discontinued from Study CDP870-027 at Week 16 due to lack of efficacy, therefore there was less overall exposure to control treatment compared to active treatments. There were neither statistically significant nor clinically relevant differences between the CZP 200 mg and

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the CZP 400 mg doses in any of the efficacy measures.

In the Safety Population, a total of 50 of 781 patients (6.4%) tested positive to anti-CZP antibodies at any time during the study (excluding 12-week follow-up samples). The overall incidence of antibody detection among patients with antibody data showed a gradual increase from Week 6 (0.1%) to a peak at Week 12 (3.0%). At Week 52, the overall incidence was at 3.7%. The incidence of antibody detection was higher in the CZP 200 mg group (10.7%) than in the CZP 400 mg group (2.1%).

PHARMACOKINETIC/ IMMUNOGENICITY RESULTS:
Overall in the Safety Population, the geometric mean CZP plasma concentrations were similar between the CZP 200 mg + MTX and CZP 400 mg + MTX groups from Week 1 through approximately Week 8. Thereafter, the geometric mean of the CZP 400 mg + MTX group was higher than in the CZP 200 mg + MTX group; 2-fold higher at Week 9 through Week 52. A patient was positive for anti-CZP antibodies if the level was >2.4 units/mL on at least 1 visit of the study. In the CZP 200 mg + MTX group, patients who tested positive for anti-CZP antibodies (n=42) had substantially lower geometric mean CZP plasma concentrations at all visits from Week 4 to 52 (mean CZP concentrations in antibody positive patients ranged from approximately 20% to 33% of those in antibody negative patients between Weeks 8 and 52) compared with patients who tested negative (n=350). Among patients in the CZP 400 mg group, patients who tested positive for anti-CZP antibodies (n=8) had mean CZP plasma concentrations reduced to approximately 7% to 50% at all visits from Week 4 to 52 compared with patients who tested negative (n=381).

Incidence of anti-CZP antibodies was low and inversely related to dose (10.7% in CZP 200 mg; 2.1% in CZP 400 mg) and the slightly reduced ACR-20 responses in patients with antibody-positive status had no meaningful effect on the overall study population.

SAFETY RESULTS:
When assessing the reported incidence and numbers of AEs, the overall exposure to investigational product should be considered. Not only was randomization to the three treatment groups unequal but also, due to the large number of placebo dropouts at Week 16, the extent of exposure was lower in the placebo group compared to patients treated with CZP. Direct comparisons between the 3 treatment groups are therefore difficult as the safety data were not adjusted for differences in exposure.

In this study, the median number of placebo doses taken was 8.0, compared to 26.0 in the combined CZP treatment groups (25.0 for CZP 200 mg and 26.0 for CZP 400 mg). Taking the total numbers of patients into account, there was an approximately 3 times greater exposure to CZP than placebo. Small numerical imbalances seen in some AEs presented by System Organ Class (SOC) could therefore potentially be due to differences in treatment exposure.

A total of 3226 treatment-emergent adverse events (TEAEs) were reported by 706 patients across the 3 treatment groups, with 57.8% of patients in the placebo group experiencing 411 TEAEs, compared to 74.7% and 76.6% in the CZP 200 mg and CZP 400 mg groups, respectively, experiencing a total of 2815 TEAEs. The majority of events were mild or moderate in intensity. The percentage of patients with severe events was higher in the CZP treatment groups, with 8.2% in the CZP 200 mg group and 9.8% in the CZP 400 mg

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group. In comparison, only 6.5% of patients in the placebo group experienced severe TEAEs. The number of patients withdrawing from the study due to AEs was higher in the CZP treatment groups than in the placebo group.

There was no difference in the percentage of patients with TEAEs attributed to the investigational product for the CZP treatment groups (42.6% for CZP 200 mg and 42.7% for CZP 400 mg); in comparison, 25.1% of placebo-treated patients had TEAEs attributed to investigational product. Across all 3 treatment groups the highest incidences of related events were in the SOCs of "Infections and Infestations", "General Disorders and Administration Site Conditions", and "Investigations."

Overall, treatment-emergent serious adverse events (SAEs) were reported for 104 patients during the study, with 7 patients having a fatal outcome. In addition, 1 patient in the CZP 200 mg group died in the post-treatment period. The number of patients with SAEs was comparable between the CZP treatment groups, but higher than in the placebo group. The number of fatalities was higher in the CZP 400 mg + MTX treatment group (n=4) than in the CZP 200 mg + MTX treatment group (n=2). Only 1 patient died in the placebo + MTX group. Causes of death included cardiac arrest (2 patients, 1 in each active treatment group), myocardial infarction (1 in the CZP 400 + MTX group and 1 in the placebo + MTX group), unidentified (1 patient in the 400 mg treatment group, for whom atrial fibrillation and fatigue were reported) and cerebrovascular accident (1 patient in the CZP 400 mg + MTX group). One patient in the CZP 200 mg + MTX treatment group died of a hepatic neoplasm. One patient in the CZP 200 mg + MTX group died post-study of peritonitis and hepatic cirrhosis.

In the CZP 200 mg group, the percentage of patients with TEAEs by SOC was higher in patients who tested positive for anti-CZP antibodies compared to those who tested negative for anti-CZP antibodies, but the percentage of patients with TEAEs of severe intensity was higher in those patients who tested negative to anti-CZP (8.6% compared to 4.8% in patients who tested positive for anti-CZP antibodies). In comparison, the percentage of patients with TEAEs in the CZP 400 mg group was higher in patients who tested negative for anti-CZP antibodies compared to those who tested positive for anti-CZP antibodies, but the percentage of patients with TEAEs of severe intensity was higher in patients who tested positive to anti-CZP (25.0% compared to 9.4% in patients who tested negative for anti-CZP antibodies). However, the number of antibody-positive patients was low, making comparisons and meaningful analyses difficult.

Overall, 5 patients experienced tuberculosis in the CZP treatment groups. It is suspected that the high incidence of this event is due to an inadequate screening procedure. As the patients were in endemic areas for TB, a positive PPD reaction was more likely to be due to reactivation of latent tuberculosis and not prior BCG vaccination as originally outlined in the protocol. Of these 5 patients, at screening, 3 had a positive PPD reaction (5 mm, 16 mm and 20 mm), 1 had PPD reactions of 1 mm, and 1 had a PPD reaction of 0 mm. All 5 patients had Baseline chest X-rays that were interpreted as normal.

The extent of exposure was lower in the placebo + MTX group (median 8.0 injections) compared to patients treated with either CZP 200 mg + MTX (25.0) or CZP 400 mg + MTX (26.0 injections). This difference was mainly due to the large number of protocol-mandated placebo dropouts at Week 16. However, taking the difference in exposure into account, there were no important differences between the two active treatment groups or detectable trends noted in the overall incidence of AEs between the two.

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However, when making comparison with the placebo + MTX group, there was an increased incidence of AEs in the SOCs: "Infections and Infestations", "General Disorders and Administration Site Conditions", "Respiratory, Thoracic, and Mediastinal Disorders", and "Vascular Disorders" in the two CZP+ MTX treatment groups. For the SOCs of "Infections and Infestations" and "Vascular Disorders" the AEs of urinary tract infection, nasopharyngitis, upper respiratory tract infection and hypertension occurred in ≥ 5% of patients in both of the CZP + MTX treatment groups, compared to <5% of patients in the placebo + MTX group (with the exception of urinary tract infection which occurred in 6.5% of patients).

Mean actual values were at the upper end of normal for the hematological parameters of WBC, neutrophils, and platelets, and were higher in the placebo group compared to the CZP treatment groups. Basophils and eosinophils were at the upper end of normal for the reference range for these parameters, but remained stable across the treatment groups throughout the study. Although there were some differences between the 3 treatment groups, all mean values remained within normal limits for all biochemistry parameters. No clear trends or differences between the 3 treatment groups were noted for weight, vital signs (except for a higher incidence of AEs of hypertension in the CZP groups), or chest X-rays.

CONCLUSIONS:

- CZP + MTX is effective in reducing signs and symptoms of patients with active RA as demonstrated by the significant improvement in ACR-20, ACR-50 and ACR-70 responses (including all ACR components) and DAS28 (ESR) remission rates in the CZP groups compared to the control group up to 12 months.
- CZP + MTX is effective in the prevention of structural damage in patients with active RA as demonstrated by the significantly reduced change from Baseline in mTSS (including joint space narrowing and erosion scores) at 6 and 12 months in the CZP groups compared to the control group.
- Significant improvements in physical function and disability (HAQ-DI and SF-36 PCS and PF domain), health-related quality of life (SF-36, Physical and Mental Component Summaries and domains) and reduction in tiredness (FAS and SF-36 Vitality domain), as well as improvements in productivity within and outside home (WPS) and health state (EQ-5D) were reported in the CZP groups compared to the control group.
- Incidence of anti-CZP antibodies was low and inversely related to dose (10.7% in CZP 200 mg; 2.1% in CZP 400 mg) and the slightly reduced ACR-20 responses in patients with antibody-positive status had no meaningful effect on the overall study population.
- Higher incidence of severe and serious infections was recorded in the CZP groups compared to the control group. However, there were no clear trends for any 1 focal point of infection across the treatment groups. No clear differences between the 3 treatment groups were noted for hematological or biochemistry parameters, weight, vital signs (except for a higher incidence of AEs of hypertension in the CZP groups), or chest X-rays.
- Five patients in the CZP + MTX treatment groups experienced tuberculosis. It is suspected that the high incidence of this event is due to an inadequate screening procedure. As the patients were in endemic areas for TB, a positive PPD reaction was more likely to be due to reactivation of latent tuberculosis and not prior BCG vaccination as originally outlined in the protocol.
- The AE and safety profile was in line with other anti-TNFs.
  Both CZP 200 mg and CZP 400 mg regimens in combination with MTX treat effectively active RA with a rapid onset of benefit and maintenance for up to a year in patients with incomplete response to

* Study has been registered as CDP 870-027 on EudraCT (subsequently addition of information on 28th of Aug 2015)

Name of Sponsor/Company: UCB Inc	Individual Study Table Referring to Module 5.3.5.1	*(For National Authority Use only)*
Name of Finished Product: Cimzia™	Volume:	
Name of Active Ingredient: Certolizumab pegol (CZP or CDP870)	Page:	

MTX. The differences between the 2 treatment groups were neither significant nor clinically meaningful.

- In conclusion, CZP has comparable safety profile to the anti-TNF class with both dose regimens having a positive benefits/risk ratio; the lack of any significant incremental efficacy benefit of the 400 mg over the 200 mg provides support for the 200 mg regimen as the recommended regimen.

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