UCB reference No.: RXCE07D2324

Approved by UCB 04-Jun-2008

Clinical Study Summary (CSS)

DEV/SGE/01678.2008

CT Registry ID#: NCT00152386
Study No.: C87027

These results are supplied for informational purposes only. Prescribing decisions should be made based on the approved package insert.

Based on Clinical Study Report document reference code: RRCE06D1020

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
CIMZIA® liquid formulation	Certolizumab Pegol	Rheumatoid Arthritis

Name of Sponsor/Company: UCB Inc

Title of Study:
A Phase III multicentre, 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) (number only): 147

Study Center(s) (number only): 147

Length of Study:
Date first patient enrolled: 18-Feb-2005
Date last patient completed: 12-Sep-2006

Phase of Development: Phase III

Abstract:
The primary objective of the study was to assess the efficacy of 2 dose regimens of certolizumab pegol (CDP870 or CZP) in combination with methotrexate (MTX) compared to MTX alone in the treatment of signs and symptoms in subjects with active rheumatoid arthritis (RA) and the prevention of structural damage in subjects with RA. The primary efficacy variables were the American College of Rheumatology (ACR) 20 response at Week 24 and the change from baseline in modified Total Sharp Score (mTSS) at Week 52. Safety assessments included the monitoring of adverse events (AE), clinical safety laboratory tests, vital signs, physical examination, body mass index, concomitant medication, and chest X-ray. Subjects had to be at least 18 years old, have a diagnosis of adult-onset RA (of ≥ 6 months duration but no longer than 15 years prior to screening) as defined by the 1987ACR classification criteria, have active RA disease at screening and baseline (defined as ≥ 9 tender joints, ≥ 9 swollen joints, and either ≥ 30 mm/h erythrocyte sedimentation rate or C-reactive protein > 15 mg/L), have received treatment with MTX (with or without folic acid) for ≥ 6 months, stable for at least 2 months, prior to baseline, and to have discontinued all disease modifying antirheumatic drug therapy at least 28 days prior to the first dose of study drug. The subjects could be on a stable dose of prednisone (or equivalent) ≤ 10 mg/day and nonsteroidal anti-inflammatory drugs. CZP 200 mg, CZP 400 mg, or placebo (PBO) was injected every 2 weeks for 52 weeks. Subjects randomized to the CZP 200 mg group received an initial regimen of CZP 400 mg at baseline, Week 2 and Week 4. Subjects not meeting ACR20 criteria at Week 12 (confirmed at Week 14) were withdrawn at Week 16. Subjects who completed the study of who failed to achieve an ACR20 response at Week 12 were eligible to participate in the open label follow-up study (CDP870-028).
For the primary analysis of the ACR20 response at Week 24, treatment comparisons versus PBO 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. For the co-primary endpoint of change from baseline in the mTSS, treatment comparisons versus PBO 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.

CT Registry ID#: NCT00152386
Study No.: C87027

Number of Subjects:	**PBO + MTX**	**CZP 200 mg + MTX**	**CZP 400 mg + MTX**
Planned, N:	190	380	380
Intent-to-Treat population, N[(a)]:	199	393	390
Completed, n (%):	43 (21.6)	255 (64.9)	274 (70.3)
Number of Subjects Withdrawn, n (%):	156 (78.4)	138 (35.1)	116 (29.7)
Withdrawn due to adverse events, n (%):	3 (1.5)	17 (4.3)	22 (5.7)
Withdrawn due to lack of efficacy, n (%):	141 (70.9)	98 (24.9)	74 (19.0)
Withdrawn for patient decision, n (%)	10 (5.0)	15 (3.8)	11 (2.8)
Withdrawn for protocol non-compliance, n (%):	0	4 (1.0)	3 (0.8)
Withdrawn for lost to follow-up, n (%):	1 (0.5)	1 (0.3)	1 (0.3)
Withdrawn for other reasons, n (%):	3 (1.5)	5 (1.3)	6 (1.5)

[(a)] Excluding 10 subjects from the disqualified site.
Note: More than 1 reason for withdrawal could be recorded for a subject.

Demography:	**PBO + MTX (N=199)**	**CZP 200 mg + MTX (N=393)**	**CZP 400 mg + MTX (N=390)**
Gender (Females/Males):	167/32	324/69	326/64
Age (years), mean (SD):	52.2 (11.2)	51.4 (11.6)	52.4 (11.7)
Race, n (%):			
Caucasian	179 (89.9)	363 (92.4)	349 (89.5)
African-American	2 (1.0)	4 (1.0)	2 (0.5)
Hispanic/Latin American	16 (8.0)	20 (5.1)	34 (8.7)
Other	2 (1.0)	6 (1.5)	5 (1.3)

Safety Outcomes:

- Summary of treatment emergent adverse events, deaths, other serious adverse events and certain other significant adverse events:

Overall, 74.7% and 76.6% of the subjects in the CZP 200 mg and 400 mg group, respectively versus 57.8% of the subjects in the PBO group reported treatment-emergent AEs (TEAEs) during the trial. The most commonly reported class of TEAEs during the treatment period were infections and infestations (43.6% and 47.3% of the subjects in the CZP 200 g and 400 mg group, respectively versus 26.1% of the subjects in the PBO group), musculoskeletal and connective tissue disorders (19.9%, 19.0%, 19.1% of the subjects in the CZP 200 mg, CZP 400 mg, and PBO groups, respectively), and general disorders and administration site conditions (20.9%, 17.0%, and 10.1% of the subjects in the CZP 200 mg, CZP 400 mg, and PBO group, respectively). Drug-related AEs were reported for 42.6%, 42.7%, and 25.1% of the subjects in the CZP 200 mg, CZP 400 mg, and PBO group, respectively.

Serious AEs (SAEs) were reported for 11.5%, 12.3%, and 5.5% of the subjects in the CZP 200 mg, CZP 400 mg, and PBO group, respectively, of which 7 subjects had an SAE with fatal outcome (2 and 4 subjects in the CZP 200 mg and 400 mg group, respectively, versus 1 subject in the PBO group). TEAEs leading to permanent drug discontinuation were reported for 4.3% and 5.7% of the subjects in the CZP 200 mg and 400 groups, respectively versus 1.5% of the subjects in the PBO group.

CT Registry ID#: NCT00152386
Study No.: C87027

Treatment Emergent AEs (TEAE):	**PBO + MTX (N=199)**	**CZP 200 mg + MTX (N=392)**	**CZP 400 mg + MTX (N=389)**
Subjects with at least one TEAE, n (%):	115 (57.8)	293 (74.7)	298 (76.6)
Primary System Organ Class with an incidence of ≥ 15% in any group	*n (%) [n considered drug-related by the Investigator]*		
Infections and infestations	52 (26.1) [17]	171 (43.6) [71]	184 (47.3) [78]
Musculoskeletal and connective tissue disorders	38 (19.1) [4]	78 (19.9) [15]	74 (19.0) [15]
General disorders and administration site conditions	20 (10.1) [7]	82 (20.9) [54]	66 (17.0) [39]
Investigations	23 (11.6) [12]	64 (16.3) [29]	70 (18.0) [35]
Gastrointestinal disorders	26 (13.1) [7]	61 (15.6) [13]	67 (17.2) [15]
Skin and subcutaneous tissue disorders	10 (5.0) [4]	50 (12.8) [25]	60 (15.4) [32]
Death and Other SAEs:	**PBO + MTX (N=199)**	**CZP 200 mg + MTX (N=392)**	**CZP 400 mg + MTX (N=389)**
Death, n (%):	1 (0.5)	2 (0.5)	4 (1.0)
Subjects with SAEs, n (%):	11 (5.5)	45 (11.5)	48 (12.3)
Primary System Organ Class with an incidence of ≥ 1.5% in any group	*n (%) [n considered drug-related by the Investigator]*		
Infections and infestations	2 (1.0) [2]	16 (4.1) [10]	23 (5.9) [15]
Musculoskeletal and connective tissue disorders	3 (1.5) [0]	9 (2.3) [2]	5 (1.3) [0]
Neoplasm benign, malignant and unspecified (incl cysts and polyps)	0	8 (2.0) [0]	2 (0.5) [1]
Injury, poisoning and procedural complications	1 (0.5) [0]	3 (0.8) [0]	6 (1.5) [0]

Primary Outcomes:
The odds of being an ACR20 responder at Week 24 were 9.247 times higher for subjects in the CZP 200 mg treatment group and 10.072 times higher for subjects in the CZP 400 mg treatment group as compared to PBO. These results are statistically significant as evidenced by the 97.5% CIs [5.486, 15.585] and [5.970, 16.991], respectively, which do not contain the unit value, as well as, the p-value of < 0.001.
The change from baseline in mTSS was significantly lower in both active treatment groups (p < 0.001). The mean (SD) change from baseline are 0.4 (5.7) for CZP 200 mg and 0.2 (4.8) for CZP 400 mg compared to 2.8 (7.8) for PBO.

ARC20 response at Week 24	**PBO + MTX (N=199)**	**CZP 200 mg + MTX (N=393)**	**CZP 400 mg + MTX (N=390)**
N	198	388	388
Responder, n (%)	27 (13.6)	228 (58.8)	236 (60.8)
Odds ratio versus PBO + MTX [97.5% CI]		9.247 [5.486, 15.585]	10.072 [5.970, 16.991]
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]
Difference vs PBO + MTX [97.5% CI]		-0.5 [-1.5, 0.0]	-0.6 [-1.5, 0.0]
p-value		< 0.001	< 0.001

Publication Reference(s) based on the study: None

Date of report: 04-Jun-2008