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Clinical Study Summary (CSS)

DEV/SGE/01679.2008

CT Registry ID#: NCT00160602
Study No.: C87050

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Based on Clinical Study Report document reference code: RRCE06D1018

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, multi–center, double–blind, placebo–controlled, parallel-group, 24–week study to assess the efficacy and safety of 2 dose regimens of liquid certolizumab pegol as additional medication to methotrexate in the treatment of signs and symptoms of rheumatoid arthritis and in prevention of joint damage in patients with active rheumatoid arthritis who have an incomplete response to methotrexate

Investigator(s) (number only): 76

Study Center(s) (number only): 76

Length of Study:
Date first patient enrolled: 30-Jun-2005
Date last patient completed: 19-Sep-2006

Phase of Development: Phase III

Abstract:
The primary objective of the study was to compare the efficacy of 2 dose regimens of a liquid formulation of certolizumab pegol (CDP870 or CZP) in combination with methotrexate (MTX) to MTX alone in the treatment of signs and symptoms in subjects with active rheumatoid arthritis. The primary efficacy variable was the American College of Rheumatology (ACR)20 response at Week 24. Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, body mass index, concomitant medications, chest X-ray, and physical examination. Subjects had to be at least 18 years old; have a diagnosis of adult-onset rheumatoid arthritis (of ≥ 6 months duration but not longer than 15 years prior to screening) as defined by the 1987 ACR classification criteria; have received treatment with MTX (with or without folic acid) for ≥ 6 months prior to baseline with a stable dose of MTX for at least 2 months prior to baseline; have active rheumatoid arthritis disease at screening and baseline, defined as ≥ 9 tender joints, ≥ 9 swollen joints and fulfilling 1 of the following 2 criteria, namely, ≥ 30 mm/hour erythrocyte sedimentation rate (Westergren) or C-reactive protein > 15 mg/L; and 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 or 400 mg) or placebo (PBO) was injected every 2 weeks for 24 weeks. Additionally, subjects in the CZP 200 mg group received an initial regimen of CZP 400 mg at baseline, Week 2 and Week 4. Subjects who did not meet ACR20 criteria for response at Week 12 (confirmed at Week 14) were withdrawn at Week 16 of the study. These subjects and subjects who completed the study at Week 24 were offered the choice of entering CDP870-051, an open-label follow-up study. For the analysis of the ACR20 response at Week 24, subjects who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards. Treatment comparisons versus PBO for the 2 CZP dose groups on the ACR20 response at Week 24 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.

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Number of Subjects:	**PBO + MTX**	**CZP 200 mg + MTX**	**CZP 400 mg + MTX**
Planned, N:	118	236	236
Enrolled, N[(a)]:	127	246	246
Completed, n (%):	17 (13.4)	174 (70.7)	181 (73.6)
Number of Subjects Withdrawn, n (%):	110 (86.6)	72 (29.3)	65 (26.4)
Withdrawn due to Adverse Events, n (%):	2 (1.6)	11 (4.5)	6 (2.4)
Withdrawn due to Lack of Efficacy, n (%):	107 (84.3)	54 (22.0)	53 (21.5)
Withdrawn due to Protocol Violation, n (%):	1 (0.8)	1 (0.4)	2 (0.8)
Withdrawn due to Withdrawal of Consent, n (%):	0	5 (2.0)	3 (1.2)
Withdrawn for Other Reasons, n (%):	0	1 (0.4)	1 (0.4)

[(a)] Excluding 15 subjects from the disqualified site.

Demography:	**PBO + MTX (N=127)**	**CZP 200 mg + MTX (N=246)**	**CZP 400 mg + MTX (N=246)**
Gender (Females/Males):	107/20	206/40	192/54
Age (years), mean (SD):	51.5 (11.8)	52.2 (11.1)	51.9 (11.8)
Race, n (%):			
Caucasian	126 (99.2)	239 (97.2)	242 (98.4)
African-American	0	0	1 (0.4)
Hispanic	1 (0.8)	6 (2.4)	1 (0.4)
Other	0	1 (0.4)	2 (0.8)

Safety Outcomes:

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

Overall, 56.0% and 50.8% of the subjects in the CZP 200 mg and CZP 400 mg groups, respectively, versus 52.8% of the subjects in the PBO group reported treatment-emergent (TE) AEs. The most commonly reported class of TEAEs during the treatment period were infections and infestations (27.8%, 21.5%, and 20.8% of the subjects in the CZP 200 mg, CZP 400 mg and PBO groups, respectively) and investigations (12.9%, 16.3%, and 17.6% of the subjects in the CZP 200 mg, CZP 400 mg and PBO groups, respectively). Drug-related AEs were reported for 24.6%, 22.8%, and 18.4% of the subjects in the CZP 200 mg, CZP 400 mg and PBO groups, respectively.

Serious AEs (SAEs) were reported for 7.3% of the subjects in both CZP groups versus 3.2% of the subjects in the PBO group. Two subjects died during the study (1 in each CZP group). Neither of these SAEs leading to death was considered drug-related by the investigator. TEAEs leading to discontinuation occurred in 4.8%, 2.8%, and 1.6% of the subjects in the CZP 200 mg, CZP 400 mg and PBO groups, respectively (Safety population).

Treatment Emergent AEs (TEAE):	**PBO + MTX (N=125)[(a)]**	**CZP 200 mg + MTX (N=248)[(a)]**	**CZP 400 mg + MTX (N=246)**
Subjects with at least one TEAE, n (%):	66 (52.8)	139 (56.0)	125 (50.8)
MedDRA Primary System Organ Class with an incidence of ≥ 10% in any group	*n (%) [n considered drug-related by the Investigator]*		
Infections and infestations	26 (20.8) [6]	69 (27.8) [23]	53 (21.5) [21]
Investigations	22 (17.6) [15]	32 (12.9) [18]	40 (16.3) [20]
Musculoskeletal and connective tissue disorders	14 (11.2) [2]	24 (9.7) [5]	20 (8.1) [2]

[(a)] Two subjects randomized to PBO + MTX had investigational product in their PK analysis samples and were included in the CZP 200 mg + MTX treatment group of the Safety population

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Death and Other SAEs:	**PBO + MTX (N=125)**	**CZP 200 mg + MTX (N=248)**	**CZP 400 mg + MTX (N=246)**
Death, n (%):	0	1 (0.4)	1 (0.4)
Subjects with SAEs, n (%):	4 (3.2)	18 (7.3)	18 (7.3)
MedDRA Primary System Organ Class with an incidence of ≥ 0.5% in any group	*n (%) [n considered drug-related by the Investigator]*		
Infections and infestations	0	8 (3.2) [7]	6 (2.4) [5]
Injury, poisoning and procedural complications	1 (0.8) [0]	2 (0.8) [0]	2 (0.8) [0]
Cardiac disorders	0	2 (0.8) [1]	1 (0.4) [0]
Musculoskeletal and connective tissue disorders	1 (0.8) [1]	1 (0.4) [0]	2 (0.8) [0]
Nervous system disorders	1 (0.8) [0]	2 (0.8) [0]	1 (0.4) [0]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.8) [0]	0	1 (0.4) [1]

Primary Outcomes:
Both active treatment groups displayed clinically relevant efficacy ACR20 response at Week 24 occurring in 141 subjects (57.3%) in the CZP 200 mg + MTX group and 141 subjects (57.6%) in the CZP 400 mg + MTX group, as compared to 11 (8.7%) in the PBO + MTX group. The odds of being an ACR20 responder at Week 24 were 14.428 and 14.332 times greater for subjects in the CZP 200 mg and CZP 400 mg treatment groups, respectively, as compared to PBO. This was statistically significant as evidenced by the 97.5% CI [6.711, 31.020] and [6.669, 30.800], which do not contain the unit value and have the significance p-value of < 0.001.

ACR20 at Week 24	**PBO + MTX (N=127)**	**CZP 200 mg + MTX (N=246)**	**CZP 400 mg + MTX (N=246)**
N	127	246	245
Responder[(a)], n (%)	11 (8.7)	141 (57.3)	141 (57.6)
Odds ratio vs PBO + MTX		14.428	14.332
97.5% CI for Odds ratio		[6.711, 31.020]	[6.669, 30.800]
p-value		< 0.001	< 0.001

[(a)] Subjects who withdrew for any reason or used rescue medication were considered as non-responders from that time-point onwards.

Publication Reference(s) based on the study: None

Date of report: 04-Jun-2008