Clinical Study Summary (CSS)

CT Registry ID#: NCT00329550
Study No.: CDP870-047

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Based on Clinical Study Report document reference code: RRCE08D0104

Proprietary Drug Name	**INN**	**Therapeutic area and indication(s)**
CIMZIA® liquid formulation	Certolizumab pegol	Crohn's disease

Name of Sponsor/Company: UCB, Inc.

Title of Study:
A 26-week, multi-center, open-label study to investigate the efficacy and safety of CDP870 in active Crohn's disease patients, who showed clinical efficacy in a remission induction study (Study CDP870-037), at Week 26 after subcutaneous administration of CDP870 400mg from Week 8 until Week 24 at 4-week intervals

Investigator(s) (number only): 26

Study Center(s) (number only): 16

Length of Study:
Date first patient enrolled: 10-May-2006
Date last patient completed: 03-Apr-2008

Phase of Development: Phase II

Abstract:
The primary objective of the study was to evaluate the efficacy of certolizumab pegol 400mg in active Crohn's disease (CD) subjects showing clinical efficacy at Week 6 of the induction study (Study CDP870-037). The primary efficacy variable was the Crohn's Disease Activity Index (CDAI) response (clinical response [CDAI reduction from Baseline ≥100 points] or remission [CDAI ≤150 points]) at Week 26. Secondary objectives were to evaluate the safety of certolizumab pegol 400mg over the treatment period and to assess the time to disease progression in subjects showing clinical efficacy at Week 6 in Study CDP870-037. Safety assessments included monitoring of adverse events (AEs), clinical laboratory tests, vital signs, concomitant medications, chest x-ray, tuberculosis test, and physical exam. Male or female subjects aged at least 16 years and under the age of 65 who participated in the induction study (Study CDP870-037) and showed clinical efficacy at Week 6 (reduction of ≥100 points from Baseline in CDAI or remission [CDAI ≤150]) after 3 doses of study medication were eligible for entry. Subjects who enrolled in Study CDP870-047 received open-label certolizumab pegol 400mg at Weeks 8, 12, 16, 20, and 24 (relative to the start of Study CDP870-037) (i.e., Weeks 0, 4, 8, 12, and 16 of Study CDP870-047). Three Safety Follow-up visits were conducted 4, 8, and 12 weeks post last dose. No formal statistical hypothesis testing was performed. For the primary variable, the frequency, incidence, and 95% confidence interval (CI) for the percentage response were summarized. For all responder analyses, subjects who received rescue therapy in Study CDP870-047 or who withdrew for any reason were considered as non-responders from that timepoint onwards. In corresponding sensitivity summaries, the last data prior to withdrawal or rescue therapy were imputed by carrying forward the last non-missing post-Baseline measurement. Other analyses were not adjusted for missing data and observed summaries were presented. The number and percentage of subjects who met the criteria for time to disease progression at each visit post Week 6 (relative to the start of Study CDP870-037) were summarized together with the corresponding 95% CI. Furthermore, time to disease progression was calculated using a Kaplan-Meier approach.

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Number of Patients:	**037-Placebo**	**037-CDP870 200mg**	**037-CDP870 400mg**	**Overall**
Planned, N:	-	-	-	35
Enrolled, N:	9	15	16	40
Completed, n (%):	5 (55.6%)	11 (73.3%)	12 (75.0%)	28 (70.0%)
Number of Patients Withdrawn, n (%):	4 (44.4%)	4 (26.7%)	4 (25.0%)	12 (30.0%)
Withdrawn due to Adverse Events, n (%):	3 (33.3%)	4 (26.7%)	2 (12.5%)	9 (22.5%)
Withdrawal of Consent, n (%)	1 (11.1%)	0	1 (6.3%)	2 (5.0%)
Withdrawn for Other Reasons, n (%):	0	0	1 (6.3%)	1 (2.5%)
Demography:	**037-Placebo N=9**	**037-CDP870 200mg N=15**	**037-CDP870 400mg N=16**	**Overall N=40**
Gender (Males/Females):	7/2	12/3	12/4	31/9
Age (years), mean (SD):	32.7 (10.4)	29.3 (9.1)	33.3 (10.0)	31.7 (9.7)
Race, n (%):				
Asian/Pacific Islander (Japanese)	9 (100%)	15 (100%)	16 (100%)	40 (100%)

Safety Outcomes:
The safety of certolizumab pegol was a secondary outcome measure.

The overall incidence of treatment-emergent adverse events (TEAEs) was 87.5% and was similar across the 037-CDP870 200mg (80.0%), 037-CDP870 400mg (93.8%), and 037-placebo (88.9%) groups. As expected with an anti-TNFα therapy, TEAEs were reported most often in the Infections and Infestations system organ class (SOC) (57.5% overall, and 40.0%, 87.5%, and 33.3% in the 037-CDP870 200mg, 037-CDP870 400mg, and 037-placebo groups, respectively).

Nasopharyngitis was the most commonly reported TEAE overall (37.5% of subjects). Other TEAEs reported by ≥10% of subjects overall were Crohn's disease (25.0%), DNA antibody positive (12.5%), nausea (10.0%), influenza (10.0%), vomiting (7.5%), pyrexia (7.5%), headache (7.5%), drug hypersensitivity (5.0%), urinary tract infection (5.0%), insomnia (5.0%), rhinitis allergic (5.0%), and seborrhoeic dermatitis (5.0%).

The majority of TEAEs in all three -037 treatment groups were mild or moderate in severity. Severe events were reported by 2 subjects in the 037-CDP870 200mg group (Crohn's disease and pyrexia) and 1 subject in the 037-placebo group (ileal perforation and peritonitis); no subject in the 037-CDP870 400mg group reported a severe event.

The most commonly reported related TEAE overall was nasopharyngitis (27.5%), which was reported at a rate of 13.3%, 50.0%, and 11.1% in the 037-CDP870 200mg, 400mg, and placebo groups, respectively. Other events considered related to study medication that were reported by ≥10% of subjects overall were Crohn's disease (20.0%), DNA antibody positive (12.5%), influenza (10.0%), nausea (7.5%), headache (7.5%), vomiting (5.0%), urinary tract infection (5.0%), and seborrhoeic dermatitis (5.0%).

Overall, 12 (30.0%) subjects reported treatment-emergent serious adverse events (SAEs), including 5 (33.3%) subjects in the 037-CDP870 200mg group, 5 (31.3%) subjects in the 037-CDP870 400mg group, and 2 (22.2%) subjects in the 037-placebo group. Crohn's disease was the only SAE occurring in more than 1 subject (4 subjects [26.7%] in the 037-CDP870 200mg group, 3 subjects [18.8%] in the 037-CDP870 400mg group, and 1 subject [11.1%] in the 037-placebo group). Most of the SAEs were of moderate intensity (9 of 13) and were considered possibly related (9 of 13) to study medication by the investigator. There were no deaths reported during or after the study.
Study medication was discontinued due to TEAEs in 9 (22.5%) subjects overall; Crohn's disease was the only

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TEAE leading to discontinuation that occurred in more than 1 subject (3 subjects in the 037-CDP870 200mg group, 1 subject in the 037-CDP870 400mg group, and 1 subject in the 037- placebo group).

No clinically meaningful changes from Baseline, shifts from Baseline, or incidence of markedly abnormal values were noted in hematology, biochemistry, or urinalysis parameters during treatment.

No clinically meaningful changes in systolic BP, diastolic BP, pulse rate, temperature, or weight were noted during treatment.

Treatment Emergent AEs (TEAE)	**037-Placebo N=9**	**037-CDP870 200mg N=15**	**037-CDP870 400mg N=16**	**Overall N=40**
Patients with at least one TEAE, n (%):	8 (88.9%)	12 (80.0%)	15 (93.8%)	35 (87.5%)
Patients with TEAEs (by Primary System Organ Class)	*n(%) [n considered drug-related by the Investigator]*			
Any TEAE	8 (88.9%) [6]	12 (80.0%) [10]	15 (93.8%) [7]	35 (87.5%) [23]
Blood and lymphatic system disorders	0	1 (6.7%) [0]	0	1 (2.5%) [0]
Cardiac disorders	1 (11.1%) [0]	1 (6.7%) [0]	0	2 (5.0%) [0]
Endocrine disorders	1 (11.1%) [0]	0	0	1 (2.5%) [0]
Gastrointestinal disorders	4 (44.4%) [2]	6 (40.0%) [5]	5 (31.3%) [3]	15 (37.5%) [10]
Eye disorders	0	1 (6.7%) [1]	0	1 (2.5%) [1]
General disorders and administration site conditions	2 (22.2%) [1]	2 (13.3%) [0]	1 (6.3%) [1]	5 (12.5%) [2]
Hepatobiliary disorders	2 (22.2)% [0]	0	1 (6.3%) [0]	3 (7.5%) [0]
Immune system disorders	1 (11.1%) [0]	1 (6.7%) [1]	1 (6.3%) [0]	3 (7.5%) [1]
Infections and infestations	3 (33.3%) [1]	6 (40.0%) [4]	14 (87.5%) [4]	23 (57.5%) [9]
Injury, poisoning, and procedural complications	1 (11.1%) [0]	0	1 (6.3%) [0]	2 (5.0%) [0]
Investigations	2 (22.2%) [2]	2 (13.3%) [2]	4 (25.0%) [3]	8 (20.0%) [7]
Musculoskeletal and connective tissue disorders	1 (11.1%) [0]	2 (13.3%) [0]	1 (6.3%) [0]	4 (10.0%) [0]
Nervous system disorders	1 (11.1%) [0]	1 (6.7%) [1]	3 (18.8%) [0]	5 (12.5%) [1]
Psychiatric disorders	0	1 (6.7%) [0]	2 (12.5%) [0]	3 (7.5%) [0]
Respiratory, thoracic, and mediastinal disorders	2 (22.2%) [0]	3 (20.0%) [0]	1 (6.3%) [0]	6 (15.0%) [0]
Skin and subcutaneous tissue disorders	2 (22.2%) [1]	2 (13.3%) [1]	2 (12.5%) [1]	6 (15.0%) [3]
Death, SAEs, and Other SAEs	**037-Placebo N=9**	**037-CDP870 200mg N=15**	**037-CDP870 400mg N=16**	**Overall N=40**
Death, (n %):	0	0	0	0
Patients with SAEs, n (%):	2 (22.2%)	5 (33.3%)	5 (31.3%)	12 (30.0%)
Patients with SAEs (by Primary System Organ Class)	*n(%) [n considered drug-related by the Investigator]*			
Any SAE	2 (2.2%) [2]	5 (33.3%) [3]	5 (31.3%) [3]	12 (30.0%) [8]
Gastrointestinal disorders	2 (22.2%) [2]	5 (33.3%) [3]	3 (18.8%) [2]	10 (25.0%) [7]
General disorders and administration site conditions	0	0	1 (6.3%) [1]	1 (2.5%) [1]
Psychiatric disorders	0	0	1 (6.3%) [0]	1 (2.5%) [0]

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Primary & Secondary Outcomes:
The primary outcome measure was the efficacy of certolizumab pegol evaluated at Week 26 in active Crohn's disease subjects showing clinical efficacy at Week 6 of the induction study (Study CDP870-037). A secondary outcome measure was the time to disease progression in subjects showing clinical efficacy at Week 6 in Study CDP870-037.

Efficacy/Pharmacokinetic/Immunologic Results:

Efficacy Results:
Primary Variable
Overall, 61.5% of subjects achieved CDAI response (clinical response [CDAI reduction from Baseline ≥100 points] or remission [CDAI ≤150 points]) at Week 26. A higher percentage of subjects in the 037-CDP870 200mg (73.3%) and 400mg (60.0%) groups achieved a CDAI response at Week 26 compared with subjects in the 037-placebo group (44.4%).

No clinically meaningful differences were noted on the primary efficacy variable for subgroups of gender, duration of CD, Baseline CDAI score, or entero-cutaneous fistulae status; however, differences were noted for subgroups of history of anti-TNFα therapy, history of re-anti-TNFα therapy, disease condition (inflammatory disease or structuring disease), and history of surgical resection – these subgroups may have an impact on the primary efficacy variable. Due to the limited number of subjects in some subgroups, definitive conclusions are difficult to draw.

CDAI response at Week 26	**037-Placebo N=9**	**037-CDP870 200mg N=15**	**037-CDP870 400mg N=16**	**Overall N=39**
Frequency	4 (44.4%)	11 (73.3%)	9 (60.0%)	24 (61.5%)
95% CI for percentage	(12.0%, 76.9%)	(51.0%, 95.7%)	(35.2%, 84.8%)	(46.3%, 76.8%)

Secondary Variable
Results for the primary variable were supported by data from the secondary variables of percentage of subjects with clinical response (CDAI reduction from Baseline of ≥100 points), percentage of subjects with a CDAI reduction from Baseline of ≥70 points, and subjects achieving remission. In these analyses, a higher percentage of subjects in the 037-CDP870 200mg and 400mg groups achieved a clinical response by the Week 26 or Last/Withdrawal Visit assessment compared with subjects in the 037-placebo group. There was no difference between the -037 treatment groups in mean reduction in CDAI scores.

In Kaplan-Meier analyses, overall, the majority of subjects did not show disease progression by Week 26. As less than 50% of subjects had progressed (i.e., lost CDAI response) by Week 26, it is not possible to discuss median time to disease progression either between the treatment groups or overall.

Meaningful improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) total score (defined as mean change of ≥16 points from Baseline) was observed at each study visit overall, and for each 037-treatment group. Mean changes from Baseline in IBDQ bowel symptoms, emotional function, and IBDQ systemic symptoms domain scores were generally highest for the 037-CDP870 200mg. Mean changes in IBDQ social function domain scores were similar across the -037 treatment groups.

Geometric mean ratio to Baseline C-reactive protein (CRP) values remained generally stable for the 037-CDP870 200mg group and increased slightly for the 037-CDP870 400mg group. Values for the 037-placebo group were

variable during the treatment period.

Pharmacokinetic/Immunologic Results:
At Week 6, geometric mean certolizumab pegol plasma concentrations were approximately 2.4 times higher in 037-CDP870 400mg subjects compared with 037-CDP870 200mg subjects. The mean value was near the limit of quantification for 037-placebo subjects. At Week 12 and through the Last/Withdrawal Visit, geometric mean certolizumab pegol plasma concentrations were similar for all three -037 treatment groups.

All subjects, with one exception, remained anti-certolizumab pegol antibody negative throughout the treatment period. Few changes were noted in autoantobodies during the study in subjects treated with certolizumab pegol.

The majority of subjects had negative ANA assay findings at Baseline which remained negative at the end of study. Most subjects were negative for both anti-ds-DNA IgG and anti-ds-DNA IgM at Baseline and remained negative throughout the study.

Publication Reference(s) based on the study: None

Date of report: 03-Dec-2008