CLINICAL STUDY SUMMARY: CDP870-037

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Clinical Trial Registry Identifier: NCT00291668

Title of study:

A Phase 2, multi-center, double-blind, placebo-controlled, parallel-group, dose-response study to assess the safety and efficacy of CDP870/certolizumab pegol, dosed subcutaneously in patients with active Crohn's disease

Investigator(s):

Twenty-six investigators participated in the study. The Principal/Coordinating Investigator was Toshifumi Hibi, MD, Professor and Chairman, Keio University School of Medicine.

Study site(s):

Twenty sites in Japan enrolled subjects in the study.

Publication(s) (reference[s]):

None

Studied period: 1 year, 8 months **First subject enrolled:** 02 Mar 2006 **Last subject completed:** 07 Nov 2007	**Phase of development:** Phase 2

Objective(s):

The primary objective of the study was to estimate the dose response in subjects with active Crohn's disease (CD), and to evaluate the efficacy of certolizumab pegol in these subjects. Secondary objectives were to evaluate the safety and tolerability of certolizumab pegol in subjects with active CD and to obtain data on the plasma certolizumab pegol concentrations and anti-certolizumab pegol antibody levels up to Week 16 following dosing at Weeks 0, 2, and 4 (induction period).

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Methodology:

This was a multi-center, randomized, double-blind, parallel-group comparative study. All doses of study medication were administered subcutaneously. After a Screening (observation) Period of 7 to 14 days, subjects were randomized to receive certolizumab pegol doses of 200mg or 400mg, or placebo, at Weeks 0 (first dose; Baseline), 2, and 4. Efficacy was assessed at Week 6, and safety was evaluated up to 12 weeks after the final study drug administration (Week 16) for subjects not entering an open-label extension study.

Number of subjects (planned and analyzed):

A total of 125 subjects were screened to provide 94 subjects who were randomized: 32 subjects received placebo, 30 subjects received certolizumab pegol 200mg, and 32 subjects received certolizumab pegol 400mg. Eight subjects were followed-up to Week 16 in this study and 86 subjects were followed-up for 12 weeks post last dose in the open-label extension studies CDP870-047 and CDP870-048.

Diagnosis and main criteria for inclusion:

Male or female subjects aged at least 16 years and under the age of 65 who must have had CD for a minimum of 24 weeks with a Crohn's disease Activity Index (CDAI) score between 220 and 450 (inclusive) prior to the first dose of study drug were eligible for entry. Key exclusion criteria included evidence of severe obstruction, treatment with other biological preparations possessing an anti-tumor necrosis factor α (TNFα) action within 12 weeks prior to the start of the observation period, previous treatment with any anti-TNFα therapy where there was a lack of clinical response to the first treatment.

Test product, dose(s) and mode of administration, batch number(s):

Certolizumab pegol 200mg or 400mg, administered subcutaneously as two 1mL injections, batch numbers CELp013 and CELp041

Duration of treatment:

Administration at Weeks 0, 2, and 4 for a total of 3 doses.

Reference therapy, dose(s) and mode of administration, batch number(s):

Placebo (saline) administered subcutaneously as two 1mL injections, batch number 05J24C

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Criteria for evaluation:

Efficacy:

Primary efficacy

- CDAI response (clinical response [CDAI reduction from Baseline ≥100 points] or remission [CDAI ≤150 points]) at Week 6

Secondary efficacy

- CDAI scores by visit
- CDAI response (clinical response or remission) by visit
- CDAI reduction from Baseline of at least 70 points
- CDAI remission by visit
- Clinical response by visit
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score by visit
- IBDQ domain scores by visit
- C-reactive protein (CRP) values by visit

Other efficacy

- Fistulae
- General examination

Pharmacokinetic:

- Certolizumab pegol plasma concentrations
- Anti-certolizumab pegol antibodies

Immunologic:

- Autoantibodies (anti-nucleic antibody [ANA], anti-double-stranded deoxyribonucleic acid immunoglobin G [anti-ds-DNA IgG], and anti-double-stranded deoxyribonucleic acid immunoglobin M [anti-ds-DNA IgM])

Safety:

- Adverse events
- Clinical laboratory parameters (hematology, biochemistry, and urinalysis)
- Vital signs

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Statistical methods:

No formal statistical hypothesis testing was performed, with the exception of an exploratory analysis of the primary endpoint. All efficacy summaries were performed on the Full Analysis Set (FAS) and all safety summaries were performed on the Safety Population.

The primary efficacy endpoint, CDAI response, was defined as the percentage of subjects with clinical response or remission at Week 6. Clinical response was defined as at least a 100 point decrease from the Week 0 CDAI score, where change = (CDAI score at Week 6) - (CDAI score at Week 0). Remission was defined as a CDAI score of ≤150 points.

For the primary summary, a frequency table with the number and percentage of subjects with a CDAI response at Week 6 was presented. Subjects who withdrew for any reason or who received rescue therapy were considered as nonresponders from that time point onwards. This table was repeated, where missing values due to subject withdrawal, or because of data exclusion after the use of rescue therapy, were imputed by carrying forward the last nonmissing efficacy measurement before the date of withdrawal or receipt of rescue therapy. The frequency, incidence, and 95% confidence interval (CI) for the percentage response were summarized.

In an exploratory analysis, data for the primary efficacy endpoint were pooled for the certolizumab pegol 200mg and 400mg treatment groups and compared against the placebo group using logistic regression with factors for treatment, corticosteroid use at Week 0, immunosuppressant use at Week 0, and pooled geographic region. This exploratory analysis was also performed comparing each active treatment group separately against placebo.

Secondary variables of IBDQ total and domain scores were summarized using mean, standard deviation, median, minimum and maximum values and 95% CIs. C-reactive protein data were transformed on the logarithmic scale. Actual and ratio to Baseline data were summarized using geometric mean, coefficient of variation, median, minimum and maximum values, and 95% CIs.

Certolizumab pegol plasma concentration data were transformed on the logarithmic scale; the following descriptive statistics were presented: n, geometric mean, coefficient of variation, median, minimum, and maximum.

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Shifts from Baseline in auto-antibody values (ANA, ds-DNA IgG, and ds-DNA IgM) were summarized at Week 6 by treatment group.

Adverse events were summarized using Medical Dictionary for Regulatory Activities (MedDRA®) version 9.0.

Summary and conclusions:

Subject disposition:

A total of 125 subjects were screened to provide 94 subjects who were randomized. Eighty-eight subjects completed the study and 6 subjects withdrew due to an adverse event (5 subjects) or lack/loss of efficacy (1 subject).

Efficacy results:

There was a clinically meaningful difference in the frequency of subjects achieving CDAI response (clinical response [CDAI reduction from Baseline ≥100 points] or remission [CDAI ≤150 points]) at Week 6 in the certolizumab pegol 200mg (46.7%, 95% CI = [28.8%, 64.5%]) and 400mg (45.2%, 95% CI = [27.6%, 62.7%]) groups compared to the placebo group (25.0%, 95% CI = [10.0%, 40.0%]).

No clinically meaningful differences were noted for the primary efficacy variable for subgroups of gender, duration of CD, Baseline CDAI score, CD expression site, CD condition, entero-cutaneous fistulae status at Baseline, history of surgical resection, or use of immunosuppressants and/or corticosteroids at Baseline. In the subgroup of history of anti-TNFα therapy, little difference in CDAI response was noted based on prior anti-TNFα therapy in subjects treated with either dose of certolizumab pegol; in contrast, in the placebo group, fewer subjects with a history of anti-TNFα therapy achieved CDAI response compared to subjects with no history of anti-TNFα therapy. Definitive conclusions regarding these subgroups are difficult to draw, however, due to the limited number of subjects in some subgroups.

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Results for the primary variable were supported by data for the secondary variables of mean reduction in CDAI score, 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 secondary efficacy summaries, efficacy of certolizumab pegol 200mg and 400mg was demonstrated as early as Week 2 and continued through the Week 6 or Last/Withdrawal Visit assessment.

Mean changes from Baseline for IBDQ total score were similar at Weeks 2, 4, and 6 or the Last/Withdrawal Visit for the certolizumab pegol 200mg, certolizumab pegol 400mg, and placebo groups, although there was a trend toward higher mean changes in subjects receiving certolizumab pegol 200mg (although this group had the lowest Baseline total scores). Changes in the IBDQ bowel symptoms, systemic symptoms, and emotional function domain scores were also generally highest in the certolizumab pegol 200mg group, while changes in the social function domain scores were similarly high in subjects receiving certolizumab pegol 200mg and placebo.

Geometric mean CRP values were lower compared to Baseline at Weeks 2, 4, and 6 or the Last/Withdrawal Visit in the certolizumab pegol 200mg and 400mg groups compared to the placebo group, which also supports results from the primary efficacy variable.

In an exploratory analysis, when data from both certolizumab pegol groups were pooled, the odds of achieving CDAI response at Week 6 were 2.84 times higher in the pooled certolizumab pegol group than in the placebo group. This result was statistically significant (odds ratio=2.84, p=0.043). However, in further adhoc analyses, when exploring each active group separately versus placebo, the odds of achieving CDAI response were not statistically significant.

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Pharmacokinetics/immunologic results:

The geometric mean certolizumab pegol plasma concentrations were approximately 2 times higher in subjects treated with certolizumab pegol 400mg (Week 2: geometric mean 27.869µg/mL, 95% CI = [24.720, 31.419]) compared to certolizumab pegol 200mg (Week 2: 13.796µg/mL, 95% CI = [12.542, 15.176]) from Week 2 onward, which is consistent with the linear pharmacokinetic profile of certolizumab pegol.

The majority of subjects in the certolizumab pegol 200mg, 400mg, and placebo treatment groups had negative ANA assay findings at Baseline which remained negative at the end of the study.

All subjects in the certolizumab pegol 200mg and 400mg treatment groups remained anti-certolizumab pegol antibody negative throughout treatment.

Safety results:

The incidence of treatment-emergent adverse events (TEAEs) was similar across the certolizumab pegol 200mg (56.7%), certolizumab pegol 400mg (59.4%), and placebo (65.6%) groups. As expected with an anti-TNFα therapy, TEAEs were reported most often in the Infections and infestations System Organ Class (SOC) in all treatment groups (26.7%, 25.0%, and 34.4% for the certolizumab pegol 200mg, 400mg, and placebo groups, respectively).

Nasopharyngitis was the most reported preferred term (PT) in the certolizumab pegol 200mg (23.3%), 400mg (21.9%), and placebo (31.3%) groups. Other TEAEs reported by ≥5% of subjects were nausea, vomiting, pyrexia, and pharynolaryneal pain (6.7% each) in the certolizumab pegol 200mg group; pyrexia (9.4%), and nausea, white blood cell decreased, pharynx discomfort, and upper respiratory tract inflammation (6.3% each) in the certolizumab pegol 400mg group; and Crohn's disease (12.5%) and pyrexia, hepatic function abnormal, headache, and comedone (6.3% each) in the placebo group. None of the 5 subjects who had a history of hypersensitivity reactions to previous anti-TNFα therapies had an acute hypersensitivity reaction during the study.

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

The majority of TEAEs in all 3 treatment groups were mild or moderate in severity. The most commonly reported related TEAE in each treatment group was nasopharyngitis, which was reported at a similar rate in the certolizumab pegol 200mg (23.3%) and 400mg (18.8%) groups, and at a slightly higher rate in the placebo group (28.1%). Events considered related to study medication in the certolizumab pegol groups, but not in the placebo group, were pyrexia, vomiting, pharynolaryneal pain, and white blood cell count decreased.

There were no deaths reported in any treatment group during or after the study. Serious adverse events were reported by 1 subject in the certolizumab pegol 200mg group (3.3%), 3 subjects in the certolizumab pegol 400mg group (9.4%), and 3 subjects in the placebo group (9.4%). Serious adverse events occurring in more than 1 subject included pyrexia (2 subjects [6.3%] in the certolizumab pegol 400 mg group) and Crohn's disease (3 subjects [9.4%] in the placebo group). Most of the serious adverse events were of moderate intensity and were considered possibly related to study medication by the investigator.

Crohn's disease was the only TEAE leading to discontinuation that occurred in more than 1 subject (2 subjects in placebo group, 6.3%). The only TEAEs leading the discontinuation in the certolizumab pegol treatment groups were pneumonia aspiration (1 subject in the 200mg group, 3.3%) and sepsis (1 subject in the 400mg group, 3.1%).

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

None of the small changes in systolic blood pressure (BP), diastolic BP, pulse rate, temperature, or weight were considered clinically meaningful, either within or among treatment groups.

Name of company: UCB Japan Co., Ltd	**Individual study table referring to part of the dossier:** Not applicable	*(For National Authority Use Only)*
Name of finished product: Cimzia®	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol (CDP870)	**Page:** Not applicable	

Conclusions:

Certolizumab pegol, administered as 200mg or 400mg at Weeks 0, 2, and 4, was effective in the treatment of Japanese subjects with active Crohn's disease. No meaningful difference in efficacy was noted between the certolizumab pegol doses of 200mg and 400mg.

Both certolizumab pegol doses had an acceptable safety profile. As expected following anti-TNFα therapy, infections were commonly reported; nasopharyngitis was the most commonly reported event. Most adverse events were managed with concomitant medication or required no corrective treatment, and few events led to discontinuation of certolizumab pegol.