C87065, 2006-003871-11

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB Pharma SA

Allée de la Recherche 60

1070 Anderlecht (Brussels)

Belgium

Official study title:

C87065 (COSPAR II): An open-label, multi-center trial to examine the long term safety, efficacy, and corticosteroid-sparing effect of certolizumab pegol in patients with moderate to severe Crohn's disease who have failed tapering of corticosteroids, needed corticosteroids after completion of tapering, or have successfully completed the trial C87059 (COSPAR I)

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Name of finished product: Cimzia	**Volume:** Not applicable	
Name of active ingredient: Certolizumab pegol	**Page:** Not applicable	

Title of study: C87065 (COSPAR II): An open-label, multi-center trial to examine the long term safety, efficacy, and corticosteroid-sparing effect of certolizumab pegol in patients with moderate to severe Crohn's disease who have failed tapering of corticosteroids, needed corticosteroids after completion of tapering, or have successfully completed the trial C87059 (COSPAR I).

Investigator(s): This was a multicenter study, 49 investigators enrolled subjects in this study.

Study site(s): This was a multicenter study conducted at 75 centers in the [redacted] of which a total of 49 centers enrolled subjects.

Publication(s) (reference[s]): none

Studied period: Subjects were allowed to remain on treatment until the study was closed by UCB. **First subject enrolled:** 04 Jan 2007 **Last subject completed:** 23 Feb 2010	**Phase of development:** Phase 3b

Objective(s): The primary objective of this study was to continue to assess the safety of CZP as per adverse event (AE) reporting.

Secondary objectives of this study included:

- Describing the evolution of long-term efficacy (through maintenance of clinical remission) in CD subjects who completed C87059 (COSPAR I)
- Assessing the effect of induction/treatment with CZP in subjects who failed to maintain clinical remission off steroids in C87059 (COSPAR I)

Methodology: This was an open-label, long-term, multicenter, extension clinical study. Subjects who could not tolerate the corticosteroid tapering schedule in C87059, subjects who required reintroduction of corticosteroids after completion of the tapering schedule but prior to Week 38 for maintaining a clinical remission in C87059, or subjects who completed the C87059 study were eligible to participate in this study (C87065).

The study medication (CZP 400mg) was administered as 2 subcutaneous (sc) injections of 200mg, every 4 weeks, unless the subject lost response. If the subject lost response

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(Crohn's Disease Activity Index [CDAI] >150 points and a minimum increase in CDAI of 70 points versus Week 0 in C87059), an escalation of the dose of CZP to 400mg every 2 weeks was allowed for 3 doses (induction) to attempt to bring the subject into remission. If successful, the subject was allowed to continue in the study, but reverted to dosing 400mg every 4 weeks as maintenance therapy. If unsuccessful, the subject was discontinued from the study.

For subjects entering this study who could not complete corticosteroid tapering or who required reintroduction of corticosteroids during C87059, tapering of the corticosteroid was at the discretion of the Investigator for C87065.

This long-term follow-up study continued beyond Week 34 until UCB suspended the development of the investigational drug in this indication. Subjects were then able to transition to a compassionate use study C87092 (COMPAS) for continued treatment of CD.

Number of subjects (planned and analyzed): It was expected that the total number of subjects who participated in this study would be ≥352 subjects. However, the number of subjects randomized to the C87059 study only reached 174 subjects due to slower than expected enrollment. Thus, the expected enrollment for this study was ≤174. The actual enrollment was 106 subjects. Of the enrolled subjects, 30 subjects had completed C87059 (14 subjects previously treated with placebo and 16 subjects previously treated with CZP 400mg) and 73 subjects did not complete C87059 (40 subjects previously treated with placebo and 33 subjects previously treated with CZP 400mg).

Diagnosis and main criteria for inclusion: Subjects enrolled were males or females, 18 years or older who were previously enrolled in C87059 and included subjects treated with placebo and/or active drug who were unable to complete corticosteroid tapering or who needed to be restarted on corticosteroids, and subjects suffering from CD who had successfully completed C87059 in remission. Subjects could have been on immunosuppressants or 5- aminosalicylates (5-ASA) therapy if the dose had been stable for 8 weeks or 4 weeks, respectively, prior to and throughout C87059. If a subject had withdrawn from C87059 for any other reason, he/she was not eligible for participation in this study.

Test product, dose(s) and mode of administration, batch number(s): Certolizumab pegol, an anti-tumor necrosis factor alpha (anti-TNFα) humanized antibody Fab' fragment–polyethylene glycol (PEG) conjugate, was provided as a solution for injection in 10mM sodium acetate buffer and 125mM sodium chloride, pH 4.7. It was supplied in 3mL vials with a fill of 1.4mL (for an extractable volume of 1mL corresponding to a dose of 200mg).

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The study medication, CZP 400mg, was administered as 2 subcutaneous injections of 1mL at 2 distinct sites (lateral abdominal wall or upper, outer thigh) using separate syringes and needles at each injection site. Batch numbers: [redacted]

Duration of treatment: Subjects were allowed to remain on treatment until the study was closed by UCB, at which point they were able to transition to Study C87092, a compassionate use named patients program (COMPAS).

Reference therapy, dose(s) and mode of administration, batch number(s): none

Criteria for evaluation:

Efficacy: The primary efficacy variable was the proportion of subjects who completed C87059 and had remained off corticosteroids and in disease remission (CDAI≤150 points). The secondary and exploratory efficacy variables were:

- Proportion of subjects with remission (CDAI≤150 points) off steroids at each study visit.
- Cumulative proportion of subjects with relapse/treatment failure at each study visit after Week 0, with relapse/treatment failure defined as a CDAI>150 points and an increase in CDAI of ≥70 points vs. Week 0 of C87059, for successful completers of C87059 only.
- Time to relapse/treatment failure was evaluated for the successful completers of C87059 only.
- Per-subject median weekly dose and cumulative dose of corticosteroids over the duration of the study, and change from Baseline in the median weekly dose were evaluated separately for the successful completers of C87059 and those entering C87065 using corticosteroids.
- CDAI scores at each study visit and changes from Week 0 of C87059.
- Health economics outcomes: direct cost parameters (eg, number of medical procedures, consultations not planned by the protocol, hospitalization, and length of hospital stay).

Safety: Safety variables were the following:

- Adverse Events
- Laboratory evaluations

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- Vital signs
- Physical examinations
- Weight

Statistical methods: All randomized subjects who received at least 1 injection of study medication were included in the intention-to-treat (ITT) population; this population was used for analysis of efficacy and safety. All randomized subjects who received at least 1 injection of study medication, excluding subjects who were not in remission (CDAI>150 points) at Visit 2 (Week 0), were included in the conditional ITT (CITT) population. No per-protocol (PP) population was defined. Baseline was defined as the last non-missing value collected prior to the first injection of C87059, except for weight, which was the last nonmissing value collected prior to the first injection of study medication in C87065, and unless otherwise defined.

Study periods were defined as below:

- Pretreatment Period (from time of first injection in C87059 included, to the injection time on Visit 2 of C87065 not included)
- Treatment Period (from Visit 2 injection time of C87065 included to the date of the last Evaluation Visit)
- Follow-Up Period (up to the Follow-Up Visit or 84 days after last dose)
- Overall Treatment Period (Treatment Period + Follow-Up Period)
- Overall Period (Pretreatment Period + Treatment Period + Follow-Up Period)

Descriptive statistics appropriate for continuous variables (number of available observations, mean, standard deviation [SD], median, minimum, maximum, and 25th and 75th percentiles) and categorical variables (numbers and percentages of subjects) were provided. Data from individual study centers were not pooled or analyzed by individual study center.

No formal statistical testing was performed in this single-arm, open-label study. For the primary efficacy variable, a sensitivity analysis was performed by calculating the remission rate off corticosteroids excluding subjects with a CDAI score missing at a particular visit or who withdrew before the assessment from the analysis population. The denominator at each visit was the number of subjects from the ITT population who completed C87059 and with a nonmissing CDAI score. This denominator was then different at each visit.

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The proportion of subjects with remission off steroids who completed C87059 was also analyzed by visit on the CITT population.

Summary and conclusions:

Subject disposition: A total of 106 subjects were enrolled in the study: 52 subjects who were previously treated with CZP 400mg and 54 subjects who were previously treated with placebo. Of the ITT subjects, 43 subjects (41.7%) completed the study: 81.3% and 64.3% of the CZP 400mg and placebo completers from the prior study, respectively, and 6.1% and 47.5% of the noncompleters from the prior study, respectively. The most common reason overall for early discontinuation was lack/loss of efficacy, which occurred more frequently in noncompleters (54.5% CZP 400mg and 37.5% placebo) compared with completers (6.3% CZP 400mg and 14.3% placebo). Other reasons for discontinuation included AE (8.7% overall), other reasons (6.8% overall), and withdrawal of consent (5.8% overall), all of which occurred more frequently in the CZP 400mg/noncompleter group compared with the other groups.

All but 3 enrolled subjects (49 subjects in the CZP 400mg group and 54 subjects in the placebo group) received at least 1 injection of study medication and were included in the ITT and Safety populations, the primary populations for analysis of efficacy and safety, respectively.

Efficacy results: The primary efficacy variable of this study was to determine the proportion of subjects in disease remission (CDAI≤150 points) and off corticosteroids by visit for the ITT population of subjects who completed C87059. From Week 2 to Week 18, at least half (≥50% overall) of all subjects who completed C87059 continued to be in disease remission and off corticosteroids. Initially, subjects who had been treated with placebo in C87059 and were receiving CZP 400mg treatment for the first time in this study had a greater proportion of subjects in disease remission and off corticosteroids compared with CZP 400mg-treated subjects. Starting at Week 18 and continuing through the remainder of the study, a greater proportion of CZP 400mg-treated subjects were in remission and off corticosteroids compared with placebo-treated subjects.

The results of the secondary and other efficacy variables further evaluated the long-term efficacy of CZP 400mg:

- Of the subjects who did not complete C87059, a greater proportion of subjects who were previously treated with placebo were in disease remission and off corticosteroids compared with those who were previously treated with CZP 400mg at nearly every visit throughout the study. The maximum proportion of subjects who achieved clinical

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remission and were off corticosteroids was 47.5% for placebo/noncompleter subjects (at Week 22) compared with 15.2% of CZP 400mg/noncompleter subjects (at Weeks 14 and 26).

- The completer groups generally had a greater proportion of subjects in continuous remission (CDAI≤150 points) compared with the respective noncompleter groups. For subjects who completed C87059, subjects with continuous remission and off corticosteroids occurred up to Week 78 in the CZP 400mg group compared with up to Week 50 in the placebo group.
- Cumulative proportion of subjects with relapse/treatment failure at each study visit after Week 0 for successful completers of C87059 was lower in the CZP 400mg compared with the placebo group (14.3% vs. 30.8% at Week 90).
- The mean time to relapse for successful completers of C87059 was longer for the CZP 400mg group compared with the placebo group (597.0 vs 436.3 days, respectively).
- Of the subjects who had a change in the dose of corticosteroids during the study, all had a median reduction from the Run-In Period of C87059 in corticosteroid use regardless of C87059 status. Unsuccessful completers had the greatest median reduction in the Overall Treatment Period for both the CZP 400mg and placebo groups (-133 and -140mg, respectively) compared with successful completers of C87059 (-121 and -101mg, respectively), noncompleters who were using corticosteroids upon entering C87065 (-79 and -96mg, respectively), and noncompleters who were not using corticosteroids upon entering C87065 (-120 and -68mg, respectively).
- Few subjects had a change in the dose of corticosteroids after Visit 2 and those with changes did not show a consistent trend over time between the CZP 400mg and placebo groups, regardless of C87059 status. The cumulative dose of corticosteroids varied greatly among the groups and no meaningful conclusions can be drawn due to the small number of subjects in each group.
- Mean CDAI scores and changes from Baseline (last nonmissing pretreatment value from C87059) were variable across visits in both treatment groups with a general trend towards a decrease from Baseline over time. Noncompleter subjects tended to have greater mean CDAI values and values greater than Baseline (C87059) at the start of C87065 (Week 0) compared with completer subjects. Noncompleter subjects generally had greater mean Baseline (C87065) values and greater mean decreases from Baseline

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(C87065) compared with completer subjects. No important differences were observed between the placebo and CZP 400mg groups. The mean CDAI score for both treatment groups was <150 points at most time points beyond Screening.

- Resource use was generally similar between CZP 400mg-treated subjects and placebo-treated subjects:
  - The majority of subjects overall did not start any medications potentially affecting CD during the Treatment Period, including corticosteroids (87.4%) or antibiotic medication (70.9%). No subjects started anti-TNFα, 5-ASAs, or infliximab, and only 1 subject (3.0%; CZP 400mg/noncompleter) started immunosuppresants.
  - The majority of subjects overall had started at least 1 general concomitant medication (excluding medications potentially influencing CD) during the Treatment Period (64.1%). General concomitant medication use was generally similar between the noncompleter subjects (3.061 medications CZP 400mg, 3.425 medications placebo) and completer subjects (4.125 medications CZP 400mg, 2.714 medications placebo).
  - Low resource utilizations were observed during the Treatment Period with the majority of subjects having no emergency room visits, hospital stays, or medical procedures, and having no more than 1 unforeseen healthcare provider consultation. Similar findings were reported between the two treatment groups.

Safety results:

- The mean duration of exposure to study medication was generally similar between the CZP 400mg/completer (313 days), placebo/completer (281 days), and placebo/noncompleter (290 days) subjects, while the CZP 400mg/noncompleter subjects had a shorter mean duration of exposure of 181 days. The mean number of study medication doses received was generally similar between the CZP 400mg/completer (9.1 doses), placebo/completer (7.9 doses), and placebo/noncompleter (9.2 doses) subjects, with the CZP 400mg/noncompleter subjects receiving fewer mean doses (5.3 doses).
- Nearly all subjects (86.4%) experienced at least 1 study TEAE, the majority of which were mild or moderate in intensity (78.6%). A greater proportion of subjects previously treated with CZP 400mg reported nonserious AEs compared with subjects previously treated with placebo.

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- As expected with the use of an anti-TNFα therapy in subjects with CD, study TEAEs were reported most commonly in the SOC categories of Gastrointestinal disorders (57.3%), Infections and infestations (47.6%), and Musculoskeletal and connective tissue disorders (31.1%).
- Exacerbation of CD was the most commonly reported study TEAE (21.4%), followed by arthralgia (18.4%), upper respiratory tract infection (13.6%), nasopharyngitis (11.7%), headache (10.7%), and nausea (10.7%). These 6 most common study TEAEs generally occurred at a higher incidence within the two noncompleter groups vs the corresponding completer groups.
- Headache was the most commonly reported drug-related study TEAE (4.9%). Other commonly reported drug-related study TEAEs included exacerbation of CD (3.9%), dizziness (2.9%), influenza-like illness (2.9%), and myalgia (2.9%).
- No deaths were reported during or within 30 days after this study. Study treatment-emergent SAEs were reported in 15 subjects (14.6%) during the Overall Treatment Period. Treatment-emergent SAEs reported in more than 1 subject included exacerbation of CD (5 subjects [4.9%]) small intestinal obstruction (3 subjects [2.9%]), abdominal pain (2 subjects [1.9%]), perianal abscess (2 subjects [1.9%]), and sepsis (2 subjects [1.9%]). There were no reports of TB.
- Study TEAEs that led to permanent study medication discontinuation were reported in 24 subjects (23.3%) during the Overall Treatment Period, with the highest incidence occurring in the CZP 400mg/noncompleter group (45.5%). Exacerbation of CD was the most common study TEAE leading to permanent study medication discontinuation (20 subjects [19.4%]) and occurred most frequently in the CZP 400mg/noncompleter group (36.4%).
- No malignancies were reported as SAEs or led to study discontinuation.
- The proportion of subjects reporting study TEAEs was greatest during the first 3 months of the study (76.7%), then decreased over time. The most common study TEAEs generally occurred at a greater incidence in the noncompleter groups compared with the corresponding completer groups at each exposure duration. Arthralgia and nausea were most prevalent earlier in the study (6 months or less). No other trends were apparent amongst the most common study TEAEs. Drug-related study TEAEs occurred at a higher incidence within the first 3 months of exposure compared to later time intervals; whereas, the proportion of subjects reporting severe TEAEs, SAEs, and

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TEAEs leading to discontinuation showed no trend over time.

- Study TEAEs related to injection reactions occurred at a low incidence with 10 subjects (9.7%) reporting injection site reactions. All but 1 injection reactions were considered to be mild or moderate in intensity. No injection reaction AEs led to permanent study medication discontinuation, temporary study medication discontinuation, or dose changes. None of the injection reaction AEs were considered serious and no deaths resulted. No systemic (acute or delayed) injection reactions were reported during the Overall Treatment Period.
- No clinically meaningful changes from Baseline (C87059 or C87065) or shifts in values from Baseline (C87059 or C87065) were noted in hematology or chemistry parameters. Markedly abnormal (Grade 3 or Grade 4) chemistry values were observed for 4 subjects (2 placebo/noncompleter subjects and 2 CZP 400mg/noncompleter subjects) during the Treatment Period and Follow-Up Period. Two placebo/noncompleter subjects [redacted] had markedly abnormal low (Grade 3) values for potassium. Two CZP 400mg/noncompleter subject [redacted] had markedly abnormal high (Grade 3) values for GGT.
- None of the small changes in SBP, DBP, heart rate, or weight were considered clinically meaningful, either within or between treatment groups. No TB infections were reported.
- Overall, the type and incidence of study TEAEs reported by subjects treated with CZP 400mg was consistent with that expected in subjects with CD receiving anti-TNFα therapy.

Conclusions: Long-term treatment with CZP 400mg was well tolerated. The AE profile was consistent with use of an anti-TNFα therapy in subjects with CD and no new safety signals were detected.

Subjects who were continuing treatment with CZP 400mg from C87059 were generally able to maintain clinical remission. Those who were receiving CZP 400mg for the first time were generally able to achieve and maintain clinical efficacy. Subjects who had been previously treated with CZP 400mg but failed to complete C87059 did not respond to CZP 400mg as well as the other subjects. Further studies are needed to confirm the observations from these subpopulations of subjects.

It should be noted that enrollment in this study (N=103) and the previous double-blind

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study C87059 (N=174) were lower than expected (only 49% of the expected enrollment) due to slower than expected enrollment resulting from stringent inclusion and exclusion criteria.

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