C87046, 2006-001729-24

CLINICAL STUDY REPORT SYNOPSIS

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This synopsis may include approved and non-approved uses, formulations or treatment regimens. The results from a single study may not reflect the overall results for the specific product. Prescribing decisions should be made by healthcare professionals based on the approved labeling information for the specific product in the respective country.

Personal information has been removed to protect the privacy of patients and the individuals named in the synopsis.

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Sponsor:

UCB Pharma SA

Allée de la Recherche 60

1070 Anderlecht (Brussels)

Belgium

Official study title:

Open-label long-term clinical trial evaluating efficacy and safety of chronic therapy with certolizumab pegol, a PEGylated Fab fragment of humanized antibody to tumor necrosis factor alpha (TNF) in patients suffering from Crohn's disease and having completed C87042 study

CLINICAL STUDY REPORT SYNOPSIS: C87046

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Name of active ingredient: Certolizumab pegol	**Page:** Not applicable	

Title of study: Open-label long-term clinical trial evaluating efficacy and safety of chronic therapy with certolizumab pegol, a PEGylated Fab fragment of humanized antibody to tumor necrosis factor alpha (TNF) in patients suffering from Crohn's disease and having completed C87042 study

Investigator(s): This was a multicenter study, ~~70~~ * investigators enrolled subjects in this study.

Study site(s): This was a multicenter study conducted at 70 * centers in 12 countries:
[redacted]

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

Studied period: Subjects were allowed to remain on treatment until the study was closed by UCB. **First subject enrolled:** 18 Oct 2006 **Last subject completed:** 14 Apr 2010	**Phase of development:** Phase 3b

Objective(s): The three objectives of this study were:

- To continue to assess the safety of certolizumab pegol (CZP) 400mg as per adverse event (AE) reporting.
- To describe the evolution of long-term efficacy (through maintenance of clinical response) in Crohn's disease (CD) subjects who completed C87042.
- To assess the effect of subcutaneous (sc) CZP 400mg on direct cost parameters.

Methodology: This was a multicenter, open-label, extension study. Subjects who completed the Maintenance Phase of C87042 were offered the possibility to enter C87046. After study closure, subjects were able to transition to a compassionate use study (C87092; COMPAS), for continued treatment of CD.

All subjects were treated with an open-label administration. Subjects who remained on their randomized CZP dose of 400mg every 2 weeks (Q2W) or every 4 weeks (Q4W) in the double-blind Maintenance Phase in C87042 were treated with CZP 400mg every 4 weeks. The first administration of study medication began 4 weeks following the last study

* This note was added for correction purpose afterwards on 19 May 2015:
The original text contains the wrong number of investigators and sites by error.
The correct information is as following:
79 Investigators participated in the study, which includes investigator changes occurring at five sites throughout the study conduct.
This was a multicenter study involving 74 centers in 12 countries, out of those 72 sites enrolled subjects.
The inconsistencies noted do not have an impact on the overall assessment regarding the safety and tolerability profile and clinical benefit of certolizumab pegol as assessed in this study and described in the CSR, and hence are not considered substantial. Therefore, a revision or amendment of the Clinical Study Report of study C87046 is not considered necessary.

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medication administration in C87042. In the case of loss of response (defined as both a Crohn's disease activity index [CDAI] score >150 points and a minimum increase of CDAI of 70 points versus Week 0 as confirmed at 2 consecutive visits) an escalation dose to CZP 400mg sc Q2W was allowed.

Subjects from either randomized group who moved to the open-label 400mg Q2W administration during the Maintenance Phase of C87042 continued Q2W treatment. The first administration of study medication began 2 weeks following the last study medication administration in C87042.

Number of subjects (planned and analyzed): It was expected that approximately 230 to 250 subjects would be participating in this study based on the number of subjects having completed C87042; ultimately, 233 subjects were enrolled in C87046. All but 4 enrolled subjects (229 subjects) received at least 1 injection of study medication and were included in the intention-to-treat (ITT) population

Diagnosis and main criteria for inclusion: This study included male or female subjects with a CD diagnosis who completed the Maintenance Phase of C87042. Females agreed to continue using adequate contraception during the study and for 12 weeks after the last dose of CZP 400mg

Test product, dose(s) and mode of administration, batch number(s): Certolizumab pegol, an anti-TNFα, humanized antibody Fab' fragment-polyethylene glycol conjugate, was provided as a powder for solution for injection (lyophilized formulation, 200mg/vial) in 0.9mg/mL (10mM) lactate, with pH 5.2. The preparation was presented in a 5mL vial, for single use, with a 13mm laminated rubber stopper and was reconstituted with 1mL sterile water for injection. Administration of CZP 400mg consisted of 2 sc injections of 1mL at 2 distinct sites (lateral abdominal wall and 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 a compassionate use named patients program study (C87092; COMPAS).

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

Criteria for evaluation:

Efficacy: As this was primarily a safety study, a primary efficacy variable was not defined. The efficacy variables that were examined in this study included:

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- The proportion of subjects who maintained clinical response (defined as a 100-point decrease from Baseline of C87042 in CDAI) over time
- The proportion of subjects with a clinical response (defined as a 100-point decrease from Baseline of C87042 in CDAI)
- The proportion of subjects achieving a clinical remission (defined as a CDAI score ≤150 points) by visit
- CDAI scores by visit and changes from Week 0 of C87042
- Time to loss of response (defined as both a CDAI score >150 points and a minimum increase in CDAI of 70 points versus Week 0 as confirmed at 2 consecutive visits) after Week 0 of C87046
- Health economics outcomes: direct cost parameters (eg, number of medical procedures, consultations not planned by the protocol, hospitalization, and length of hospital stay)

Immunologic measurements: Plasma samples for anti-nuclear antibody (ANA) and anti-double-stranded deoxyribonucleic acid (anti-dsDNA) analysis were taken at Visit 1 (Week 0) and the Last/Withdrawal Visit.

Safety: Safety variables included the following:

- AEs
- Laboratory evaluations
- Vital signs
- Weight
- Physical examinations
- Chest x-ray

Statistical methods: The ITT population consisted of subjects enrolled and treated in C87046. All statistical analyses were performed on the ITT population. The Safety population was defined by the protocol as the set of subjects who received at least 1 dose of study medication; therefore, the Safety population was the same as the ITT population. The modified ITT population was defined as the subset of ITT subjects who were correctly randomized at Week 6 of C87042 (ie, who were in clinical response and randomized at Week 6 of C87042). The distinction between ITT and modified ITT populations was made

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because some subjects were randomized into the Maintenance Phase of C87042 while not achieving a clinical response at Week 6 (as required by protocol). No per-protocol population was defined.

Some study periods were delimited by visit dates or injections times. The periods were defined as below:

- Pretreatment Period: from first study medication administration in C87042 until first study medication administration in C87046
- Treatment Period: from the first administration of study medication within C87046 to the withdrawal/last study medication administration visit
- Follow-Up Period: up to 84 days after the last injection
- Overall Period: Treatment Period + Follow-Up Period

For demography, the Baseline evaluation was Visit 1 (Screening) of C87042. For Baseline characteristics other than demography, the Baseline evaluation was Visit 2 (Week 0) of C87042. For safety (labs/vital signs) and efficacy endpoints (except maintenance of response and time to loss of response), the last nonmissing pretreatment value of C87042 was the Baseline value. For the maintenance of response and time to loss of response, the Baseline was defined as either Week 26 of C87042 (ie, Week 0 of C87046) or Visit 2 (Week 0) of C87042. Note that AEs were categorized into 1 of 2 categories: prestudy and study-emergent (using the start of C87046 as the reference). However, treatment-emergent adverse events recorded in both C87042 and C87046 were displayed according to duration of exposure and onset of AE.

Percentages were calculated using the number of subjects in the relevant population or subgroup, for whom data were available for that variable, as the denominator. Summary statistics were provided for all efficacy, safety, and Baseline/demographic variables. Summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum, maximum, 25th and 75th percentiles) were tabulated.

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Summary and conclusions:

Subject disposition: A total of 233 subjects from C87042 were enrolled, 229 (98.3%) of whom were included in the ITT population and 208 (89.3%) were included in the modified ITT population.

Within the ITT population, 71 subjects (30.5%) completed the study. The most common reasons for early discontinuation were lack/loss of efficacy (80 subjects [34.3%]), followed by AE (44 subjects [18.9%]) and withdrawal of consent (24 subjects [10.3%]). Other reasons for discontinuation included Investigator decision to remove due to non-compliance, moved to another region, protocol violation, quality of life issue for the subject, Investigator decision to stop study medication, subject needed prohibited concomitant medication, and subject entered another clinical study.

Efficacy results: The main efficacy variables are summarized below for the Overall treatment group of the ITT population.

- The majority of subjects with an available CDAI assessment per visit maintained a clinical response through Visit 31 (Week 118).
- The majority of subjects with an available CDAI assessment per visit had a clinical response at each visit.
- The majority of subjects with an available CDAI assessment per visit were in clinical remission at nearly every visit.
- The mean CDAI scores and changes from Baseline were variable across visits with a general trend towards a greater decrease from Baseline over time.
- The median time to loss of response after Week 0 (C87046) was 97.0 days, although this varied considerably across cohorts. .

Across the treatment cohorts, subjects in the Q4W followed by Q4W and Q2W followed by Q4W cohorts generally had the greatest proportions of subjects who maintained a clinical response over time, who had a clinical response at each visit, and who were in clinical remission at each visit. In comparison, subjects in the Q4W followed by Q4W-Q2W and Q2W followed by Q4W-Q2W cohorts had the smallest proportions for each of these efficacy parameters. A similar pattern among treatment cohorts was observed at the Last/Withdrawal Visit. Mean changes in CDAI scores and time to loss of response after Week 0 (C87046) were highly variable between treatment cohorts with no general pattern evident.

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Subgroups analyses of the main efficacy variables provided the following results:

- By anti-infliximab status, subjects who were positive for anti-infliximab antibody had a general trend towards a greater proportion of subjects with a clinical response at most visits, a greater proportion of subjects in clinical remission at most visits, and greater mean changes in CDAI scores over time compared with subjects who were negative for anti-infliximab antibody. No pattern was observed between the positive and negative anti-infliximab antibody subgroups regarding the proportion of subjects who maintained a clinical response.
- By reason for discontinuing infliximab, subjects who discontinued due to a hypersensitivity reaction (HSR) to infliximab had a general trend towards a greater proportion of subjects who maintained a clinical response, a greater proportion of subjects in clinical remission at most visits, and greater mean changes in CDAI scores at most visits compared with those who discontinued due to loss of response (LOR) but no experience of hypersensitivity reaction to infliximab. The small number of subjects who discontinued due to LOR and HSR precludes any meaningful conclusions. There was no particular trend between subgroups based on reason for discontinuing infliximab in the proportion of subjects with a CDAI assessment per visit who had a clinical response.

Health economic outcomes suggest low resource utilization for subjects in this long-term study, with no meaningful differences between treatment cohorts.

- In general, concomitant medications potentially influencing CD were kept stable and the majority of subjects overall did not start any medications potentially affecting CD (immunosuppressants, corticosteroids, or 5-aminosalicylic acid) during the Treatment Period, with the exception of antibiotics; 55.5% of subjects started at least 1 antibiotic during the Treatment Period. No subjects were using anti-TNFα medications other than CZP.
- The majority of subjects overall had started at least 1 general concomitant medication (excluding medications potentially influencing CD) during the Treatment Period (80.8%).
- Low resource utilizations were observed during the Treatment Period with the majority of subjects having no emergency room visits or hospital stays and 1 or 0 concomitant medical procedures or unforeseen healthcare provider consultations.

Immunologic results: The majority of subjects had no change from Baseline to the

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Last/Withdrawal Visit in the concentration of auto-antibodies, ANA (68.3%) and anti-dsDNA (89.5%).

Safety results:

- The sc administration of CZP 400mg in C87046 was generally well tolerated with subjects having received on average approximately 19 study medication injections with a mean duration of exposure to study medication of approximately 430 days (approximately 15 months).
- Nearly all subjects (92.6%) experienced at least 1 study-emergent AE, the majority of which were mild or moderate in intensity (62.4%).
- As expected with the use of an anti-TNFα therapy in subjects with CD, AEs were reported most commonly in the System Organ Class (SOC) categories of Gastrointestinal disorders (72.9%), Infections and infestations (68.1%), and General disorders and administration site conditions (43.7%).
- Nasopharyngitis was the most commonly reported AE (27.5%) followed by exacerbation of CD (26.2%), abdominal pain (21.4%), pyrexia (20.5%), and headache (20.5%).
- Nasopharyngitis was the most commonly reported drug-related AE (8.7%). Other commonly reported drug-related AEs included pyrexia (6.6%), sinusitis (4.4%), arthralgia, and headache (3.9% of subjects each).
- One death was reported during the study. A subject in the Q4W followed by Q4W group died following Visit 2 due to an intestinal obstruction followed by septic shock 8 days later. The Investigator considered both events to be severe, serious, and possibly related to study medication.
- Study-emergent serious adverse events (SAEs) were reported in 73 subjects (31.9%). The most commonly reported SAEs included exacerbation of CD (22 subjects [9.6%]); abdominal abscess, colonic stenosis, and perianal abscess (5 subjects [2.2%] each); abdominal pain (4 subjects [1.7%]); and chest pain (3 subjects [1.3%]). One subject (a [redacted]-year-old [redacted] female) reported an SAE of acute renal failure 330 days after the first injection in C87042 (22 days after the last injection in C87046) that occurred in conjunction with anemia and abdominal abscess. Both events were considered to be possibly related to study medication.
- Adverse events of special interest reported in this study included opportunistic and viral

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infections, abscesses, gastrointestinal obstructions and perforations, malignancies, and hepatits. In the Infections and infestations SOC, herpes simplex was reported at the highest incidence (24 subjects [10.5%]). In the Gastrointestinal disorders SOC, colonic stenosis (8 subjects [3.5%]; 5 subjects with SAEs) was reported with the highest incidence. There was no evidence of heart failure in this study. Palpitations were the most common event (2 subjects [0.9%]) in the Cardiac disorders SOC. Malignancies occurred in a small number of subjects. No malignancies were considered to be serious; although, 1 subject reported an AE of basal cell carcinoma that was considered to be probably related to study medication and led to permanent study medication discontinuation. Hepatitis was reported in a single subject.

- Two pregnancies were reported. One subject (a [redacted]-year-old [redacted] female) became pregnant approximately 4 months after discontinuing study medication having received 23 injections of study medication over the course of both studies. Another subject (a [redacted]-year-old [redacted] female) reported an ectopic pregnancy approximately 3 months after discontinuing study medication having received 15 injections of study medication over the course of both studies.
- Suspected tuberculosis was reported in 1 subject.
- The proportion of subjects reporting AEs was generally consistent for each duration of exposure interval. Of the most common AEs, abdominal pain, exacerbation of CD, headache, and pyrexia were more prevalent within the first 3 months. Events of nasopharyngitis were commonly reported throughout the study. The proportion of subjects reporting severe AEs, drug-related AEs, SAEs, and AEs leading to discontinuation showed no trend over time.
- Study-emergent AEs related to injection reactions occurred at a low incidence with 14 subjects (6.1%) reporting injection site reactions, no subjects reporting acute systemic injection reactions, and 4 subjects (1.7%) reporting delayed systemic injection reactions. Most injection reactions were considered to be mild or moderate in intensity. Two subjects (0.9%) reported delayed systemic injection reactions resulting in permanent study medication discontinuation, and 1 subject (0.4%) reported an injection site reaction which led to temporary study medication discontinuation.
- No clinically meaningful changes in mean values from Baseline or shifts in abnormal values from Baseline were noted in hematology or chemistry parameters. The majority of subjects had normal hematology and chemistry values at each study visit. The proportion of subjects with markedly abnormal values was low and generally consistent

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across study visits. No clinically meaningful changes occurred in urinalysis parameters.

- Mean changes in systolic blood pressure, diastolic blood pressure, and heart rate were small and not considered clinically meaningful. Mean changes in weight from Baseline showed a trend towards increasing over time.
- Overall, the type and incidence of study-emergent AEs reported by subjects treated with CZP 400mg Q4W or Q2W 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. No new safety signals were detected.

Overall, the majority of subjects who were treated with CZP 400mg in this extension study were able to achieve a clinical response and/or clinical remission throughout the study with a median time to loss of response of 3.2 months. In addition, of those subjects who were responders at the start of this study, the majority were able to maintain a clinical response over an extended treatment period.

Low resource utilizations were observed during the Treatment Period with the majority of subjects having no emergency room visits or hospital stays and at most 1 concomitant medical procedure or unforeseen healthcare provider consultation.

Report date: 11 Oct 2011