C87043, 2005-003977-25

CLINICAL STUDY REPORT SYNOPSIS

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

Sponsor:

UCB S.A. – Pharma Sector

Chemin du Foriest

1420 Braine-l'Alleud

Belgium

Official study title:

A Phase IIIB multicentre open label 54 weeks clinical trial evaluating certolizumab pegol, a PEGylated Fab fragment of humanized antibody to tumor necrosis factor alpha (TNFα) on endoscopic and mucosal healing in patients suffering from active Crohn's disease

CLINICAL STUDY REPORT SYNOPSIS: C87043

Name of company: UCB Pharma	**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	**Page:** Not applicable	
Title of study: A Phase IIIB multicentre open label 54 weeks clinical trial evaluating certolizumab pegol, a PEGylated Fab fragment of humanized antibody to tumor necrosis factor alpha (TNFα) on endoscopic and mucosal healing in patients suffering from active Crohn's disease		
Investigator(s): This was a multicenter study, 17 investigators enrolled subjects in this study.		
Study site(s): This was a multicenter study conducted at 25 centers in the [redacted] of which a total of 17 centers enrolled subjects.		
Publication(s) (reference[s]): none		
Studied period: The duration of the treatment period was 54 weeks followed by an undefined extension period. **First subject enrolled:** 13 Feb 2006 **Last subject completed:** 31 Dec 2009	**Phase of development:** Phase 3b	
Objective(s): The primary objective of this study was to assess the efficacy of subcutaneous certolizumab pegol (CZP) 400mg subcutaneous (sc) administered at Weeks 0, 2, 4 and 8 in subjects suffering from moderately to severely active Crohn's disease (CD). Efficacy was assessed using the Crohn's Disease Endoscopic Index of Severity (CDEIS) score at Week 10 compared with Baseline. The secondary objectives of the study were to: • Assess the efficacy of CZP 400mg sc in subjects suffering from CD evaluated as the proportion of subjects achieving mucosal healing (defined as complete absence of mucosal ulcerations) at Week 10 and Week 54. • To assess the efficacy of CZP 400mg sc in subjects suffering from CD evaluated as the proportion of subjects achieving CDEIS endoscopic response (defined as CDEIS decrease from Baseline of more than 5 points), endoscopic remission (defined as a CDEIS below 6 points), or complete endoscopic remission (defined as a CDEIS below 3 points) at Week 10 and Week 54. • Assess the clinical efficacy of CZP 400mg sc in subjects suffering from CD evaluated as improvement from the baseline in the mean histological CD score (combines active		

inflammatory changes: infiltration of mononuclear cells, polymorphonuclear cells, presence of erosions and/or ulcers, and chronic architectural changes) at Week 10.

- Assess the clinical efficacy of CZP 400mg sc in subjects suffering from CD evaluated as proportion of subjects achieving clinical response (defined as a decrease of at least 100 points on Crohn's Disease Activity Index [CDAI] score) at Week 10.
- Assess the efficacy of CZP 400mg sc in subjects suffering from CD evaluated as proportion of subjects achieving a clinical remission (defined as CDAI score ≤150) at Week 10.
- Evaluate the effect of CZP 400mg therapy on the mean C-reactive protein (CRP) plasma levels and to correlate them with the endoscopic, histological and clinical scores.
- Evaluate the clinical efficacy of CZP 400mg sc in subjects suffering from CD evaluated as proportion of subjects with mucosal healing, mean CDEIS and mean histological scores at Week 54/withdrawal.
- Evaluate the safety and tolerability of CZP 400mg.

Exploratory objectives of the study were to assess:

- Efficacy of CZP 400mg sc in subjects suffering from CD evaluated on Simplified Endoscopic Score – CD (SES-CD) improvement from the baseline at Week 10 and 54/Withdrawal and to look for a correlation with CDEIS and with the clinical score.
- Efficacy of CZP 400mg sc, every 4 weeks (Q4W) or every 2 weeks (Q2W), evaluated as time to loss of response (defined as both a CDAI score >150 points and a minimum increase in CDAI score of 70 points at 2 consecutive visits versus Week 10) in responders by CDAI with or without mucosal healing at Week 10.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated as response and remission rates at Week 54/Withdrawal in the responders by CDAI with or without mucosal healing at Week 10.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated on CDEIS at Week 54 in the responders by CDAI with or without mucosal healing at Week 10.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated as proportion of subjects in clinical response and remission who have tapered and discontinued corticosteroids at Week 54/Withdrawal.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated on Inflammatory Bowel Disease Questionnaire (IBDQ) overall score at Weeks 10/Withdrawal and 54/Withdrawal.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated on the Investigator's Global Evaluation Scale (GES) at Weeks 10/Withdrawal and 54/Withdrawal.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated on the Patient's GES at Weeks 10/Withdrawal and 54/Withdrawal.
- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated as number of flares.

- Efficacy of CZP 400mg sc (Q4W or Q2W) evaluated as number and length of hospitalizations in subjects with or without mucosal healing at Week 10.

Methodology: This was a multicentre, open label, uncontrolled, 1 arm, non-randomized Phase 3b study. Subjects must have had CD for a minimum of 3 months duration with a Crohn's Disease Activity Index (CDAI) score between 220 and 450 points inclusive scored over the 7 days prior to the first dose of study medication. After a screening period of 1 week, subjects entered a Treatment Period that lasted 52 weeks.

During the study, subjects were treated with CZP 400mg (2 x 200mg) sc at Weeks 0, 2, and 4 (induction doses) and then every 4 weeks (Q4W) starting from Week through Week 52. If neither clinical response nor clinical remission was achieved at Week 10 or if clinical response was lost (defined as both a CDAI score >150 points and a minimum increase in CDAI score of 70 points at 2 consecutive visits versus Week 10) after Week 10, investigators were allowed at any time to escalate the dose to CZP 400mg (2 x 200mg) sc every 2 weeks (Q2W). In this case, additional study visits were to have taken place (Visit xbis, eg, Visit 8bis to 18bis [Week 14 to 50]).

Two weeks after the last dose of study medication during the Treatment Period all subjects, including those withdrawn from study treatment, had a Safety Follow-Up (Control) Visit (Week 54).

After Week 54, subjects were able to continue receiving the treatment (either Q4W or Q2W according to the administration frequency at Week 54) during the treatment Extension Period of the study.

Number of subjects (planned and analyzed): planned: 85 subjects, analyzed: 89 subjects

Diagnosis and main criteria for inclusion: Male or female subjects ≥18 years of age who had CD for a minimum of 3 months duration with a CDAI score between 220 and 450 points inclusive scored over the 7 days prior to the first dose of study medication, at least 2 segments with endoscopic ulcerative lesions with CDEIS ≥8 at the baseline, and who needed to be treated with an anti-TNFα therapy.

Test product, dose(s) and mode of administration, batch number(s): Certolizumab pegol, an anti-TNFα, humanized antibody Fab' fragment-PEG conjugate, was provided as a powder for solution for injection (lyophilized formulation, 200mg/vial) in 75mM lactic acid, 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 subcutaneous injections of 1mL at 2 distinct sites (lateral abdominal wall; upper, outer thigh; or upper arm) using separate syringes and needles at each injection site. Batch numbers: [redacted]

Duration of treatment: The duration of the treatment period was 54 weeks, which included study medication administration every 2 or 4 weeks, followed by an undefined extension period.

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

Criteria for evaluation:

Efficacy: The primary efficacy variable was the CDEIS score at Week 10 compared with

Baseline. The secondary variables of the study were:

- Proportion of subjects achieving mucosal healing at Week 10 and Week 54
- Change from Baseline in the mean histological CD score at Week 10 and 54
- Proportion of subjects achieving a clinical response at Week 10
- Proportion of subjects achieving a clinical remission at Week 10
- Proportion of subjects achieving CDEIS endoscopic response, remission, or complete remission at Week 10 and Week 54
- CRP plasma levels at Weeks 0, 2, 4, 6, 8, 10, 12, 16, 20, 24, etc. every 4 weeks until Week 54, and Last/Withdrawal along with the ratio to Baseline
- Correlation of the mean CRP plasma levels with the endoscopic, histological, and clinical scores

Exploratory variables of the study were:

- Proportion of subjects who discontinued corticosteroids at the last visit or before Week 54
- Proportion of subjects in clinical response and remission who have tapered and discontinued corticosteroids at Week 54/Withdrawal
- Proportion of subjects with improvement in ulcerations from Baseline, assessed at Week 10 and Week 54
- SES-CD improvement from Baseline at Week 10 and Week 54/Withdrawal
- Correlations between SES-CD and CDAI, SES-CD and CDEIS, and CDEIS and CDAI
- Investigator's GES at Weeks 10 and 54/Withdrawal
- Patient's GES at Weeks 10 and 54/Withdrawal
- IBDQ overall score at Weeks 10 and 54/Withdrawal
- Number and length of hospitalizations in subjects with or without mucosal healing at Week 10

Pharmacokinetics/pharmacodynamics:

The pharmacokinetic (PK) and immunologic variables included:

- Mean CZP plasma concentration at Visits 2 (Week 0), 6 (Week 8), 12 (Week 26) and 20 (Week 54)/Withdrawal after Visit 7.
- Anti-CZP antibody status at Visits 2 (Week 0), 6 (Week 8), 12 (Week 26) and 20 (Week 54)/Withdrawal after Visit 7.
- Change in autoantibodies, anti-nuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA), fromVisit 2 (Week 0) to Visits 6 (Week 8), 12 (Week 26) and 20 (Week 54).

Safety: Safety variables included the following:

- Adverse events (AEs)
- Laboratory evaluations
- Vital signs
- Weight
- Physical examinations
- Chest x-ray
- Tuberculosis (TB) testing

Statistical methods:

The intention-to-treat (ITT) population was defined as all subjects who were enrolled and received at least 1 dose of study medication.

For the CDEIS analyses as per local assessment, a distinction was made between "Full ITT population" and "ITT population with an endoscopic assessment at Week 10/Week 54". The latter restricted the ITT population to the subjects with available CDEIS data at Week 10/Week 54. The "Full ITT population" included all subjects in the ITT population, using some imputation rules. The ITTQ2W population was defined as the subset of subjects from the ITT population who switched to Q2W treatment sometime after Week 10. The per-protocol (PP) population was defined as a subset of the ITT populations who did not have any major protocol deviations before or on Week 10 Visit.

For the blinded central endoscopy results, CDEIS and SES-CD analyses were restricted to 2 sub-populations from the ITT: "ITT population with blinded central review by experts at Baseline and Week 10" (ITTBW10) and "ITT population with blinded central review by experts at Baseline and Week 54" (ITTBW54). Subjects eligible for this blinded central review were subjects for whom at least a baseline (Visit 1 and/or 2) and Week 10 (Visit 7) and/or Week 54 (Visit 20) endoscopy was done. Among them, all the subjects who signed the Patient Consent Form of the Addendum found in protocol amendment 8 were reviewed.

Study periods were defined as:

- Screening period was from Visit 1 date included to Visit 2 injection date and time excluded
- Treatment period Q4W (TRTQ4W) was from Visit 2 injection date and time included to the last visit date included. Should the subject switch to Q2W treatment as authorized by protocol, the TRTQ4W period ended right before the date and time of the first Q2W injection.
- Treatment period Q2W (TRTQ2W) was from date and time of the first Q2W injection to the last visit date included.
- Treatment period (TRT) was from Visit 2 injection date and time included to the last visit date included. For subjects having a TRTQ4W and a TRTQ2W period, the TRT period was the concatenation of these 2 periods. For subjects having only a TRTQ4W

period, the TRT period was the same as the TRTQ4W period.

No formal statistical testing was performed in this single-arm open-label study except for the primary efficacy variable. Summary statistics were provided for all efficacy, safety and Baseline/demographic variables. Summary statistics consisted of frequency tables with associated 95% 2-sided confidence intervals (CI) (only for efficacy analyses) for categorical variables. For continuous variables, descriptive statistics (number of available observations, mean, median, standard deviation, minimum, maximum, 25th and 75th percentiles) were tabulated. 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.

For the primary efficacy analysis, the actual value and change from Baseline at Week 10 in the CDEIS score was presented with a 95% 2-sided CI along with other descriptive statistics. The Student's t-test was performed for the primary efficacy variable to compare actual value versus baseline; however, only the 95% CI for mean change was used for interpretation. A "waterfall plot" was prepared for the change at Week 10 in CDEIS, displaying graphically the individual results in the ITT population with an endoscopic assessment at Week 10.

For sensitivity purpose, the same analysis was performed on the ITTBW10 population using data provided by the blinded central endoscopy reading review.

Summary and conclusions:

Subject disposition: A total of 118 subjects were screened for the study and 89 subjects were enrolled. All enrolled subjects were included in the ITT population, 49 subjects (55.1%) were included in the ITTQ2W population, 44 subjects (49.4%) were included in the ITTBW10 population, 31 subjects (34.8%) were included in the ITTBW54 population, and 58 subjects (65.2%) were included in the PP population.

Within the ITT population, 53 subjects (59.6%) completed the study until Week 54. The most common reasons for early discontinuation before Week 54 were lack/loss of efficacy (18 subjects [20.2%]), followed by AE (13 subjects [14.6%]). Nine subjects (10.1%) completed the Extension Period (Table 14.1.1:2). The most common reasons for early discontinuation during the Extension Period were lack/loss of efficacy (27 subjects [30.3%]), followed by withdrawal of consent (8 subjects [9.0%]) and AE (6 subjects [6.7%]).

Efficacy results: Treatment with CZP 400mg showed a significant improvement in the mean CDEIS score at Week 10 compared with Baseline (primary efficacy variable; -6.47 points; 95% CI: -7.60, -5.34) for subjects in the ITT population with an endoscopic assessment at Week 10. Overall, analyses using blinded (central) assessments were supportive of the non-blinded (local) assessments and analyses in other populations were generally consistent with the ITT population during the TRT period. Secondary efficacy variables also indicated endoscopic improvement at Week 10 with CZP 400mg treatment for subjects in the ITT population:

- A small proportion of subjects showed mucosal healing at Week 10 (5.1%); however, the proportion had increased by Week 54 (13.2%). Results were unaffected by number of segments explored.

- CDEIS endoscopic response, endoscopic remission, and complete endoscopic remission were achieved at Week 10 by 61.5%, 42.3%, and 11.5% of subjects, respectively. These proportions were maintained at Week 54 for endoscopic response and complete endoscopic remission (62.3% and 18.9%, respectively) but decreased slightly for endoscopic remission (28.3%).
- Mean histological CD score histological biopsy samples of the colon showed improvement from Baseline (-2.7 points) at Week 10 that was maintained at Week 54 (-3.3 points). Similar improvements were observed in mean histological score of the ileum.
- At Week 10, approximately half of subjects achieved a clinical response (50.6%) or clinical remission (46.1%). The proportion of subjects achieving a clinical response or clinical remission was slightly lower at Week 54 (32.6% and 27.0%, respectively).
- Mean CRP plasma levels decreased from Baseline and remained consistent from Week 2 to Week 44, then showed a slight increase starting at Week 48, although the means were still lower than Baseline at all assessments.
- Correlations between mean CRP plasma levels and endoscopic, histological, and clinical scores were only weakly positive at Weeks 10 and 52/54. For each of these correlations (CRP and CDEIS; CRP and histological CD score; CRP and CDAI), a trend towards a higher positive association was observed from Week 10 to Week 52/54.

Results of exploratory efficacy analyses provided further indications of a positive CZP 400mg treatment effect in the ITT population:

- The majority of subjects discontinued corticosteroid treatment on or before Week 54 (59.5%). Of these subjects, 36.4% were in clinical response and 36.4% were in clinical remission at Week 54.
- At Week 10, nearly half of subjects showed improvement in ulcerations (46.8%), shifting from deep ulcerations at Baseline to superficial ulcerations (41.6%) or no ulcerations (5.2%) at Week 10. Improvements occurred in all segments of the lower intestinal tract (ileum, colon, and rectum).
- Change in mean SES-CD score indicated endoscopic improvement at Week 10 (-7.38 points) that was maintained at Week 54 (-5.71 points).
- A strongly positive correlation between SES-CD and CDEIS was observed at Weeks 10 and 54. No correlation was observed between SES-CD and CDAI or CDEIS and CDAI at either time point.
- Investigators indicated a marked or moderate improvement for the majority of subjects at Week 10 (75.3%) and Week 54 (64.2%) on the Investigator GES. Similarly, a majority of subjects indicated a marked or moderate improvement at Week 10 (67.1%) and Week 54 (74.5%) on the Patient GES.
- The mean change in IBDQ total score and all subscores from Baseline to Week 10 and Week 54 were positive, indicating improvement in quality of life. The proportion of subjects in IBDQ remission (total score ≥170 points) was 43.8% at Week 10, which

decreased slightly at Week 54 (29.2%).

- The mean number of hospital stays for subjects between subjects with and without endoscopic response, remission, or complete remission was approximately 1.00 day and the majority of subjects had no hospital stays, regardless of endoscopic status. The mean duration of hospitalization between subjects with and without complete endoscopic remission and endoscopic remission ranged from 3.44 days to 3.99 days. Subjects with endoscopic response had a slightly longer duration of hospitalization (4.44 days) compared to subjects without endoscopic response (3.10 days).

Subgroups analyses of the primary and key secondary variables provided the following results:

- Across the various subgroup analyses of mean CDEIS score, CDEIS response, CDEIS remission, or CDEIS complete remission at Week 10, results suggest that subjects not using corticosteroids at baseline and subjects with a longer duration of CD (≥5y) had a greater response to CZP 400mg treatment. Use of immunosuppresants, mean CDAI score at Baseline, and behavior of CD had no effect on mean CDEIS score or proportion of subjects in CDEIS response, remission, or complete remission at Week 10.
- The mean change in CDEIS score was greater for subjects with a CDEIS score ≥median at Baseline compared with those whose score was <median (-7.92 vs -4.78 points) and a greater proportion of the subjects with a CDEIS score ≥median at Baseline had a CDEIS response at Week 10 (69.0% vs 52.8).
- Across the various subgroup analyses of efficacy status at Week 10, results suggest that the occurrence of flares was lower in subjects with complete endoscopic remission (no trend observed in subjects with endoscopic remission or response) and the time to loss of clinical response was greater in subjects with an endoscopic response/remission. Mean CDEIS score was lower in subjects with complete endoscopic remission, endoscopic remission, or endoscopic response and was unaffected by CDAI status. Clinical response and clinical remission were unaffected by CDEIS response, remission, or complete remission at Week 10, regardless of CDAI status.

Pharmacokinetics results::

- Mean (geometric) plasma CZP concentrations for subjects with a negative anti-CZP status increased from Week 8 (<14.2µg/mL) to Week 26 (27.8µg/mL) and then were unchanged at Week 54 (28.6µg/mL) and the Last/Withdrawal Visit (22.8µg/mL).
- As expected, subjects treated during the TRTQ4W period had slightly lower mean (geometric) plasma CZP concentrations at Week 26, Week 54, and Last/Withdrawal Visit compared with subjects in the ITTQ2W population.

Immunologic results:

- The majority of subjects were anti-CZP negative at Screening and throughout the study. Four subjects developed antibodies to CZP during the study (3 subjects during treatment and 1 subject after treatment).
- The majority of subjects had no change from Baseline to the Last/Withdrawal Visit in the concentration of auto-antibodies, ANA (69.2%) and anti-dsDNA (100%).

Safety results:

- The sc administration of CZP 400mg was generally well tolerated with subjects having received on average approximately 22 study medication injections with a mean duration of exposure to study medication of approximately 422 days.
- Nearly all subjects (97.8%) experienced at least 1 treatment-emergent AE (TEAE), the majority of which were mild or moderate in intensity (61.8%).
- As expected with use of an anti-TNFα therapy in subject with CD, TEAEs were reported most commonly in the SOC categories of Gastrointestinal disorders (79.8%), Infections and infestations (76.4%), and General disorders and administration site conditions (51.7%).
- Headache was the most commonly reported TEAE (33.7%) followed by arthralgia (30.3%), nasopharyngitis (23.6%), abdominal pain (22.5%), and asthenia (21.3%).
- Headache was the most commonly reported drug-related TEAE (12.4%). Other commonly reported drug-related TEAEs included arthralgia (9.0%), injection site erythema (7.9%), exacerbation of CD (6.7%), and abdominal pain (5.6%).
- No deaths were reported during or within 30 days after this study. Treatment-emergent serious adverse events (SAEs) were reported in 34 subjects (38.2%). Treatment-emergent SAEs reported in more than 1 subject included anal abscess and exacerbation of CD (5 subjects [5.6%] each); diarrhea (4 subjects [4.5%]); abdominal pain and perianal abscess (3 subjects [3.4%] each); and anal fistula, malnutrition, perineal fistula, and pyrexia (2 subjects [2.2%] each). One subject (a [redacted]-year-old [redacted] male) reported a malignancy of colon cancer 8 days after initiation of CZP treatment that was considered to be unrelated to study medication. One pregnancy was reported by a [redacted]-year-old [redacted] female after having received 8 injections of study medication on TRTQ4W. The subject gave birth to a healthy baby via c-section delivery and both were in good health at last follow-up 3 months after the delivery. There were no reports of TB.
- TEAEs related to injection reactions occurred at a low incidence with 9 subjects (10.1%) reporting injection site reactions, 4 subjects (4.5%) reporting acute systemic injection reactions, and 12 subjects (13.5%) reporting delayed systemic injection reactions. Most injection reactions were considered to be mild or moderate in intensity. Two subjects (2.2%) reported delayed systemic injection reactions resulting in permanent study medication discontinuation, and 1 subject (1.1%) reported an injection site reaction which led to temporary study medication discontinuation.

- No clinically meaningful changes from Week 0 or shifts in possibly clinically significant (PCS) values from Week 0 were noted in hematology or chemistry parameters. No clinically meaningful changes occurred in urinalysis parameters.
- None of the changes in systolic blood pressure, diastolic blood pressure, pulse rate, or weight were considered clinically meaningful.
- Overall, the type and incidence of TEAEs reported by subjects treated with CZP 400mg was consistent with that expected in subjects with CD receiving anti-TNFα therapy.

Conclusions: Certolizumab pegol 400mg demonstrated significant endoscopic improvement from Baseline in subjects with moderately to severely active CD following 10 weeks of treatment. Treatment with CZP 400mg was also clinically effective with benefits clearly visible following 10 weeks of treatment.

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.

Report date: 12 Oct 2010