C87085, 2007-001913-41

CLINICAL STUDY REPORT SYNOPSIS

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Sponsor:

UCB Celltech

208 Bath Road

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United Kingdom

Official study title:

A phase IIIb, multinational, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of certolizumab pegol, a pegylated Fab' fragment of a humanized anti- TNF-alpha monoclonal antibody, administered subcutaneously at Weeks 0, 2 and 4 in subjects with moderately to severely active Crohn's disease

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Name of company: UCB	**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, multinational, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of certolizumab pegol, a pegylated Fab' fragment of a humanized anti- TNF-alpha monoclonal antibody, administered subcutaneously at Weeks 0, 2 and 4 in subjects with moderately to severely active Crohn's disease.

Investigator(s): This was a multicenter study; 118 Investigators enrolled subjects.

Study site(s): This was a multicenter study; 120 sites enrolled subjects.

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

Studied period: The total duration of the study for each subject was a maximum of 22 weeks. **First subject enrolled:** 18 Mar 2008 **Last subject completed:** 09 Oct 2009	**Phase of development:** Phase 3b

Objective(s): Following global protocol amendment 1 the primary objective was changed to assess the efficacy of CZP versus placebo for induction of clinical remission in subjects with moderately to severely active CD. The original primary objective of the study was to assess the efficacy of CZP versus placebo for induction of clinical response in subjects with moderately to severely active CD.

Methodology: This was a multicenter, parallel-group, randomized, placebo-controlled (6 weeks), double blind, 2-arm study of induction dosing (3 doses of CZP 400mg versus placebo given sc at Weeks 0, 2, and 4). Following assessment and confirmation of eligibility (1 to 2 week Screening Period), subjects with moderately to severely active Crohn's disease (CD) were randomized to CZP 400mg or placebo in a 1:1 ratio. The randomization was stratified by country, C-reactive protein at entry, use of corticosteroids at entry and immunosuppressants at entry. There was a Safety Follow-Up Period of 12 weeks after the last dose of study drug. Subjects who completed Week 6 of this study had the opportunity to continue into the open-label extension study (C87088).

Number of subjects (planned and analyzed): 414 subjects were planned to be enrolled (207 per treatment group); ultimately, 439 subjects were enrolled (223 subjects in the CZP 400mg group and 216 subjects in the placebo group).

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Diagnosis and main criteria for inclusion: Subjects enrolled were male or females, 18 to 75 years of age, with moderately to severely active CD (Crohn's Disease Activity Index [CDAI] score ≥220 to ≤450 points) and no prior treatment with an anti-tumor necrosis factor-alpha (TNFα) agent. Subjects with perianal disease, active fistulae, abscess, obstructive strictures, 2 or more bowel resections, or chest x-ray suggestive of malignancy or infection (including tuberculosis) were not enrolled.

Test product, dose(s) and mode of administration, batch number(s): CZP for subcutaneous injection, 200mg/vial containing the active ingredient (CDP870 Fab' PEG) presented as a lyophilized product which was reconstituted with water for injection. Batch numbers: [redacted]

Duration of treatment: The duration of treatment was 6 weeks; 3 doses of CZP 400mg were given subcutaneously every 2 weeks

Reference therapy, dose(s) and mode of administration, batch number(s): Placebo was commercially available saline (NaCl 0.9%) preservative-free solution of pharmacopoeial (USP/Phr.Eur) quality. Batch numbers: [redacted].

Criteria for evaluation:

Efficacy: The primary efficacy variable was the proportion of subjects in clinical remission at Week 6. Clinical remission was defined as a total CDAI score of 150 points or less.

The secondary efficacy variables were:

- The proportion of subjects in clinical remission at Weeks 2 and 4
- The durability of remission at Weeks 4 and 6
- The proportion of subjects achieving a clinical response (defined as at least a 100 point decrease from the Week 0 CDAI) at Weeks 2, 4, and 6
- The change from Week 0 in the Harvey Bradshaw Index (HBI) score at Week 6
- The total CDAI score and the change from Week 0 in the total CDAI score by visit
- CRP levels and change from Week 0 in CRP levels by visit
- The proportion of subjects in Inflammatory Bowel Disease Questionnaire (IBDQ) remission (defined as a total IBDQ score of 170 points or more) at Weeks 2, 4, and 6

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The exploratory efficacy variables were:

- The proportion of subjects in IBDQ response (defined as a total IBDQ score increase from Week 0 of 16 points or more) at Weeks 2, 4, and 6
- The IBDQ total and domain scores and the change from Week 0 in the IBDQ total and domain scores by visit
- The proportion of subjects in HBI response (defined as a drop of at least 3 points from the Week 0 HBI score) at Week 6
- The proportion of subjects in HBI remission (defined as an absolute score of 4 points or less) at Week 6

Pharmacokinetics/pharmacodynamics: Blood samples were drawn for determination of CZP plasma concentrations and plasma concentration of anti-CZP antibodies at Weeks 0 (Baseline), 2, 4, and 6/or Withdrawal, and 16/or Follow-Up.

Safety: The safety variables were:

- Adverse events
- Hematology, biochemistry, and urinalysis parameters
- Vital signs
- Serum concentrations of autoantibodies (anti-double stranded-DNA [anti-dsDNA] antibodies and antinuclear antibodies [ANA])

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Statistical methods: The intention-to-treat (ITT) population included all randomized subjects irrespective of any protocol deviations who received at least 1 injection of study treatment and who had at least 1 efficacy measurement after the first injection. All subjects eligible for the ITT population who did not have any major protocol deviations, were included in the per protocol (PP) population.

The primary efficacy variable was the proportion of subjects in clinical remission at Week 6. The 2 treatments were compared at the 5% significance level using the Cochran-Mantel-Haenszel test allowing for randomization strata. To summarize the differences between placebo and CZP 400mg the odds ratio and associated 95% confidence interval were derived from the Mantel-Haenszel estimate of the common odds ratio adjusting for randomization strata. In addition, a point estimate of the difference in remission rates between the placebo and CZP 400mg groups and an associated 95% confidence interval was derived. The primary efficacy variable was analyzed using the ITT and PP populations.

All secondary efficacy variables were analyzed using the ITT population only. Clinical remission at Weeks 2 and 4, the proportion of subjects in clinical response at Weeks 2, 4, and 6, the proportion of subjects in IBDQ remission at Weeks 2, 4, and 6, durability of remission, and proportion of responder subjects (remission or clinical response) at Weeks 2, 4, and 6 were compared using the same statistical test as used for the primary efficacy variable. The total CDAI score and the change from Week 0 in the total CDAI score, actual CRP concentration and the change from Week 0 in CRP, and HBI score and the change from Week 0 in the HBI score were summarized using descriptive statistics only.

All other efficacy variables were analyzed using the ITT population only. The proportion of subjects in HBI response or remission at Week 6 and the proportion of subjects in IBDQ response at Weeks 2, 4, and 6 were compared using the same statistical test as used for the primary efficacy variable. The total IBDQ scores and the 4 domain scores (bowel symptoms, systemic symptoms, emotional function, and social function), the change from Week 0 in the total and domain scores, and the results of the Investigator's clinical assessment were summarized by visit using descriptive statistics only.

The primary efficacy variable of clinical remission and the secondary efficacy variables of clinical response, and responders (clinical response or remission) at Week 6 were also investigated in subgroup analyses.

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Summary and conclusions:

Subject disposition: A total of 439 subjects were randomized into the study; 223 in the CZP 400mg group and 216 in the placebo group. Note that 1 subject in the placebo group was randomized but did not receive any double-blind study drug.

The majority of subjects in both treatment groups completed the study (92.8% of the CZP 400mg group and 88.9% of the placebo group); slightly fewer subjects withdrew in the CZP 400mg group (7.2%) compared to the placebo group (11.1%). The most common reason for withdrawal was AE, which was reported at a similar rate in both groups (3.6% in the CZP 400mg group and 3.2% in the placebo group). Fewer subjects withdrew due to lack of efficacy in the CZP 400mg group (1 subject; 0.4%) compared to the placebo group (5 subjects; 2.3%). Ten subjects withdrew due to other reasons, 2 subjects in the CZP 400mg group (0.9%; 1 subject for noncompliance and 1 early rollover [into C87088] due to lack of efficacy) and 8 subjects in the placebo group (3.7%; 1 subject each for low CDAI score, unblinding, positive stool culture, entered C87088 extension, protocol violation, Sponsor decision, and 2 subjects for noncompliance). Most subjects (91.8%) continued into the open-label extension (C87088) after completing the study.

Efficacy results: For the primary efficacy variable of the proportion of subjects in clinical remission at Week 6, treatment with CZP 400mg did not demonstrate a statistically significant difference from placebo in producing clinical remission at Week 6 (p=0.174). The rate of clinical remission was numerically higher in the CZP 400mg group at each visit (28.9%, 32.4%, and 37.8% at Weeks 2, 4, and 6) compared to the placebo group (20.7%, 24.5%, and 31.3%, respectively) and reached statistical significance at Week 2 (p=0.033), but a high rate of clinical remission in the placebo group at Weeks 4 and 6 resulted in a loss of statistical significance at the later timepoints.

A similar trend was noted in the analyses of clinical response and responders, as well as in the majority of other secondary efficacy measures. The exception was the proportion of subjects in IBDQ remission which was statistically significantly different in favor of CZP 400mg at Week 4 (p=0.011) and Week 6 (p=0.040).

Across the various subgroup analyses of remission, clinical response, and responders, results suggest that subjects with more severe CD (CDAI >300 points) or more active inflammation (CRP ≥10mg/L), younger subjects (18 to <40 years), and subjects taking corticosteroids (alone or in combination with immunosuppressants) may benefit more from CZP treatment.

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Pharmacokinetics/pharmacodynamics results: Following injection at Week 0, CZP plasma concentrations increased to approximately 19µg/mL at Week 2 and then stabilized at approximately 25µg/mL and 27µg/ml at Weeks 4 and 6, respectively, consistent with the attainment of steady state after 3 half-lives.

Safety results: The overall incidence of treatment-emergent adverse events (TEAEs) was similar across the CZP 400mg (51.1%) and placebo (46.5%) groups. As expected with an anti-TNFα therapy, TEAEs were reported most often in the Gastrointestinal disorders (19.7% vs 20.0%, respectively), Infections and infestations (16.1% vs 11.6%, respectively), and General disorders and administration site conditions (14.3% vs 11.2%, respectively) SOCs. The majority of TEAEs in both the placebo and CZP 400mg treatment groups were mild or moderate in severity.

Headache was the most commonly reported TEAE in both the CZP 400mg (5.4%) and placebo (4.7%) groups. Other TEAEs reported by ≥4% subjects in either group were abdominal pain, nausea, fatigue, pyrexia, and arthralgia.

Headache was also the most commonly reported related TEAE and was reported by 3.6% of subjects in the CZP 400mg group and 1.4% of subjects in the placebo group. Other related TEAEs reported by ≥1% of subjects in either group were nausea, pyrexia, and upper respiratory tract infection.

There were no deaths reported in either the placebo or CZP 400mg treatment group during or after the study. Treatment-emergent SAEs were reported by 12 subjects (5.4%) in the CZP 400mg group and 8 subjects (3.7%) in the placebo group. The only treatment-emergent SAEs reported by more than 1 subject in either treatment group were exacerbation of Crohn's disease (3 subjects in the CZP 400mg group and 1 subject in the placebo group) and pyrexia and intestinal obstruction (2 subjects each in the CZP 400mg group and 0 in the placebo group). Most of the SAEs were moderate to severe in intensity and were considered unrelated to study drug by the Investigator. One malignancy (not related to treatment) was reported in the CZP 400mg group in a subject with a history of breast cancer. No pregnancies or cases of TB were reported during the study in either treatment group.

No clinically meaningful changes from Week 0, shifts from Week 0, or incidence of markedly abnormal values were noted in hematology, biochemistry, or urinalysis parameters in either treatment group during treatment. None of the small changes in systolic BP, diastolic BP, pulse rate, or weight were considered clinically meaningful in either the CZP 400mg or placebo treatment group.

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Seven of 223 subjects (3.1%) in the CZP 400mg group became anti-CZP antibody positive during the study through the 12-week Safety Follow-Up Period. Four of the subjects became positive by Week 2 and 1 additional subject became positive by each of Week 4, Week 6, and Safety Follow-Up. One subject in the CZP 400mg group changed from negative to positive in the ANA assay (by Week 6) compared to no subjects in the placebo group; this subject reported no TEAEs.

Conclusions: Certolizumab pegol 400mg, administered at Weeks 0, 2, and 4 did not demonstrate a statistically significant difference from placebo in inducing remission at Week 6 in subjects with moderately to severely active CD.

The safety profile was as expected of an anti-TNFα therapy. No new safety signals were detected.

Report date: 15 Jun 2010