C87042, 2005-004104-37

CLINICAL STUDY REPORT SYNOPSIS

This synopsis is provided for informational purposes only and is not intended or recommended as a substitute for professional medical advice.

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:

A Phase IIIb multicenter, open-label induction and double-blind comparison of two maintenance schedules evaluating clinical benefit and tolerability of certolizumab pegol, a pegylated Fab' fragment of humanized antibody to tumor necrosis factor (TNF) over 26 weeks in subjects suffering from Crohn's disease (CD) with prior loss of response or intolerance to infliximab

2. SYNOPSIS

Name of Sponsor/Company: UCB Pharma SA	Individual Study Table Referring to Module 5.3.5	*(For National Authority Use only)*
Name of Finished Product: Cimzia™	Volume: Not applicable	
Name of Active Ingredient: Certolizumab pegol (CDP870)	Page: Not applicable	
Title of Study: A Phase IIIb multicenter, open-label induction and double-blind comparison of two maintenance schedules evaluating clinical benefit and tolerability of certolizumab pegol, a pegylated Fab' fragment of humanized antibody to tumor necrosis factor (TNF) over 26 weeks in subjects suffering from Crohn's disease (CD) with prior loss of response or intolerance to infliximab		
Investigator(s): ~~One hundred thirty-seven~~* Investigators participated in the study [redacted]		
Study Center(s): This was a multicenter study involving 121* centers in 14 countries: [redacted].		
Publication: Not applicable		
Studied Period (years): April 2006-August 2008	**Phase of Development:** Phase IIIB	

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This note was added for correction purpose afterwards on 29. January 2015:
The original text contains the wrong number of investigators and sites by error.

The correct information is a following:
One hundred thirty three Investigators participated in the study,
which includes investigator changes occurring at six sites throughout the study conduct.
This was a multicenter study involving 127 centers in 14 countries.
The inconsistancies 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 C87042 is not considered necessary.

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Objectives:

Primary objective

To assess the clinical efficacy of certolizumab pegol 400mg sc at Week 6, following administration at 0, 2, and 4 weeks for the treatment of signs and symptoms of active CD (CDAI between 220 and 450 inclusive: scored over 7 days before the first administration of the study drug) in subjects who had previously received and responded to infliximab, but who no longer had a sustained response and/or tolerance to infliximab.

Secondary objectives

- To assess and compare the clinical efficacy of certolizumab pegol 400mg sc maintenance therapy administered Q4W or Q2W over 26 weeks (last study treatment administered at Week 24) in subjects with CD who responded to certolizumab pegol induction therapy.
- To assess the clinical efficacy of certolizumab pegol 400mg sc as induction and two regimens of maintenance therapy on patient reported outcome scores.
- To evaluate tolerability and safety of certolizumab pegol induction and maintenance therapy in subjects who have previously received and responded to infliximab, but who no longer have a sustained response and/or have tolerance to infliximab.
- To evaluate the effect of certolizumab pegol induction and maintenance therapy on plasma c-reactive protein (CRP) levels.

Exploratory objectives

- To assess the clinical efficacy of certolizumab pegol 400mg sc as induction and 2 regimens of maintenance therapy over the entire period of the study in the subset of population with elevated CRP levels at inclusion. Elevated CRP level is defined as above the ULN (upper limit of normal) assumed by each center.
- To investigate the clinical efficacy of certolizumab pegol 400mg sc therapy over the entire period of the study in the subset of anti-infliximab antibody positive population.
- To assess the effect of certolizumab pegol 400mg sc as induction and 2 regimens of maintenance therapy on direct and indirect cost parameters.

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Methodology:
This was a Phase IIIb multicenter, open-label induction and double-blind maintenance therapy clinical efficacy study.

After a Screening Period of 7 to 14 days prior the first dose of the study drug administration, subjects meeting the inclusion/exclusion criteria and having a CDAI score between 220 and 450 points inclusive were enrolled in the study and received the study treatment.

Open-Label Induction Phase: subjects were dosed with a 400mg certolizumab pegol (two sc injections of 200mg) at Week 0, 2, 4.

Double-Blind Maintenance Phase:
At Week 6, based on the CDAI score (with a decrease of at least 100 points from the Baseline), subjects who were evaluated as study treatment responders were randomized to the following treatment groups, receiving the first randomized dose at Week 6:

- 400mg sc injection of certolizumab pegol every 4 weeks (2 x 200mg sc injections) (Q4W)
- 400mg sc injection of certolizumab pegol every 2 weeks (2 x 200mg sc injections) (Q2W)

Subjects randomized in the Q4W group were dosed alternately with 400mg certolizumab pegol sc and placebo every 2 weeks, starting with a placebo injection at Week 6.

Subjects who did not meet the definition of response were considered as treatment failure and were not randomized into the double-blind phase of the study. These subjects attended a safety follow-up assessment 12 weeks after the last dose of certolizumab pegol.

If the clinical response was not maintained (loss of response is defined as both a CDAI score >150 points and a minimum increase in CDAI of 70 points compared to Week 6 at 2 consecutive visits) after the randomization, subjects in either randomized arm, without unblinding were allowed to receive an open-label Q2W treatment.

After completion of the Study Period (26 weeks including study drug administration until Week 24), the subjects who wanted to continue to be treated with certolizumab pegol were allowed to enter a long-term follow-up study until the drug is on the market.

A follow-up visit was planned 12 weeks after the last administration for subjects who withdraw the study and for those who did not wish to continue the treatment in the follow-up study.

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Number of Subjects:
Number of subjects who entered open-label induction phase: 539
Number of subjects randomized to double-blind treatment: 370

Diagnosis and Main Criteria for Inclusion:
Male or female subjects at least 18 years of age suffering from CD with a CDAI score between 220 and 450, scored over the 7 days prior to the first study treatment dose. Subjects must have been treated and must have responded to infliximab (estimated by the Investigator and documented by the subject's medial file) but were no longer responding or had developed intolerability due to acute or delayed infusion reactions.

Test Product:	**Dose and Mode of Administration:**	**Batch Number:**
Certolizumab pegol	400mg administered subcutaneously (sc) as two 1mL injections	[redacted]

Duration of Treatment:
The Study Period lasted 28 weeks and the Treatment Period lasted 24 weeks. There was a follow-up assessment 12 weeks after the final dose of certolizumab pegol for subjects who did not enter the extension program. Thus, the maximum duration of the study for a subject was 38 weeks.

Reference Therapy:	**Dose and Mode of Administration:**	**Batch Number:**
Placebo (Saline)	Placebo administered sc as two 1mL injections	[redacted]

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Criteria for Evaluation:

Efficacy/Pharmacokinetics/Pharmacodynamics:
Primary efficacy

- CDAI response (clinical response [CDAI reduction from Baseline ≥100 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 (CDAI score ≤150 points) by visit.
- Inflammatory Bowel Disease Questionnaire (IBDQ) total score by visit.
- IBDQ response by visit. An IBDQ responder is defined as 'a patient having an increase from Baseline in the IBDQ overall score of at least 16 points'.
- IBDQ overall score ≥170 (defined as IBDQ remission rate) by visit.
- CRP values by visit.

Exploratory outcome research:

- Direct cost parameters at each visit
- Number of additional medications, number of outpatient visits, number of hospitalizations and mean length of hospitalizations, number of emergency room visits, number of medical procedures
- Indirect cost parameters by visit
- Work Productivity and Activity Impairment-Crohn's disease (WPAI-CD) Questionnaire

Pharmacokinetic

- Certolizumab pegol plasma concentrations and anti-certolizumab pegol antibodies
- Plasma concentration of infliximab and anti-infliximab antibodies (HACA)

Immunologic

- Autoantibodies (anti-nucleic antibody [ANA] and double-stranded deoxyribonucleic acid [ds-DNA]

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Safety:

- Adverse event monitoring
- Clinical laboratory (hematology, chemistry, urinalysis, immunology, stool collection, CRP, pregnancy testing for females)
- Vital signs (systolic and diastolic blood pressure, pulse rate) and weight change
- Physical examination
- Chest X-ray
- Tuberculin skin test
- Concomitant medication monitoring

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Statistical Methods:

The Intention-to-Treat (ITT) population in the Open-label Induction Period (ITTI) is defined as all subjects who were enrolled and received at least one dose of study medication. In the Double-blind Maintenance Phase of the study, the ITT population (ITTR) consisted of all randomized subjects who received at least one dose of study drug after randomization. The Per Protocol (PP) population was defined as the subset of the ITT population excluding subjects with major protocol deviations. The PPI population was defined as the subset of the ITTI population, excluding subjects with major protocol deviations affecting the Open-label Induction Phase evaluation. The PPR population was defined as the subset of the ITTR population, excluding subjects with major protocol deviations affecting the Double-blind Randomized period evaluation. It corresponded to major deviations that occurred during the Double-blind Randomized period and also to any relevant major deviation at Baseline or during the Open-label Induction period. As per protocol, only subjects who were CDAI responders at Week 6 were to be randomized into the double-blind Maintenance Phase. The modified ITTR (mITTR) population consists in the population of ITTR subjects who did qualify as CDAI responders at Week 6 (therefore, excluding subjects who were erroneously randomized into the Maintenance Phase). The ITT Open-label Q2W (ITTO) population was defined as the subsets of subjects from the ITTR population who switched to Open-Label Q2W treatment sometime after randomization.

The primary efficacy variable was the response rate at Week 6, response being defined as at least 100 points decrease of CDAI score from Baseline. The number and percent of responders at Week 6 was presented in the ITTI population, along with its 95% confidence interval (CI). The CI was calculated using a normal approximation to the binomial. The primary endpoint was also investigated in subgroups defined by the following variables: CRP level at Baseline, anti-infliximab antibody at Baseline, category of reason for stopping infliximab, use of corticosteroids at Baseline, use of immunosuppressant at Baseline, category of Baseline CDAI score, category of CD, and history of resections.

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.

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. The proportion of subjects with and without antibodies to certolizumab pegol was summarized at each scheduled visit and overall.

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

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SUMMARY-CONCLUSIONS:

EFFICACY/PHARMACOKINETIC/PHARMACODYNAMIC RESULTS:

In the ITTI population, a total of 62.0% (334/539) of subjects achieved the primary efficacy variable of clinical response (decrease in CDAI Score ≥100 points from Baseline) at Week 6 of the Open-Label Induction Period. At Week 6 in the PPI population, 65.5% (283/432) of subjects achieved the primary efficacy endpoint of clinical response.

Results for the primary variable were supported by data from the secondary variables of the percentage of subjects with a CDAI reduction from Baseline of ≥70 points at Week 6 (69.2%), change from Baseline in CDAI score (mean change of -120.33 at Week 6), and subjects achieving remission (CDAI score ≤150) at Week 6 (39.3%). In these analyses, efficacy of certolizumab pegol 400 mg Q2W was demonstrated as early as Week 2 and continued through the Week 6 assessment.

Slight differences in terms of clinical reponse and clinical remission rates by covariates were observed, but no definitive conclusions can be made regarding the treatment effect. These results have to be interpreted with caution considering the intrinsic limitations of the nature of the exploratory analyses and also the clinical relevance of these findings.

The CRP geometric mean values were lower at Weeks 2, 4, 6, and last visit on or before Week 6 visit compared with Baseline.

For subjects in the ITTI population who reached Week 6 or whose last visit was on or before Week 6, there was a statistically significant difference and meaningful change from Baseline in mean IBDQ scores.

Meaningful improvement in IBDQ total score (defined as mean change of ≥16 points from Baseline) was observed in 62.3% subjects receiving certolizumab pegol 400mg Q2W treatment at Week 6. At this visit, 34.9% of subjects were in IBDQ remission.

During the Open-Label Induction Phase in the ITTI population, the certolizumab pegol plasma concentrations increased from 21.52µg/mL at Week 2 to 28.85µg/mL at Week 6.

For subjects in the ITTR population, 36.5% achieved a clinical response at Week 26. Similar results were seen with certolizumab pegol 400mg Q2W (35.5%) and certolizumab pegol 400mg Q4W (37.4%), with no significant difference between treatment groups (p=0.696). Results seen with the mITTR population were similar to those seen with the ITTR population with a clinical response of 41.9% at Week 26; 41.0% in the certolizumab pegol 400mg Q2W treatment group and 42.9% in the certolizumab pegol 400mg Q4W treatment group.

The results seen for clinical response in the ITTR population were supported by data from additional secondary variables including the percentage of subjects with a CDAI reduction from Baseline of ≥70 points

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(40.2% at Week 26), change from Baseline in CDAI score (mean change of -172.67 at Week 26), and subjects achieving remission (CDAI score ≤150) (27.6% at Week 26). There was no difference between the certolizumab pegol 400mg Q2W and certolizumab pegol 400mg Q4W treatment groups for any parameter. Similarly, results seen with the mITTR population were similar to those seen with the ITTR at Week 26.

In the ITTR population at Week 26, there was a quantitative treatment-by-baseline corticosteroid intake interaction of statistical significance on clinical response rate (p=0.025) and remission rate (p=0.054).

For subjects in the ITTR population, 35.9% achieved an IBDQ response and 22.5% achieved an IBDQ remission at Week 26. Similar results were seen with certolizumab pegol 400mg Q2W and certolizumab pegol 400mg Q4W, with no noticeable difference between treatment groups.

In the ITTR population, the trough plasma concentrations increased throughout the Open-Label Induction Phase, approaching a plateau by Week 6. During the double-blind Maintenance Phase, certolizumab pegol trough plasma concentrations remained stable in the certolizumab pegol 400mg Q2W treatment group. As expected, the trough plasma concentrations in the certolizumab pegol 400mg Q2W treatment group were 3- to 4-fold higher than those in the Q4W treatment group. The trough concentrations in the certolizumab pegol 400mg Q2W treatment group were approximately 1.6-fold higher than the corresponding mid-dose-interval plasma concentrations in the certolizumab pegol 400mg Q4W treatment group at Weeks 10, 14, 18, and 22.

Low resource utilizations were observed during the overall study period with majority of the subjects having no emergency room visits, healthcare provider consultations and hospital stays. Similar findings were reported between the 2 treatment groups. In addition, consistent improvements were observed in both treatment groups during the study period on productivity scores as measured by WPAI:CD.

SAFETY RESULTS:

Overall Study Period

In all treated subjects who received at least 1 dose of certolizumab pegol, the incidence of TEAEs was 92%. Severe AEs were reported in 29.1% of subjects; TEAEs considered related to study drug were observed in 6.1% of subjects. Treatment-emergent AEs that led to permanent discontinuation of study medication occurred in 70 subjects (13%). Serious adverse events were reported by 116 subjects (21.5%).

One death was reported in a subject who permanently discontinued the study due to lack of efficacy during the Open-Label Induction Phase. This subject died from sudden cardiac death 51 days after the initial injection, (38 days after the last dose); the event was considered possibly related to treatment. Two other

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deaths were reported after the conclusion of the study (≥12 weeks). The first subject discontinued treatment during the Open-Label Induction Phase of the study.

One-hundred twenty-one days after receiving the last injection, the subject experienced the onset of bacterial sepsis and died. In addition, autopsy revealed a metatastic pancreatic carcinoma. These events were considered unlikely related to treatment. The second subject completed the Open-Label Induction Phase of the study and was randomized to the double-blind Maintenance Phase of the study. The subject permanently withdrew from the study due to an adverse event (pyoderma gangrenosum) after 4 double-blind injections. One-hundred five days after the last injection, the subject experienced haemolysis and acute respiratory distress syndrome and 20 days later the subject died. The events were considered unlikely related to treatment.

For the ITTR population (N=373) during the overall Entire Study Period, the mean duration of exposure was 140.8 days (20.1 weeks). The incidence of TEAEs in the ITTR population was (89.5%), and was similar between treatment groups. Severe AEs were reported in 25.5% of subjects, while 52.7% of subjects in the certolizumab pegol 400mg Q2W treatment group and 51.9% of subjects in certolizumab pegol 400mg Q4W treatment group had TEAEs that were considered related to study drug. The incidence of TEAEs that led to permanent discontinuation of study drug was 9.7% in the certolizumab pegol 400mg Q2W treatment group and 5.3% in the certolizumab pegol 400mg Q4W treatment group. The incidence of SAEs was 14.7% and the incidence of drug-related SAEs was 4.6%, with no differences seen between treatment groups. No deaths were reported during the overall Entire Study Period in the ITTR population.

For the overall Entire Study Period in the ITTR population, the most frequently reported hematologic and blood chemistry values considered PCS were decreases in hematocrit (24.1%), relative lymphocyte count (26.0%), hemoglobin (14.7%), and lymphocyte count (12.6%). The most frequent increases considered PCS were white blood cell count (WBC) (8.0%), eosinophil count (5.9%), relative eosinophil count (5.1%), and lymphocyte count (5.1%). The incidence rate in PCS parameters was similar between treatment groups. Notable exceptions for the certolizumab pegol 400mg Q2W and certolizumab pegol 400mg Q4W treatment groups included PCS decreases for hematocrit (26.9% vs 21.4%), PCS decreases for hemoglobin (17.2% vs 12.3%), and PCS increases for WBC count (7.0% vs 12.3%), respectively.

In the ITTR population for the overall Entire Study Period, none of the small changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse rate, or weight were considered clinically meaningful, either within or between treatment groups.

Open-Label Induction Phase

For the intention-to-treat (ITTI) population (N=539) during the Open-Label Induction Phase, the mean duration of exposure was 41.6 days (5.9 weeks). In the ITTI population, the incidence of treatment-emergent adverse events (TEAEs) during the Open-Label Induction Phase was 80.9%. Severe adverse events (AEs) were reported in 13.5% of subjects; 39.9% of subjects had TEAEs that were considered related to study drug. Treatment-emergent AEs that led to discontinuation of study drug occurred in 6.7% of subjects.

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Serious adverse events (SAEs) were reported by 40 subjects (7.4%), of which 2.8% were considered treatment related. No deaths reported during the Open-Label Induction Phase. The most frequently reported AEs in the ITTI population were headache (16%), nausea (10.8%), pyrexia (8.7%), and vomiting (8.3%). The most commonly reported treatment-related AEs were headache (6.9%), nausea (3.3%), pyrexia (2.8%), and arthralgia (2.8%).

In the Open-Label Induction Phase of the study, 10% of subjects experienced injection site reactions, 2.2% of subjects experienced acute systemic injection reactions, and 3.3% of subjects experienced delayed systemic injection reactions.

During the Open-Label Induction Phase, severe events were reported in 13.5% of subjects. The most frequently reported severe AEs were abdominal pain (2.2%), Crohn's disease (2.0%), and arthralgia (1.3%). Crohn's disease, abdominal pain, and aphthous stomatitis were the only TEAEs leading to discontinuation that occurred in more than 2 subjects. One breast fibroma, 1 pituitary benign tumor, and 1 skin papilloma were reported. In addition, 1 subject 121 days after receiving certolizumab pegol 400mg Q2W during the Open-Label Induction Phase experienced the onset of bacterial sepsis and died. Autopsy revealed a metatastic pancreatic carcinoma.

The most frequently reported hematologic and blood chemical values considered possibly clinically significant (PCS) were decreases in relative lymphocyte count (20.7%), hematocrit (18.2%), and hemoglobin (11.0%). The most frequent increases considered PCS were WBC count (6.1%) and lymphocyte count (3.2%).

None of the small changes in SBP, DBP, pulse rate, or weight were considered clinically meaningful.

Double-Blind Maintenance Phase

During the double-blind Maintenance Phase, the overall incidence of TEAEs in the intention-to-treat randomized (ITTR) population was (77.7%). The incidence was similar in the certolizumab pegol 400mg Q2W treatment group (78.0%) compared with the certolizumab pegol 400mg Q4W treatment group (77.5%). Overall, severe AEs were reported in 18.5% of subjects, with 33.9% of subjects in the certolizumab pegol 400mg Q2W treatment group and 39.0% of subjects in the Q4W treatment group had TEAEs that were considered related to study drug. The incidence of TEAEs that led to permanent discontinuation of study drug was 7.5% in the certolizumab pegol 400mg Q2W treatment group compared with 4.8% in the certolizumab pegol 400mg Q4W treatment group. The incidence of SAEs reported was 10.8% in the certolizumab pegol 400mg Q2W treatment group compared with 12.8% in the certolizumab pegol 400mg Q4W treatment group, of which 3.2% (in both treatment groups) were considered treatment related. No deaths were reported in any treatment group during the double-blind Maintenance Phase.

The most frequent TEAEs in the double-blind Maintenance Phase were nasopharyngitis (13.9%), headache (12.3%), pyrexia (11.8%), and nausea (10.7%). Overall, there were no important differences in TEAEs between the treatment groups, except for headache (certolizumab pegol 400mg Q2W: 9.1%, certolizumab

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pegol 400mg Q4W: 15.5%) and dizziness (certolizumab pegol 400mg Q2W: 0.5%, certolizumab pegol 400mg Q4W: 4.3%). The most frequent TEAEs in the Infection and Infestation SOC during the double-blind Maintenance Phase with certolizumab pegol 400mg Q2W and certolizumab pegol 400mg Q4W were nasopharyngitis (15.6% and 12.3%, respectively), urinary tract infection (3.8% and 5.3%, respectively), and herpes simplex (2.7% and 5.9%, respectively).

Overall, the most frequently reported SAE was Crohn's disease (3.2%). All other SAEs were reported in less than 1% of the ITTR population. The number and incidence of SAEs were similar between both treatment groups.

One pituitary benign tumor and 1 skin papilloma were reported in the certolizumab pegol 400mg Q2W treatment group, and 1 squamous cell carcinoma of skin was reported in the certolizumab pegol 400mg Q4W treatment group.

The most frequently reported hematologic and blood chemistry values considered PCS were decreases in hematocrit (20.4%), relative lymphocyte count (19.1%), and hemoglobin (13.6%). The most frequent increases considered PCS reported were WBC count (5.4%) and lymphocyte count (4.1%). The incidence rate in PCS parameters was similar between treatment groups with the exception of low hematocrit values in the certolizumab pegol 400mg Q2W (23.4%) compared with certolizumab pegol 400mg Q4W (17.5%) treatment groups and high WBC count in the certolizumab pegol 400mg Q2W (3.3%) compared with certolizumab pegol 400mg Q4W (7.7%) treatment groups.

None of the small changes in systolic BP, diastolic BP, pulse rate, or weight were considered clinically meaningful, either within or between treatment groups.

Based on the current study, the safety profile of treatment with certolizumab pegol 400mg given either Q2W or Q4W is similar in subjects with CD with prior loss of response or intolerance to infliximab.

CONCLUSIONS:
During the Open-Label Induction and double-blind Maintenance Phases, certolizumab pegol was effective in the treatment of subjects with CD with prior loss of response or intolerance to infliximab. During the double-blind Maintenance Phase, no meaningful difference in efficacy was noted between the certolizumab pegol 400mg Q2W or 400mg Q4W treatment groups.

The nature and frequency of TEAEs were generally similar to previous certolizumab pegol studies; most were not considered severe and the incidence was similar between treatment groups. None of the changes in laboratory parameters, SBP, DBP, pulse rate, or weight were considered clinically meaningful, either within or between treatment groups.

Report Date: 27 November 2008

Amendment 1 Report Date: 03 Dec 2008