Synopsis (C0168T46 ACT 2)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: REMICADE® (infliximab)		

Protocol: C0168T46 CR004783 **EudraCT No.:** Not applicable
Title of the study: A Randomized, Placebo-controlled, Double-blind Trial to Evaluate the Safety and Efficacy of Infliximab in Patients with Active Ulcerative Colitis: Final

Principal/Coordinating Investigator(s): William J. Sandborn, Mayo Medical School, Rochester, MN, US; Paul J. Rutgeerts, Univ. Leuven, Leuven, Belgium

Study Center(s): Subjects were enrolled in a total of 55 sites; (30 in North America, 21 in Europe, and 4 in Israel).

Publication (reference): None

Studied Period: 04 Jun 2002/08 Sep 2004 **Phase of Development:** 3

Objectives: The primary objective was to evaluate the safety and efficacy of infliximab in subjects with active ulcerative colitis. The major secondary objectives were to determine the proportion of subjects: 1) in clinical remission at Week 8, 2) with mucosal healing at Week 8, 3) in clinical response at Week 30, and 4) in clinical remission at Week 30.

Methodology: ACT 2 is a randomized, double-blind, placebo-controlled, parallel-group study.

Number of Subjects (Planned and Analyzed): 360 planned, 364 analyzed

Diagnosis and Main Criteria for Inclusion: Subjects must have had active ulcerative colitis as defined by a Mayo score between 6 and 12 points, inclusive, at baseline. Subjects must also have had endoscopic evidence of active colitis as indicated by an endoscopy subscore of ≥ 2. In addition, subjects must have met at least 1 of the following criteria:

- Had concurrent treatment with at least 1 of the following: corticosteroids, azathioprine, 6-mercaptopurine (6-MP), or 5-ASA compounds.
- Had failed to successfully taper, tolerate, or respond to corticosteroids within the previous 18 months.
- Had failed to tolerate or respond to 6 MP or azathioprine within the previous 5 years.
- Had failed to tolerate or respond to 5-ASA compounds within the previous 18 months.

Test Product, Dose and Mode of Administration, Batch Number: 5 mg/kg or 10 mg/kg infusions at Weeks 0, 2, and 6, and every 8 weeks thereafter through Week 22. Multiple batch numbers.

Duration of Treatment: 22 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number: placebo (supplied as lyophilized solid for reconstitution with sterile water for injection) infusions. Multiple batch numbers.

Criteria for Evaluation: The primary analysis, all secondary efficacy analyses, and the health economic analyses used the intent-to-treat principle. In contrast, safety analyses were performed on all treated subjects (randomized subjects who received at least 1 infusion of study agent [partial or complete]) according to the actual treatment received during the study.

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Pharmacokinetics/Pharmacodynamics: Serum concentrations of infliximab were determined using an enzyme-linked immunosorbent assay. Blood samples used for determining the concentrations of infliximab were drawn just before the infusion and 1 hour after the end of the infusion at Weeks 0 and 2, and just prior to the infusion at Weeks 6 and 14. Additional blood samples for determining the concentration of infliximab were also drawn according to the study schedule of events in the protocol. Analyses for detecting antibodies to infliximab were performed using a bridging immunoassay, in which infliximab is used to capture and then detect induced immune responses to infliximab.

Efficacy: The primary efficacy endpoint in this study was clinical response at Week 8, where clinical response was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, accompanied by a decrease in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1. Each subscore of the Mayo score was rated on a scale from 0 to 3, indicating normal to severe activity. The Mayo score was calculated as the sum of 4 subscores and thus ranged from 0 to 12. The partial Mayo score is the Mayo score without the endoscopy subscore and ranged from 0 to 9. Clinical response at Week 30, clinical remission at Week 8, clinical remission at Week 30, and mucosal healing at Week 8 were major secondary endpoints in this study. The quality of life for subjects in this study was evaluated using the inflammatory bowel disease questionnaire (IBDQ) and the SF-36.

Safety: Safety was assessed by summarizing the incidence and type of AEs and examining changes in laboratory parameters.

Statistical Methods: Statistical comparisons were made between the combined infliximab and placebo treatment groups, as well as between the individual infliximab and placebo treatment groups. For categorical variables, counts and percentages were used to describe the data. To compare the proportion of subjects achieving a specified endpoint (eg, proportion of subjects in clinical response) between treatment groups, chi-square tests, Cochran-Mantel-Haenszel chi-square tests, or Fisher's Exact Tests were used, as appropriate. Continuous variables were summarized with the sample size, mean, standard deviation, median, interquartile range, and range (minimum and maximum). Treatment group comparisons were performed using an analysis of variance on the van der Waerden normal scores.

SUMMARY – CONCLUSIONS

Study Population Results: A total of 123 were assigned to placebo, 121 to 5 mg/kg infliximab, and 120 to 10 mg/kg infliximab. All 364 randomized subjects were treated with study agent and received the treatment to which they were assigned. A total of 29.1% of subjects permanently discontinued study infusions, with approximately twice as many subjects in the placebo treatment group permanently discontinuing study agent (45.5%) as those in either the 5 mg/kg (19.8%) or 10 mg/kg (21.7%) infliximab treatment groups. Overall, 26.9% of the subjects terminated the study, with more than twice as many subjects in the placebo treatment group terminating the study than in either infliximab treatment group.

The baseline demographic characteristics were generally similar across the treatment groups. Among all subjects, 59.1% were men, 94.5% were Caucasian, and the median age was 38.0 years. The clinical disease characteristics at baseline were generally similar across the treatment groups. Among all randomized subjects, the median duration of ulcerative colitis was 4.9 years, 28.8% were refractory to corticosteroids, the median CRP concentration was 0.7 mg/dL, and 39.9% had extensive disease. At baseline, the concomitant medications subjects were receiving for ulcerative colitis were similar across all treatment groups.

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Pharmacokinetic/Pharmacodynamic Results: Pharmacokinetic analyses in subjects with ulcerative colitis demonstrated a dose proportional Cmax following multiple infusions of 5 mg/kg or 10 mg/kg infliximab. In general, the majority of subjects in both the 5 mg/kg and 10 mg/kg infliximab treatment groups maintained detectable serum infliximab concentrations from infusion to infusion.

Efficacy Results: The ACT 2 study fulfilled the criteria of success for the primary endpoint as defined in the protocol. For the primary and all major secondary efficacy endpoints, infliximab was superior to placebo, and generally, no notable differences were observed between the 5 mg/kg and 10 mg/kg infliximab treatment groups. Furthermore, no significant differences in response rates could be identified in the subgroup comparisons of baseline demographic characteristics, baseline disease characteristics, drug history, or concomitant medications at baseline.

At Week 8 and at Week 30, the proportion of subjects achieving clinical response was significantly greater in the combined infliximab treatment group (66.8% and 53.5%, respectively) than in the placebo treatment group (29.3% and 26.0%, respectively). At both Week 8 and Week 30, the proportion of subjects achieving clinical response in both infliximab treatment groups was significantly greater than the placebo treatment group. At Week 30, a greater proportion of subjects in the 10 mg/kg infliximab treatment group was in clinical response than in the 5 mg/kg infliximab treatment group (60.0% versus 47.1%).

Similarly, at Week 8 and Week 30, a greater proportion of subjects in the combined infliximab treatment group were in clinical remission (30.7% and 30.7%, respectively) than in the placebo treatment group (5.7% and 10.6%, respectively). In addition, more subjects in the combined infliximab treatment group had sustained response (47.3%) and sustained remission (18.7%) than in the placebo treatment group (15.4% and 2.4%, respectively).

A greater proportion of subjects in the combined infliximab treatment group achieved mucosal healing at Week 8 (61.0%) and at Week 30 (51.5%) than in the placebo treatment group (30.9% and 30.1%, respectively). A greater proportion of subjects in the combined infliximab treatment group compared with the placebo treatment group had Mayo subscores (ie, stool frequency, rectal bleeding, endoscopy, and physician global) that indicated little or no disease activity.

Among subjects who were receiving corticosteroids at baseline, a greater proportion of subjects in the combined infliximab treatment group were in clinical remission (23.0%) and clinical response (31.0%) while not receiving corticosteroids at Week 30 than in the placebo treatment group (3.3% and 6.7%, respectively).

At Week 8 and Week 30, quality of life was significantly improved in the combined infliximab treatment group compared with the placebo treatment group as demonstrated by the disease-specific IBDQ and the physical and mental summary scores of the generic SF 36. In addition, the mean number of hospitalizations was lower in the combined infliximab treatment group than in the placebo treatment group.

Safety Results: Infliximab was generally well tolerated with a safety profile consistent with the infliximab prescribing information. Through Week 30, 80.9% of subjects in the combined infliximab treatment group and 73.2% of subjects in the placebo treatment group had at least 1 AE with no notable differences between the 5 mg/kg and 10 mg/kg infliximab treatment groups.

The largest percentage of infliximab-treated subjects with an AE occurred in the respiratory system, system-organ class (36.5% of subjects in the combined infliximab treatment group and 22.0% of subjects in the placebo treatment group). The preferred term upper respiratory tract infections accounted for the largest percentage of AEs within that system-organ class, with similar percentages in the combined infliximab and placebo treatment groups (12.4% versus 11.4%, respectively). Pneumonia was observed in 2 subjects, both in the 10 mg/kg infliximab treatment group.

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Almost twice as many subjects in the placebo treatment group had an SAE compared with the combined infliximab treatment group (19.5% versus 10.0%, respectively). This difference largely was the result of SAEs coded to the preferred term ulcerative colitis, which occurred in 13.0% of subjects in the placebo treatment group compared with 6.2% in the combined infliximab treatment group. In addition, more than 3 times as many subjects in the placebo treatment group discontinued study infusions because of an AE compared with the combined infliximab treatment group (9.8% versus 2.9%, respectively). This difference was also largely the result of AEs coded to the preferred term ulcerative colitis (7.3% placebo versus 0.8% combined infliximab treatment groups).

Two malignancies were observed through Week 30: a basal cell carcinoma in a subject in the placebo treatment group and a rectal adenocarcinoma in a subject in the 5 mg/kg infliximab treatment group. No deaths and no cases of tuberculosis or other serious opportunistic infections were observed; no subjects had a possible anaphylactic reaction and only 1 subject had a possible delayed hypersensitivity reaction. Moreover, no instances of congestive heart failure or demyelinating neurological diseases were observed.

The percentage of subjects with an infection in the combined infliximab treatment group was slightly higher than in the placebo treatment group (27.8% versus 23.6%, respectively). In subjects with an infection, the most frequently reported infection occurred in the respiratory system, with similar percentages of subjects in the combined infliximab and placebo treatment groups (14.9% versus 14.6%, respectively).

A greater proportion of subjects in the combined infliximab treatment group had an infusion reaction compared with subjects in the placebo treatment group (11.6% versus 8.1%, respectively). However, no serious infusion reactions were observed and no subjects permanently discontinued study infusions due to an infusion reaction.

Overall, very few subjects had markedly abnormal hematological or chemistry laboratory values. Fewer subjects in the combined infliximab treatment group had a markedly abnormal decrease in hematocrit and in lymphocytes compared with subjects in the placebo treatment group (hematocrit 3.3% combined infliximab treatment group versus 10.2% placebo; lymphocytes 20.4% combined infliximab treatment group versus 31.7% placebo).

Four subjects in the combined infliximab treatment group (1.7%) and 1 subject in the placebo treatment group (0.8%) had markedly elevated ALT values. Three of the 4 infliximab-treated subjects had a single markedly abnormal ALT value, the fourth subject had 2 episodes and remained asymptomatic with near normal ALT and AST values at the end of the study. No subjects discontinued study infusions due to an AE related to liver enzyme elevations.

The overall incidence of subjects positive for antibodies to infliximab through Week 30 was 6.4%. Positive antibody to infliximab status was associated with a higher incidence of mild to moderate infusion reactions compared with antibody negative and inconclusive subjects. Clinical response and remission was comparable between antibody positive and inconclusive subjects through Week 30.

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Conclusions: In subjects with active ulcerative colitis, infliximab, administered as 5 mg/kg or 10 mg/kg infusions at Weeks 0, 2, and 6, and every 8 weeks thereafter through Week 22:

- Induced and maintained both clinical response and remission.
- Induced and maintained mucosal healing.
- Enabled subjects who were on corticosteroids at baseline and either refractory or responsive to corticosteroids, to achieve remission and discontinue corticosteroid use.
- Improved quality of life in both disease-specific functioning and general physical and mental well being.
- Reduced the number of ulcerative colitis-related hospitalizations.
- Was effective in most subgroups examined, and in particular showed similar response rates for subjects refractory to corticosteroids and for subjects not refractory to corticosteroids.
- Was generally well tolerated with a safety profile consistent with the infliximab prescribing information.

Date of Report: 23 Feb 2005

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