Synopsis (C0168T37 ACT 1)

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: C0168T37 **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: 30 Week Report

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 62 sites; 31 in North America, 17 in Europe, 9 in Australia, 4 in New Zealand, and 1 in Argentina.

Publication (reference): None

Studied Period: 19 Mar 2002/23 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: 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 current treatment with at least 1 of the following: oral corticosteroids, 6 mercaptopurine (6-MP), or azathioprine (AZA).
- Had failed to successfully taper, tolerate, or respond to oral corticosteroids within the past 18 months.
- Had failed to tolerate or respond to 6-MP or AZA within the previous 5 years.

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 46. Multiple batch numbers.

Duration of Treatment: 46 weeks (only data through Week 30 are reported in this document)

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.

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, 2, 6, and 14 and just prior to the infusion at Week 30. 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.

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Efficacy: The primary 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. The Mayo score has 4 subscores: rectal bleeding, stool frequency, physician's global assessment, and endoscopy. Each subscore was rated on a scale from 0 to 3, indicating normal to severe activity. The Mayo score was calculated as the sum of the 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), the 36-item short from health survey (SF-36), and the EQ-5D.

Safety: Safety was assessed by summarizing the incidence and type of adverse events (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 121 subjects were assigned to placebo, 121 to 5 mg/kg infliximab, and 122 to 10 mg/kg infliximab. All 364 randomized subjects were treated with study agent, and they received the treatment to which they were assigned. A total of 37.9% of subjects permanently discontinued study infusions, with approximately twice as many subjects in the placebo treatment group permanently discontinuing study agent (54.5%) as those in either the 5 mg/kg (28.1%) or 10 mg/kg (31.1%) infliximab treatment groups. Overall, 26.1% of subjects terminated the study (38.0%, 19.0%, and 21.3% in the placebo and in the 5 mg/kg and 10 mg/kg infliximab treatment groups, respectively).

The baseline demographic characteristics were generally similar across the treatment groups. Among all subjects, 61.0% were men, 93.4% were Caucasian, and the median age was 40.0 years. The clinical disease characteristics at baseline were generally similar across the treatment groups. However, subjects in the 10 mg/kg infliximab treatment group had a longer median disease duration than subjects in the placebo and 5 mg/kg infliximab treatment groups. Among all randomized subjects, the median duration of ulcerative colitis was 4.7 years, 30.8% were refractory to corticosteroids, the median C-reactive protein (CRP) concentration was 0.8 mg/dL, and 45.6% had extensive disease. At baseline, the concomitant medications subjects were receiving for ulcerative colitis were similar across all treatment groups.

Pharmacokinetic/Pharmacodynamic Results: Pharmacokinetic analyses in subjects with ulcerative colitis demonstrated a dose proportional maximum observed concentration (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 through Week 30. The postinfusion serum concentrations indicated that infliximab is distributed primarily into the vascular space.

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Efficacy Results: The ACT 1 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, with the exception of differences in the CRP subgroup, no notable differences in response rates could be identified in the subgroup analyses of baseline demographic characteristics, baseline disease characteristics, drug history, and concomitant medications at baseline.

Regardless of corticosteroid refractory status, significantly greater numbers of subjects in the combined infliximab treatment group were in clinical response at Week 8 compared with subjects in the placebo treatment group.

At Week 8 and Week 30, the proportion of subjects achieving clinical response was significantly greater in the combined infliximab treatment group (65.4% and 51.4%, respectively) than in the placebo treatment group (37.2% and 29.8%, respectively). At both Weeks 8 and 30, the proportion of subjects achieving clinical response in both infliximab treatment groups was significantly greater than the placebo treatment group.

Similarly, at Week 8 and Week 30, a greater proportion of subjects in the combined infliximab treatment group were in clinical remission (35.4% and 35.4%, respectively) than in the placebo treatment group (14.9% and 15.7%, respectively). In addition, more subjects in the combined infliximab treatment group had sustained response (47.3%) and sustained remission (24.7%) than in the placebo treatment group (23.1% and 8.3%, respectively).

A greater proportion of subjects in the combined infliximab treatment group achieved mucosal healing at Week 8 (60.5%) and at Week 30 (49.8%) than in the placebo treatment group (33.9% and 24.8%, 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 assessment) 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 (21.7%) and clinical response (28.7%) while not receiving corticosteroids at Week 30 than in the placebo treatment group (10.1% and 17.7%, respectively).

At both Week 8 and Week 30, the proportion of subjects in the combined infliximab treatment group with inflammation indicative of severe disease decreased relative to baseline, whereas the proportion of subjects with little to no inflammation increased.

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, the physical and mental summary scores of the generic SF 36, and the general health status using the EQ-5D.

The average number of ulcerative colitis-related 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, 86.0% of subjects in the combined infliximab treatment group and 81.0% 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 GI system, system-organ class (45.7% of subjects in the combined infliximab treatment group and 49.6% of subjects in the placebo treatment group). The preferred term ulcerative colitis accounted for the largest percentage of AEs within that system-organ class, with a larger percentage of subjects in the placebo treatment group than in the combined infliximab treatment group (21.5% versus 15.6%, respectively). One subject in the 5 mg/kg infliximab

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treatment group had intestinal (colonic) dysplasia. Three subjects, all in the infliximab treatment groups had pneumonia.

A greater proportion of subjects in the placebo treatment group had a serious adverse event (SAE) compared with the combined infliximab treatment group (19.8% versus 16.5%, respectively). This difference largely was the result of SAEs coded to the preferred term ulcerative colitis, which occurred in 8.3% of subjects in the placebo treatment group compared with 6.2% in the combined infliximab treatment group. A similar proportion of subjects in the combined infliximab and placebo treatment groups discontinued infusions due to an AE (6.6% versus 7.4%, respectively).

No deaths occurred and 1 malignancy was observed through Week 30: a prostatic adenocarcinoma in a subject in the 5 mg/kg infliximab treatment group. One case of tuberculosis (TB) was observed. No other serious opportunistic infections were observed; no subjects had a possible anaphylactic reaction and 4 subjects (2 in the placebo treatment group and 2 in the 5 mg/kg infliximab treatment group) had a possible delayed hypersensitivity reaction.

One subject in the 5 mg/kg infliximab treatment group had optic neuritis; no other cases of central demyelinating events were observed. Similarly, no cases of congestive heart disease were observed. One case of pancytopenia was noted in the placebo treatment group, which resolved when azathioprine was discontinued. No other hematological disease was noted.

The percentage of subjects with an infection were similar in the combined infliximab treatment group and the placebo treatment group (33.3% versus 35.5%, respectively). In subjects with an infection, the most frequent infection occurred in the respiratory system, with similar percentages of subjects in the combined infliximab and placebo treatment groups (18.5% versus 17.4%, respectively). The most frequently reported infection was upper respiratory tract infection (13.2% in the placebo treatment group versus 8.6% in the combined infliximab treatment group). No subject discontinued due to an infection except the subject with TB and a subject with upper respiratory tract infection.

A similar proportion of subjects in the combined infliximab and placebo treatment groups had an infusion reaction (9.5% versus 9.9%, respectively). No serious infusion reactions were reported and no subjects discontinued study infusions due to an infusion reaction.

Few subjects developed markedly abnormal hematological or chemistry laboratory values. A smaller proportion of 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 6.6% placebo; lymphocytes 25.8% combined infliximab treatment group versus 39.7% placebo).

All subjects who had normal ALT values at baseline, but who subsequently developed markedly elevated ALT values, were in the infliximab treatment groups (3 subjects 1.2%). Two subjects (1.7%) developed a markedly abnormal AST, 1 of whom had an elevated ALT, and both were in the 5 mg/kg infliximab group. In addition, 1 subject in the 5 mg/kg infliximab treatment group had an elevated bilirubin; however, no subject with elevated AST or ALT had a markedly elevated bilirubin. All abnormal ALT and AST elevations were transient (generally single abnormal values, 2 of which occurred at Week 30), with the maximum ALT of 191 and the maximum AST of 710. On followup, all abnormal transaminase elevations resolved despite continuation of study infusions. No subjects discontinued study infusions due to an AE of elevated ALT, AST, or bilirubin.

No subject was diagnosed with lupus. The overall incidence of subjects positive for antibodies to infliximab through Week 30 was 2.7%. Positive antibody to infliximab status was associated with a higher incidence of infusion reactions compared with antibody negative and inconclusive subjects.

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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 the quality of life in disease-specific functioning, general physical and mental well being, and health status.
- Showed a trend of decreasing 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: 04 Mar 2005

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