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<tr><td colspan="3" align="center">Synopsis (C0168T37 ACT 1)</td></tr>
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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

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 2002/15 Mar 2005	**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

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, 14, and 46, just prior to the infusion at Weeks 30 and 38, and at the study visits at Weeks 8 and 54. 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. In addition, serum and tissue based pharmacodynamic markers were assessed with data through Week 30.

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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 $\geq$ 30% and $\geq$ 3 points, accompanied by a decrease in the rectal bleeding subscore of $\geq$ 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. In addition, clinical response, clinical remission, and mucosal healing were assessed at Week 54. Quality of life for subjects in this study was evaluated using the inflammatory bowel disease questionnaire (IBDQ), the 36-item short form 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 46.7% of subjects permanently discontinued study infusions, with 62.0% in the placebo group compared to 37.2% in the 5 mg/kg and 41.0% in the 10 mg/kg infliximab treatment groups. Overall, 37.6% of subjects terminated participation in the study (47.9%, 32.2%, and 32.8% 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 54.

In biopsied colonic mucosa, infliximab treatment led to a reduction in CD3+ lymphocytes as well as the neutrophil-associated enzymes, myeloperoxidase, and gelatinase B. Furthermore, biopsies collected from infliximab-treated subjects showed reduced expression of the activation marker, HLA-DR, and the

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extracellular matrix molecule, tenascin. Relative to placebo-treated subjects, the decreases observed in infliximab-treated subjects were most notable at Week 8. The Week 30 biopsies generally revealed a placebo-response comparable with time-matched biopsies collected from infliximab-treated subjects, most notably for HLA-DR, gelatinase B, and myeloperoxidase expression.

Treatment with infliximab led to decreased serum levels of the proinflammatory molecules IL-2R, IL-6, IL-8, and ICAM-1 as early as 2 weeks following the initiation of treatment. These changes were variably maintained through Weeks 8 and 30. Slight changes or actual increases were observed for VCAM-1 and sL selectin. Serum levels of TNFα actually increased with infliximab treatment in this study, which corresponds with an earlier observation where TNF bound to infliximab was immunologically detectable, but biologically inactive (C0168T30 [ATTACH] CSR).

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.

At Weeks 8, 30, and 54, the proportion of subjects achieving clinical response was significantly greater in the combined infliximab treatment group (65.4%, 51.4%, and 44.9%, respectively) than in the placebo treatment group (37.2%, 29.8%, and 19.8%, respectively). At Weeks 8, 30, and 54, the proportion of subjects achieving clinical response in both infliximab treatment groups was significantly greater than the placebo treatment group.

Similarly, at Weeks 8, 30, and 54, a greater proportion of subjects in the combined infliximab treatment group were in clinical remission (35.4%, 35.4%, and 34.6%, respectively) than in the placebo treatment group (14.9%, 15.7%, and 16.5%, respectively). In addition, more subjects in the combined infliximab treatment group had sustained response at Week 54 (37.9%) and sustained remission at Week 54 (20.2%) than in the placebo treatment group (14.0% and 6.6%, respectively).

A greater proportion of subjects in the combined infliximab treatment group achieved mucosal healing at Weeks 8, 30, and 54 (60.5%, 49.8%, and 46.1%, respectively) than in the placebo treatment group (33.9%, 24.8%, and 18.2%, 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 response (29.4% at Week 30 and 26.6% at Week 54) and clinical remission (21.7% at Week 30 and 21.0% at Week 54) while not receiving corticosteroids than in the placebo treatment group (17.7% and 10.1% at Week 30 and 54 for clinical response; 10.1% and 8.9% for clinical remission).

At Weeks 8, 30, and 54, 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 component 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.

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Safety Results: Infliximab was generally well tolerated with a safety profile consistent with the infliximab prescribing information. Through Week 54, 89.3% of subjects in the combined infliximab treatment group and 85.1% 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 proportion of subjects with AEs reported as reasonably related was 46.5% for the combined infliximab treatment group and 42.1% for the placebo treatment group.

AEs were most frequently reported with preferred terms from the GI system disorders or respiratory system disorders system-organ classes. GI system disorders were reported by a similar proportion of subjects in the placebo treatment group and in the combined infliximab treatment group (55.4% versus 54.3%) with worsening ulcerative colitis reported by 33.1% of subjects in the placebo and 20.2% of subjects in the combined infliximab treatment groups. Respiratory system disorders (notably sinusitis and pneumonia) were reported more commonly in subjects in the combined infliximab treatment group, with 38.0% of subjects in the placebo and 46.5% of subjects in the combined infliximab treatment group reporting these AEs.

The proportion of subjects with SAEs were similar in the combined infliximab and placebo treatment groups (22.6% and 26.4%, respectively). Reasonably related SAEs were reported for 2.5% of subjects in the combined infliximab treatment group and for 1.7% of subjects in the placebo treatment group.

A similar proportion of subjects in the combined infliximab and placebo treatment groups discontinued infusions due to an AE (8.6% versus 9.1%, respectively). Worsening ulcerative colitis was the only preferred term reported as a reason for discontinuation in more than 1 infliximab-treated subject.

No deaths occurred during the 54 weeks of this study. Two malignancies were reported through Week 54. One subject in the 5 mg/kg infliximab treatment group reported a prostatic adenocarcinoma and 1 subject in the 10 mg/kg infliximab treatment group reported basal cell carcinoma. There was 1 report of intestinal dysplasia in a subject in the 5 mg/kg infliximab treatment group.

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

Infections were reported more frequently for subjects in the combined infliximab treatment group (46.5%) than in the placebo treatment group (38.8%), with a slightly higher proportion in the 10 mg/kg infliximab treatment group than in the 5 mg/kg infliximab treatment group (49.2% versus 43.8%). Most of these were in the respiratory system disorders system-organ class, with 30.5% of subjects in the combined infliximab treatment groups (24.0% in the 5 mg/kg infliximab treatment group and 36.9% in the 10 mg/kg infliximab treatment group) and 19.8% of subjects in the placebo treatment group reporting these AEs. Five cases of pneumonia were reported as an infection; all occurred in subjects in the combined infliximab treatment group. One subject in the 10 mg/kg group developed tuberculosis. Herpes zoster was reported in 2 subjects (1 in each of the 2 infliximab treatment groups), as was Varicella zoster (reported in 1 subject in the placebo treatment group and 1 in the 5 mg/kg infliximab treatment group). None of these were reported as SAEs; no other opportunistic infections were noted.

In the combined infliximab treatment group, infusion reactions were reported by 11.1% of subjects and the reactions were likely to be characterized by dizziness, headache and infusion syndrome. Subjects in the placebo treatment group, of whom 10.7% reported infusion reactions, were more likely to report hot flushes, malaise, and headache. No serious infusion reactions were reported. Two subjects discontinued study

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infusions due to an infusion reaction. No subjects had a possible anaphylactic reaction and 4 had possible delayed hypersensitivity reactions, 2 in the placebo and 2 in the 5 mg/kg infliximab treatment groups.

Few subjects developed markedly abnormal hematological or chemistry laboratory values. Markedly elevated ALT and AST values occurred only in subjects in the combined infliximab treatment group. All abnormal ALT and AST elevations were generally single abnormal values. No subject discontinued study infusions due to an elevated ALT or AST value.

Among subjects who were ANA-negative at baseline, 17.5% in the combined infliximab treatment group and 1.0% in the placebo treatment group were ANA-positive at a titer $\geq$ 1:320 at the last evaluation. Two new autoimmune disorders were reported. One subject reported LE syndrome and 1 subject reported arteritis. Both of these subjects were in the 5 mg/kg infliximab treatment group. No subject was diagnosed with lupus.

The overall incidence of subjects positive for antibodies to infliximab through Week 54 was 6.1%. Subjects who were positive for antibodies to infliximab had a higher incidence of infusion reactions compared with subjects who were negative or inconclusive for antibodies to infliximab.

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 46:

- Induced and maintained both clinical response and clinical remission.

- Induced and maintained mucosal healing.

- Enabled subjects who were on corticosteroids at baseline to achieve clinical 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 generally well tolerated with a safety profile consistent with the infliximab prescribing information.

Date of Report: 27 Sep 2005

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