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: Study Extension Through Week E-24	
Principal/Coordinating Investigators: William J. Sandborn, Mayo Medical School, Rochester, MN, US; Paul J. Rutgeerts, Univ. Leuven, Leuven, Belgium	
Study Center(s): Subjects participating in the study extension were enrolled in a total of 38 sites (18 in North America, 16 in Europe, and 4 in Israel).	
Publication (reference): None	
Studied Period: 13 Oct 2003 to 06 Jun 2005	**Phase of Development:** 3
Objectives: The objective of the study extension was primarily to provide uninterrupted access to infliximab treatment for subjects who had responded to treatment in the main study. The safety and efficacy of continued treatment during the study extension in subjects who had responded to treatment in the main study were also evaluated.	
Methodology: The main study of ACT 2 was a randomized, double-blind, placebo-controlled, parallel-group study. In the study extension, subjects continued to receive the treatment to which they were randomized in the main study. Through Week E-24, subjects and investigators were blinded to treatment.	
Number of Subjects (Planned and Analyzed): A total of 364 subjects were enrolled in the main study, among which 142 participated in the study extension.	
Diagnosis and Main Criteria for Inclusion: To enter the main study at baseline, subjects must have had active ulcerative colitis as defined by a Mayo score between 6 and 12 points, inclusive. 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. Subjects who completed treatment in the main study through Week 22 and evaluations through Week 30 and, in the opinion of the investigator could benefit from continued treatment, were eligible to enter the study extension.	
Test Product, Dose and Mode of Administration, Batch Number: 5 mg/kg or 10 mg/kg infliximab infusions during the study extension at Weeks E-0, E-8, E-16, and E-24. Multiple batch numbers. In addition, some subjects received an infusion at Week E-2.	
Duration of Treatment: 22 weeks during the main study, 24 weeks during the study extension.	
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.	

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Criteria for Evaluation: Limited efficacy and health economic analyses and safety analyses were performed on all subjects who entered the study extension. The 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: Not applicable

Efficacy: Efficacy was evaluated using the physicians' global assessment, a subscore of the Mayo score. The use of corticosteroids for ulcerative colitis was evaluated. Colectomies, ostomies, ulcerative colitis-related hospitalizations, and other ulcerative-colitis related surgeries were recorded. Quality of life 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 observed during the study extension.

Statistical Methods: No hypothesis testing was performed. Data summaries were provided for each treatment group (placebo, 5 mg/kg infliximab, and 10 mg/kg infliximab) and for the combined infliximab treatment group. For categorical variables, counts and percentages were used to describe the data. Continuous variables were summarized with the sample size, mean, SD, median, interquartile range, and range. Tabular displays and listings were used to summarize the data. SAS (Version 8.02) was used to conduct these analyses.

SUMMARY – CONCLUSIONS

Study Population Results: Of the 142 subjects who participated in the study extension, 31 (21.8%) continued to receive placebo, 52 (36.6%) continued to receive 5 mg/kg infliximab, and 59 (41.5%) continued to receive 10 mg/kg infliximab. A total of 17 (12.0%) subjects permanently discontinued study infusions between Week E-0 and Week E-24, with 3 (9.7%) in the placebo treatment group, 9 (17.3%) in the 5 mg/kg infliximab treatment group, and 5 (8.5%) in the 10 mg/kg infliximab treatment group. Fifteen (10.6%) of the subjects terminated study participation during the study extension, including 3 (9.7%) in the placebo treatment group, 7 (13.5%) in the 5 mg/kg and 5 (8.5%) in the 10 mg/kg infliximab treatment group.

The baseline demographic characteristics of subjects who entered the study extension were generally similar to the overall baseline population of the main study and across the treatment groups. Among all subjects, 54.9% were men, 95.1% were Caucasian, and the median age was 39 years. The clinical disease characteristics at baseline of subjects in the study extension were generally similar to the overall baseline population of the main study and across the treatment groups. Among all subjects in the study extension, the median duration of ulcerative colitis was 5.0 years, 31.0% were refractory to corticosteroids, the median C-reactive protein (CRP) concentration was 0.6 mg/dL, and 37.6% had extensive disease.

Pharmacokinetic/Pharmacodynamic Results: Not applicable.

Efficacy Results: During the study extension, the proportion of subjects with physician's global assessment scores indicative of normal or near normal disease was the same at Week E-0 and Week E-24 in subjects treated with 5 mg/kg infliximab, while further improvement was observed in subjects in the 10 mg/kg infliximab treatment group.

The majority of infliximab-treated subjects were not receiving corticosteroids at Week E-0 and did not receive them through Week E-24.

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From Week E-0 through Week E-24, subjects in the 5 mg/kg and 10 mg/kg infliximab treatment groups generally maintained improvements in IBDQ and SF-36 scores that were observed from baseline to Week E-0 of the study extension.

In the placebo treatment group, the improvements in the physician's global assessment, IBDQ, and SF-36 scores observed from baseline to Week E-0 of the study extension were maintained through Week E-24. In the placebo treatment group, corticosteroid use was generally unchanged during the study extension.

Safety Results: A total of 67.6% and 54.8% of subjects in the combined infliximab and placebo treatment groups had at least 1 AE during the study extension through Week E-24. In the infliximab treatment groups, 63.5% and 71.2% of subjects in the 5 mg/kg infliximab and 10 mg/kg infliximab treatment groups reported AEs. AEs were most frequently related to respiratory and GI system disorders in the combined infliximab treatment group and these were reported more often in the 10 mg/kg infliximab treatment group than in the 5 mg/kg infliximab treatment group. The most common AE in the combined infliximab treatment group was URI, reported in 9.9% of subjects in the combined infliximab treatment group and 6.5% of subjects in the placebo treatment group.

SAEs were reported in 9.9% of subjects in the combined infliximab treatment group and 3.2% of subjects in the placebo treatment group. The most frequently reported SAE was colitis ulcerative, reported in 4.5% of subjects in the combined infliximab treatment group and no subjects in the placebo treatment group.

One subject in the 5 mg/kg infliximab treatment group died of respiratory failure related to histoplasmosis.

Six (5.4%) subjects in the combined infliximab treatment group and no subjects in the placebo treatment group discontinued study agent because of AEs. Three subjects in the 10 mg/kg infliximab treatment group and 1 subject in the 5 mg/kg discontinued study agent because of infusion reactions and 1 of these events (10 mg/kg infliximab treatment group) was considered serious. Overall, infusion reactions were reported in 5.8% and 20.3% of subjects in the 5 mg/kg and 10 mg/kg infliximab treatment groups, respectively, and no subjects in the placebo treatment group. Subjects with infusion reactions in both infliximab treatment groups were generally those with a gap in treatment between the main study and the study extension; however, subjects in the 5 mg/kg treatment group with infusion reactions also experienced infusion reactions in the main study, while few subjects in the 10 mg/kg treatment group had experienced infusion reactions during the main study. No subjects had a possible anaphylactic reaction or a possible delayed hypersensitivity reaction in the study extension through Week E-24.

Infections were reported in 24.3% of subjects in the combined infliximab and 22.6% of subjects in the placebo treatment group. Most infections were related to respiratory system disorders. Three subjects in the 5 mg/kg infliximab treatment group and 1 subject in the 10 mg/kg infliximab treatment group reported serious infections, including 1 subject (5 mg/kg infliximab treatment group) while receiving commercial REMICADE during the gap period. In the combined infliximab treatment group, pneumonia was reported in 2 subjects and abscess was reported in 2 subjects.

No new cases of CHF, neurological disorder, or hematological disorder were reported during the study extension through Week E-24. In addition, no new cases of TB or malignancy were reported.

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Conclusions: In general, subjects who in the opinion of the investigator could benefit from continued treatment, regardless of treatment group, maintained their clinical benefit from Week E-0 through Week E-24.

In subjects with moderately to severely active ulcerative colitis who had already received 30 weeks of treatment, infliximab, administered as 5 mg/kg or 10 mg/kg infusions every 8 weeks from Week E-0 through Week E-24:

- Maintained clinical benefit as measured by the physician's global assessment.
- Maintained improvements in quality of life as measured by the IBDQ and SF-36.
- Enabled subjects to sustain clinical benefit while avoiding corticosteroid treatment.
- Was generally well tolerated with a safety profile consistent with the infliximab prescribing information.

Date of Report: 05 Dec 2005

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