

Synopsis (C0168T37 ACT 1)

Name of Sponsor/Company: Centocor, Inc	Associated with Module 5.3 of the Dossier	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		
Protocol: C0168T37 CR004777		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		
Principal/Coordinating Investigator(s): William J. Sandborn, Mayo Medical School, Rochester, MN, US; and Paul J. Rutgeerts, Univ. Leuven, Leuven, Belgium		
Study Center(s): Subjects participating in the study extension were enrolled at a total of 44 sites (18 in US, 4 in Canada, 12 in Europe, 7 in Australia, 2 in New Zealand, and 1 in Argentina).		
<p>Publication (reference): Feagan BG, Reinisch W, Rutgeerts P, et al. The effects of infliximab therapy on health-related quality of life in ulcerative colitis patients. <i>Am J Gastroenterol.</i> 2007;102(4):794-802.</p> <p>Reinisch W, Sandborn WJ, Bala M, et al. Response and remission are associated with improved quality of life, employment and disability status, hours worked, and productivity of patients with ulcerative colitis. <i>Inflamm Bowel Dis.</i> 2007;13(9):1135-1140.</p> <p>Rutgeerts P, Sandborn WJ, Feagan BG et al. Infliximab for induction and maintenance therapy for ulcerative colitis. <i>N Engl J Med.</i> 2005;353(23):2462-2476.</p>		
Studied Period: 02 Dec 2003/31 Aug 2007		Phase of Development: 3
Objectives: The primary objective of the main study (through Week 54) was to evaluate the safety and efficacy of infliximab in subjects with moderately to severely active ulcerative colitis (UC). 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. A further objective was to examine the safety and efficacy of long-term treatment with infliximab.		
Methodology: The main study of ACT 1 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 until the sites were unblinded. After study agent unblinding, subjects receiving placebo were discontinued from the study. Subjects receiving 5 mg/kg or 10 mg/kg infliximab continued to receive open-label infliximab every 8 weeks. Subjects receiving 10 mg/kg infliximab were given the opportunity to decrease their dose to 5 mg/kg. If subjects lost response after decreasing from 10 mg/kg to 5 mg/kg infliximab, or if subjects remaining on 5 mg/kg infliximab lost response, consideration to increase the dose to 10 mg/kg for subsequent infusions was permitted. Subjects were permitted only 1 dose increase during their participation in the study extension.		
Number of Subjects (Analyzed): A total of 364 subjects were enrolled in the main study, among which 149 participated in the study extension.		
<p>Diagnosis and Main Criteria for Inclusion: To enter the main study at baseline, subjects must have had active UC 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:</p> <ul style="list-style-type: none"> • Had concurrent treatment with at least 1 of the following: corticosteroids, azathioprine (AZA), or 6-mercaptopurine (6-MP). • 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. 		

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<p>Subjects who completed treatment in the main study through Week 46 and evaluations through Week 54 and, in the opinion of the investigator could benefit from continued treatment, were eligible to enter the study extension.</p>		
<p>Test Product, Dose and Mode of Administration, Lot Number: 5 mg/kg or 10 mg/kg infliximab IV administration every 8 weeks. Lot numbers: 01E071, 01J083, 03J121, 03J122, 04C127, 05C153, 4RMKA713, and 6ED0808103.</p>		
<p>Duration of Treatment: Treatment in the study extension continued for a maximum of 3 years or until marketing authorization was obtained for the use of infliximab for the treatment of UC and product was commercially available.</p>		
<p>Reference Therapy, Dose and Mode of Administration, Lot Number: Placebo (supplied as lyophilized solid for reconstitution with sterile water for injection) IV administration. Placebo lot numbers: 01G062, 03C157, and 5206E45.</p>		
<p>Criteria for Evaluation: Limited efficacy and health economic analyses were performed on all subjects who entered the study extension. In addition, safety analyses were performed on all treated subjects in the study extension (subjects who received at least 1 infusion of study agent [partial or complete] in the study extension) according to the actual study agent received during the study.</p> <p>Pharmacokinetics/Pharmacodynamics: Serum samples were collected to assess serum infliximab concentration.</p> <p>Efficacy: Efficacy was evaluated using the physicians' global assessment (PGA), a subscore of the Mayo score. The use of corticosteroids for UC was evaluated. Colectomies, ostomies, UC-related hospitalizations, and other ulcerative-colitis related surgeries were recorded. Health related quality of life was evaluated using the inflammatory bowel disease questionnaire (IBDQ) and the SF-36. C-reactive protein (CRP) concentrations were measured.</p> <p>Safety: Safety was assessed by summarizing the incidence and type of AEs observed during the study extension, as well as by summarizing markedly abnormal hematology and chemistry parameters, including antinuclear antibody/anti-double-stranded DNA (ANA/anti-dsDNA) and antibodies to infliximab. A colonoscopy dysplasia questionnaire was completed during the study extension.</p>		
<p>Statistical Methods: No hypothesis testing was performed. Data summaries were provided for the placebo treatment group and for the infliximab treatment group (5 mg/kg infliximab, and 10 mg/kg infliximab combined). 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.</p>		

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SUMMARY – CONCLUSIONS

Study Population Results: Of the 149 subjects who participated in the study extension, 31 subjects were in the placebo treatment group, 65 subjects were in the 5 mg/kg infliximab treatment group, and 53 subjects were in the 10 mg/kg infliximab treatment group. A total of 27.5% of subjects who participated in the study extension permanently discontinued study infusions; 32.3% in the placebo treatment group, and 26.3% in the infliximab treatment group. The baseline demographic characteristics of the subset of subjects who entered the study extension were generally similar across the treatment groups with respect to race and age, but the ratio of males to females differed between the treatment groups. Among subjects participating in the study extension, 96.0% were Caucasian, and the median age was 40. In the infliximab treatment group there were more males (59.3% vs 54.8%) and fewer females (40.7% vs 45.2%) than in the placebo group.

Pharmacokinetic Results:

- The majority of subjects maintained serum infliximab concentrations above the LLOQ (0.1 µg/mL) during the study extension.
- The median serum infliximab concentrations for subjects during the study extension were proportional to the infliximab doses administered during the study extension.
- A total of 9.5% subjects were positive for antibodies to infliximab.

Efficacy Results:

- The proportion of subjects with PGA scores indicative of normal or near normal disease was maintained during the study extension.
- The majority of infliximab-treated subjects were not receiving corticosteroids from the start of the study extension, and this was maintained throughout the study extension.
- In the infliximab treatment group, the median value of CRP was maintained at approximately 0.2 mg/dL throughout the study extension.
- In general, improvements in IBDQ and SF-36 scores were maintained during the study extension.
- There was 1 colectomy performed during the extension. The subject was in the placebo treatment group.

Safety Results:

The infliximab treatment group had an average of 105.9 weeks of treatment and 114.0 weeks of follow-up and subjects in the placebo treatment group had 48.8 weeks of treatment and 57.3 weeks of follow-up.

- A total of 88.1% and 93.5% of subjects in the infliximab and placebo treatment groups had at least 1 AE during the study extension. AEs were most frequently related to respiratory and GI system disorders in the infliximab treatment group. The most common AE in the infliximab treatment group was URI, reported for 28.8% of subjects in the infliximab treatment group.
- SAEs were reported in 24.6% of subjects in the infliximab treatment group and 29.0% of subjects in the placebo treatment group. The most frequently reported SAE was worsening of UC, which was reported in 3.4% of subjects in the infliximab treatment group and 9.7% subjects in the placebo treatment group.
- A total of 9 (7.6%) subjects in the infliximab treatment group and 6 (19.4%) subjects in the placebo treatment group discontinued study agent because of AEs. One subject in the 5 mg/kg infliximab treatment group died of pulmonary carcinoma after completion of the study extension. He discontinued from the study extension approximately 3.5 years from the start of the main study after being diagnosed with lung adenocarcinoma, and died on 10 May 2008. No subjects discontinued study agent because of infusion reactions.

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<ul style="list-style-type: none"> • Infections were reported in 57.6% of subjects in the infliximab treatment group and 35.5% of subjects in the placebo treatment group respectively. Most infections were related to respiratory system disorders. • A total of 7 (5.9%) subjects in the infliximab treatment group had 1 or more serious infections during the study extension. The only serious infection reported more than once was pneumonia (reported in 3 subjects, 1 in the 5 mg/kg infliximab treatment group and 2 in the 10 mg/kg treatment group). No serious infections were reported in the placebo treatment group during the study extension. • No subjects were reported to have opportunistic infections or active TB. • Malignancies were reported in 3 subjects during the study extension. One subject in the 5 mg/kg group had fatal pulmonary carcinoma after completion of the study. Two nonserious cancers were reported in the 10 mg/kg infliximab treatment group, a basal cell carcinoma and a malignant skin neoplasm of the nose and forearm. • Congestive heart failure was reported in 1 subject in the 5 mg/kg infliximab treatment group during the study extension, and 1 subject in the placebo treatment group reported a SAE of headache. No cases of myasthenia gravis, optic neuritis, or multiple sclerosis were observed during the study extension. There were no SAEs for hematological disorders in the study extension. • A total of 3 subjects in the infliximab treatment group (2 subjects in the 5 mg/kg group and 1 subject in the 10 mg/kg group) had markedly abnormal ALT or AST values. No elevated bilirubins were reported. In all subjects, values were transient and returned to normal with the exception of 1 subject who had two consecutive high ALT values and than the values returned to normal. • A single subject (Subject 028-009) in the 10 mg/kg infliximab treatment group had lupus arthritis in the study extension. This subject had an ANA titer of < 1:40 at baseline of the main study, and 1:160 ANA titer at Week 30 of the main study. At the beginning of the study extension, an unscheduled evaluation after the lupus arthritis was diagnosed revealed an ANA titer of 1:320. No evidence of organ involvement or damage was observed in this subject, but the event, while not a SAE, led to permanent discontinuation of the study agent. A nonserious report of LE syndrome occurred in a subject in the 5 mg/kg infliximab treatment group but this was not associated with positive ANA or anti-dsDNA titers at baseline nor during the study extension. 		
<p>Conclusions: In general, subjects maintained their clinical benefit during the study extension. In subjects with moderately to severely active UC who had already received 46 weeks of treatment, infliximab, administered as 5 mg/kg or 10 mg/kg infusions every 8 weeks during the study extension:</p> <ul style="list-style-type: none"> • Maintained clinical benefit as measured by the physician’s global assessment. • Maintained improvements in health related 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 REMICADE prescribing information. 		
<p>Date of Report: 18 Aug 2008</p>		

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