Synopsis (C0168T48)

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: C0168T48	**EudraCT No.:** 2004-000522-70

Title of the study: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Safety and Efficacy of Infliximab (REMICADE®) in Subjects with Chronic Sarcoidosis with Pulmonary Involvement

Principal/Coordinating Investigator(s): Robert P. Baughman, MD; University of Cincinnati, Cincinnati, OH, United States

Study Center(s): 34 sites in the United States and Europe

Publication (reference): None

Studied Period: 30 Sep 2003 to 15 Sep 2005	**Phase of Development:** 2

Objectives: The primary objective was to evaluate the efficacy of infliximab, as measured by pulmonary function, in subjects with chronic sarcoidosis with pulmonary involvement who are symptomatic despite current treatment.

The secondary objectives were:

- To evaluate the efficacy of infliximab in improving the symptoms and functional capacity of subjects with chronic sarcoidosis with pulmonary involvement who are symptomatic despite current treatment.
- To explore the efficacy of infliximab in the treatment of extrapulmonary manifestations of chronic sarcoidosis, with an emphasis on skin and eye involvement.
- To assess the pharmacodynamics and pharmacokinetics of infliximab in subjects with chronic sarcoidosis with pulmonary involvement.
- To assess the effect of infliximab on quality of life (QOL) in subjects with chronic sarcoidosis with pulmonary involvement.

The safety objectives of this study were:

- To evaluate the safety of infliximab in subjects with chronic sarcoidosis with pulmonary involvement.
- To evaluate the safety of infliximab in the treatment of extrapulmonary manifestations of sarcoidosis with an emphasis on skin and eye involvement.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study. Subjects received infusions of the study agent (3 mg/kg or 5 mg/kg infliximab or placebo) at Weeks 0, 2, 6, 12, 18, and 24, and were followed through Week 52. Allocation to treatment group was performed using interactive voice response system (IVRS) and was adaptive to maintain balance within centers and within subjects with skin involvement at baseline.

Number of Subjects (Planned and Analyzed): 120 planned; 138 randomized; 135 treated

Diagnosis and Main Criteria for Inclusion: To be eligible, subjects were adult men or women (excluding pregnant or nursing women, and men and women planning a pregnancy) who were at least 18 years old and had histologically proven sarcoidosis with an onset of at least 1 year prior to screening. Subjects were required to have evidence of parenchymal lung disease (Stage II and III) on chest x-ray and lung function impairment defined by forced vital capacity (FVC) ≥ 50% and ≤ 85% of the predicted value. Subjects were to be symptomatic as measured by an American Thoracic Society (ATS) dyspnea score of ≥ Grade 1. Subjects were required to have received ≥ 10 mg/day prednisone or equivalent or 1 or more immunosuppressants for at least

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3 months prior to screening. This treatment regimen was required to be stable for at least 4 weeks prior to randomization. Patients were to remain on the same background medication regimen at the same dose for the duration of the trial if condition allowed. However, if symptoms of sarcoidosis worsened, these medications could be altered. Decreasing the dose of the background medication was not allowed except for managing adverse reactions.

Test Product, Dose and Mode of Administration, Batch Number:
REMICADE (infliximab) was supplied as a sterile, white, lyophilized powder in a single use 20 mL vial. The study agent was to be reconstituted with 10 mL of Sterile Water for Injection, resulting in a concentration of 10 mg/mL infliximab for administration. Each mL of the solution contains 10 mg of infliximab, 50 mg of sucrose, 0.61 mg of dibasic sodium phosphate dihydrate, 0.22 mg of monobasic sodium phosphate monohydrate, and 0.05 mg of polysorbate 80. Subjects allocated to active treatment were to receive IV infusions of either 3 mg/kg or 5 mg/kg infliximab at Weeks 0, 2, 6, 12, 18, and 24. Three lots of infliximab (Lot 03E087, Lot 03K102, and Lot 03A051) were used during the study.

Duration of Treatment: 24 weeks active treatment; 28 weeks safety follow-up

Reference Therapy, Dose and Mode of Administration, Batch Number:
The placebo was supplied as a sterile, white, lyophilized powder in a single-use 20 mL vial. The placebo was reconstituted with 10 mL of Sterile Water for injection. Each mL of the solution contains 50 mg of sucrose, 0.61 mg of dibasic sodium phosphate dihydrate, 0.22 mg of monobasic sodium phosphate monohydrate, and 0.05 mg of polysorbate 80. Subjects allocated to placebo were to receive IV infusions of placebo at Weeks 0, 2, 6, 12, 18, and 24. Three lots of placebo (Lot 03D097, Lot 03C157, and Lot 01G061) were used during the study.

Criteria for Evaluation:

Pharmacokinetics/Pharmacodynamics:
Serum samples were used to evaluate various pharmacodynamic (eg, soluble intercellular adhesion molecule-1 [sICAM-1], monocyte chemoattractant protein-1 [MCP-1], C-reactive protein [CRP], angiotensin-converting enzyme [ACE], and TNFα) and pharmacokinetic parameters (ie, peak and trough serum infliximab concentrations), as well as antibody production to infliximab.

Efficacy: Efficacy analyses included all the randomized subjects and were performed by randomized treatment group. The primary endpoint was the change from baseline in percent of predicted FVC at Week 24. Major secondary endpoints included change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24, change from baseline in 6-minute walk distance at Week 24, change from baseline in Borg's category-ratio (CR)10 dyspnea score (score obtained before 6-minute walk) at Week 24, and proportion of Lupus Pernio Physician's Global Assessment (LuPGA) responders at Week 24 for the subset of subjects with skin involvement at baseline.

Safety: Safety data through Weeks 24 and 52 (incidence and type of AEs; markedly abnormal changes in laboratory values and vital signs; chest x-rays; and immune response) of all treated subjects (including those who received partial infusions of the study agent) were analyzed by treatment received. The incidence and the type of AEs through Weeks 24 and 52 were summarized by treatment group. Markedly abnormal changes in laboratory values and vital signs through Week 52 were summarized by treatment group.

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Statistical Methods:
Generally, continuous variables were summarized using descriptive statistics and analyzed using analysis of covariance (ANCOVA). For Borg's CR10 dyspnea score, ANCOVA on van der Waerden normal score was used. For ATS dyspnea score, Wilcoxon Rank-Sum test was used. Nonparametric analysis using van der Waerden normal score was also used to provide supportive analyses. Categorical variables were summarized using frequencies and percentages and analyzed using Fisher's exact test (for dichotomous variables) or Mantel-Haenszel test (for variables with more than 2 categories). Type I error rate of 0.05 (2-sided) was used in all the hypothesis testings. The primary endpoint and the first 2 major secondary endpoints used last observation carried forward (LOCF) to impute missing data for changes from baseline. Other imputation methods were also considered for the primary endpoint to evaluate the robustness of the result. For the primary endpoint, the test result would be considered positive only if the test for the combined infliximab treatment group versus the placebo treatment group and at least 1 of the pairwise tests between active treatment and placebo were statistically significant. If the primary endpoint was positive, the first 2 major secondary endpoints would be tested formally. Multiplicity was handled using the Hochberg step-up procedure for the 4 comparisons (2 pairwise comparisons in each of the 2 endpoints). For the other endpoints, nominal p-values were provided for descriptive purposes.

SUMMARY – CONCLUSIONS:

Study Population Results:
Treatment groups were balanced for baseline demographics and disease characteristics. Forty-six (46), 47, and 45 subjects were randomized to the 3 mg/kg infliximab, 5 mg/kg infliximab, and placebo treatment groups, respectively.

Pharmacokinetic/Pharmacodynamic Results:
Pharmacokinetic analyses demonstrated consistent and dose-proportional serum concentrations following multiple infusions of 3 mg/kg or 5 mg/kg infliximab at 6-week intervals following the induction regimen at Weeks 0, 2, and 6. For sICAM-1, MCP-1, and CRP there were initial decreases from baseline upon the start of infliximab in both the 3 mg/kg and 5 mg/kg treatment groups, but these changes did not persist and tended to return toward baseline levels as the study progressed. When compared with the placebo group, treatment with 3 mg/kg or 5 mg/kg infliximab resulted in a reduction of serum ACE levels by Week 12; this effect was maintained through Week 24. Serum ACE levels returned to baseline levels by Week 52 in the infliximab treatment groups.

Efficacy Results:
Infliximab therapy was associated with a statistically significant improvement in percent of predicted FVC after 24 weeks of therapy. Treatment benefit was not demonstrated in endpoints such as SGRQ, 6-minute walk, and Borg's CR10 dyspnea score in the overall study population. However, infliximab therapy was associated with improvement in other measures of disease activity, such as chest radiograph R-scores and serum ACE levels. Results of post-hoc, exploratory analyses suggest a greater treatment benefit in symptomatic subjects who had longer disease duration, greater impairment of lung function, and more limited exercise tolerance as measured by 6-minute walk distance.

Safety Results:
- Through Week 24, the proportion of subjects with 1 or more treatment-emergent AEs was similar among infliximab-treated subjects and placebo-treated subjects (81.3% and 79.5%, respectively).
- Through Week 52, the proportion of subjects with 1 or more treatment-emergent AEs was similar among infliximab-treated subjects and placebo-treated subjects; although infliximab-treated subjects had fewer AEs: (87.9% and 93.2%, respectively).

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- Through Week 24, the proportion of subjects with 1 or more treatment-emergent SAEs was similar among infliximab-treated subjects and placebo-treated subjects (11.0% versus 11.4%, respectively).
- Through Week 52, the proportion of subjects with 1 or more treatment-emergent SAEs was greater among infliximab-treated subjects compared with placebo-treated subjects (23.1% versus 18.2%, respectively).
- Two subjects were diagnosed with malignancies through Week 52. Through Week 24, 1 subject in the 3 mg/kg infliximab treatment group was diagnosed with squamous cell carcinoma. The investigator considered the SAE as not related to treatment with study agent. After Week 24 through Week 52, 1 subject in the 5 mg/kg infliximab treatment group was reported to have an epithelioid sarcoma. Follow-up information received after the completion of the study reported that the subject died approximately 3 months after the sarcoma was diagnosed. The investigator considered the AE as possibly related to treatment with the study agent.
- The proportion of infliximab-treated subjects versus placebo-treated subjects who discontinued study agent due to AEs was similar (5.5% and 4.5%, respectively). AEs leading to discontinuation of study agent included dyspnea, pneumonia, and allergic reaction.
- Through Week 24, 1 or more infusion reactions were more frequently reported in placebo-treated subjects than infliximab-treated subjects (13.6% and 8.8%, respectively).
- Infliximab-treated subjects had fewer infections and infections requiring oral or parenteral antimicrobial treatment than placebo-treated subjects (59.3% versus 72.7%, and 53.8% versus 61.4%, respectively).
- Similar proportions of infliximab-treated subjects and placebo-treated subjects had 1 or more serious infections (11.0% and 9.1%, respectively).
- No infliximab-treated subjects had elevations of aminotransferases (ALT or AST) greater than 3 times the ULN.
- The proportion of infliximab-treated subjects who tested positive for antibodies to infliximab at any time during the study was 8.9%.

Conclusions: This study demonstrated that chronic pulmonary sarcoidosis treated with infliximab was associated with a statistically significant improvement in the FVC. This response was seen in subjects who continued to receive stable immunosuppressive therapy as a background medication throughout the study. However, the study failed to achieve the prespecified 10% difference in percent of predicted FVC and did not demonstrate statistically significant improvement in any major secondary endpoints in the overall population. There was no evidence of new safety concerns among subjects who received treatment with infliximab.

Date of Report: 28 Apr 2006

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