Synopsis (C0168T54)

Name of Sponsor/Company: Centocor, Inc.		
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: REMICADE® (infliximab)		
Protocol: C0168T54	**EudraCT No.:** NA	
Title of the study: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Dose Finding Study Evaluating the Safety and Efficacy of Infliximab Administration in Symptomatic Subjects with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)		
Principal/Coordinating Investigator(s): Stephen Rennard, MD; University of Nebraska Medical Center, Omaha, NE		
Study Center(s): 41 sites in the USA		
Publication (reference): None		
Studied Period: 11 Dec 2002 to 03 Dec 2004	**Phase of Development:** 2	
Objectives: To evaluate safety and obtain pilot efficacy information measured by symptoms (eg, Chronic Respiratory Questionnaire [CRQ] total score), functional benefit (eg, 6-minute walk distance), and pulmonary function of 2 dosing regimens of infliximab compared with placebo in subjects with symptomatic moderate to severe COPD.		
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Subjects received intravenous infusions of the study agent (3 mg/kg infliximab, 5 mg/kg infliximab, or placebo) at Weeks 0, 2, 6, 12, 18, and 24, and were followed through Week 44. Allocation to treatment group was performed using an adaptive stratified design based on investigational site and baseline smoking status.		
Number of Subjects (Planned and Analyzed): 225 planned, 234 analyzed.		
Diagnosis and Main Criteria for Inclusion: Symptomatic subjects ≥ 40 years of age with moderate or severe COPD, a history of ≥ 10 pack-years of smoking, and a score of < 120 points on the CRQ.		
Test Product, Dose and Mode of Administration, Batch Number: REMICADE® (infliximab) was supplied as a lyophilized solid in a 100 mg formulation. The 100 mg formulation of infliximab contains 500 mg of sucrose, 6.1 mg of dibasic sodium phosphate dihydrate, 2.2 mg of monobasic sodium phosphate monohydrate, and 0.5 mg of polysorbate 80 in a 20 mL vial for reconstitution with 10 mL of Sterile Water for Injection. One lot of infliximab (Lot 01J083) was used during the study. Subjects received intravenous infusions of either 3 mg/kg or 5 mg/kg infliximab at Weeks 0, 2, 6, 12, 18, and 24.		
Duration of Treatment: 24 weeks		
Reference Therapy, Dose and Mode of Administration, Batch Number: The placebo was supplied as a lyophilized solid containing 500 mg of sucrose, 6.1 mg of dibasic sodium phosphate dihydrate, 2.2 mg of monobasic sodium phosphate monohydrate, and 0.5 mg of polysorbate 80 in a 20 mL vial for reconstitution with 10 mL of Sterile Water for Injection. Subjects received intravenous infusions of placebo at Weeks 0, 2, 6, 12, 18, and 24. Two lots of placebo (Lot 00K072 and Lot 01G061) were used during the study.		
Criteria for Evaluation: **Efficacy:** Efficacy analyses included all randomized subjects analyzed by randomized treatment. The primary endpoint was the change from baseline in CRQ total score at Week 24. Major secondary efficacy endpoints included change from baseline to Week 24 in prebronchodilator percent predicted forced expiratory volume in 1 second (FEV_1), 6-minute walk test distance, SF-36 physical component summary score, and Transition Dyspnea Index score, and the incidence of moderate or severe COPD exacerbations from baseline through Week 24.		

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Safety: Safety data through Weeks 24 and 44 (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) was analyzed by treatment received. The incidence and the type of AEs through Weeks 24 and 44 are summarized by treatment group. Markedly abnormal change in laboratory values and vital signs through Week 44 are summarized by treatment group.

Statistical Methods:
Continuous variables were summarized using descriptive statistics and analyzed using analysis of covariance. 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. For the primary endpoint, the test result would be considered positive only if the test for the combined infliximab group versus placebo and at least 1 of the pairwise tests between active treatment and placebo were statistically significant. For the other endpoints, nominal p-values were provided for descriptive purposes.

SUMMARY – CONCLUSIONS:

Study Population:
Treatment groups were balanced for baseline demographic and disease characteristics.

Efficacy:
Subjects who received treatment with infliximab (3 mg/kg or 5 mg/kg) through Week 24 showed no evidence of treatment benefit, as measured by analysis of the primary endpoint, when compared with those who received placebo. When subgroup analyses examining the primary endpoint at Week 24 were performed, no significant changes were observed in these findings. Further, none of the major secondary endpoint analyses at Week 24 indicated a significant benefit in infliximab-treated subjects.

Safety:

- Through Week 24, the proportion of subjects with 1 or more AEs was similar among infliximab-treated subjects and placebo-treated subjects (82.8% and 75.3%, respectively). The most common AEs among infliximab-treated subjects were exacerbation of COPD (29.9%), URI (10.8%), sinusitis (8.9%), pain (8.9%), and back pain (8.9%).
- Through Week 44, the proportion of subjects with 1 or more AEs was similar among infliximab-treated subjects and placebo-treated subjects (90.4% and 88.3%, respectively). The most common AEs among infliximab-treated subjects were exacerbation of COPD (37.6%), URI (14.6%), sinusitis (14.0%), pain (12.1%), back pain (9.6%), and headache (8.3%).
- Through Week 24, the proportion of subjects with 1 or more SAEs was similar among infliximab-treated subjects and placebo-treated subjects (14.6% versus 14.3%, respectively). The most common SAEs among infliximab-treated subjects were exacerbation of COPD (3.2%), pneumonia (1.3%), lobar pneumonia (1.3%), pulmonary carcinoma (1.3%), and malignant larynx neoplasm (1.3%).
- Through Week 44, the proportion of subjects with 1 or more SAEs was similar among infliximab-treated subjects and placebo-treated subjects (22.3% versus 20.8%, respectively). The most common SAEs among infliximab-treated subjects were exacerbation of COPD (7.0%), pneumonia (1.9%), lobar pneumonia (1.9%), pulmonary carcinoma (1.9%), malignant larynx neoplasm (1.3%), respiratory insufficiency (1.3%), and chest pain (1.3%).

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- Ten subjects were diagnosed with malignancies through Week 44. Malignancies occurred in 5 subjects in the 3 mg/kg infliximab treatment group, 4 subjects in the 5 mg/kg infliximab treatment group, and 1 subject in the placebo treatment group. Pulmonary carcinoma and head and neck malignancies occurred in more than 1 subject. Three of the subjects may have had their malignancy present at randomization or within 3 weeks of study entry.
- A greater proportion of infliximab-treated subjects than placebo-treated subjects discontinued study agent due to AEs (23.6% and 7.8%, respectively). With the exception of exacerbation of COPD, the most frequently reported AEs leading to discontinuation of study agent (ie, peripheral edema and serum sickness-like reactions) were reported only among infliximab-treated subjects.
- Infusion reactions occurred more frequently among infliximab-treated subjects than placebo-treated subjects (10.2% and 3.9%, respectively). Fewer infusion reactions occurred among subjects treated with 5 mg/kg infliximab than those treated with 3 mg/kg infliximab (5.0% and 15.6%, respectively).
- There were no reports of possible anaphylactic reactions and few (3.8%[6/157]) reports of possible delayed hypersensitivity (serum sickness-like) reactions in infliximab-treated subjects.
- No cases of tuberculosis were reported. Herpes zoster was reported in 4 (2.5%) subjects in the combined infliximab treatment group. There were no systemic potential opportunistic infections reported.
- Similar proportions of infliximab-treated subjects and placebo-treated subjects had reports of infections (57.3% and 59.7%, respectively), infections requiring treatment with oral or parenteral antimicrobials (51.0% and 51.9%, respectively), and serious infections (10.8% and 11.7%, respectively).
- Markedly abnormal elevated AST values (≥ 100% increase from baseline) were reported in a higher proportion of infliximab-treated subjects than placebo-treated subjects (8.5% and 2.7%, respectively), and were more frequent in the 5 mg/kg infliximab treatment group than in the 3 mg/kg infliximab treatment group (11.3% and 5.7%, respectively). In subjects with a baseline AST ≤ ULN (85.4%; 134/157), there was 1 subject in each infliximab treatment group with a postbaseline AST value of 2 to < 3 times greater than the ULN and no subjects with an AST value ≥ 3 times the ULN. In the 7 infliximab-treated subjects with elevated baseline AST values up to less than twice the ULN, there were 2 subjects (3 mg/kg group) who had a postbaseline AST value of 2 to < 3 times the ULN and no subjects with an AST value ≥ 3 times the ULN.
- Markedly abnormal elevated ALT values (≥ 100% increase from baseline) were reported in a higher proportion of infliximab-treated subjects than placebo-treated subjects (9.2% and 1.3%, respectively), and in similar proportions of the 3 mg/kg and 5 mg/kg infliximab treatment groups (8.6% and 9.9%, respectively). In subjects with a baseline ALT value ≤ ULN (84.7%; 133/157), there were no subjects with a postbaseline ALT value of 2 to < 3 times greater than the ULN and 1 subject (3 mg/kg group) with an ALT value ≥ 3 to < 5 times the ULN. In the 8 infliximab-treated subjects with elevated baseline ALT values 1 to 2 times the ULN, there were 2 subjects (3 mg/kg group) who had a postbaseline ALT value of 2 to < 3 times the ULN and no subjects with an ALT value ≥ 3 times the ULN.
- Over half (64.1%) of the infliximab-treated subjects did not develop antibodies to infliximab. The development of antibodies to infliximab occurred in a greater proportion of subjects in the 3 mg/kg infliximab treatment group than in the 5 mg/kg infliximab treatment group (34.4% and 23.9%, respectively).
- Newly positive results for anti-dsDNA antibodies occurred in 40.4% of infliximab-treated subjects compared with 4.2% of placebo-treated subjects (3 mg/kg group 40.9%; 5 mg/kg group 40.0%). These results were within the range for positive anti-dsDNA antibody response that has been observed in previous clinical trials. There was 1 report of a lupus-like syndrome and no reports of other autoimmune disease.

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Conclusions: Symptomatic subjects with moderate to severe COPD, as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, who received infliximab showed no evidence of treatment benefit through Week 24 compared with those who received placebo. An increased incidence of malignancies (primarily pulmonary and head and neck) was reported through Week 44 among infliximab-treated subjects when compared with placebo-treated subjects. In order to obtain additional information on malignancy risk, a long-term safety follow-up study is planned for all subjects who participated in this study.		
Date of Report: 24 Oct 2005		

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