Synopsis

Name of Sponsor/Company: Centocor, Inc.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: chimeric human-murine IgGκ (cA2)		

Protocol: C0168T41
Title of the study: A Randomized, Double-blind Trial of the Safety of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab) in Combination with Methotrexate Compared to Methotrexate Alone in Subjects with Rheumatoid Arthritis on Standard Disease-modifying Antirheumatic Drug Background Therapy

Principal/Coordinating Investigator(s): R Westhovens, UZ Gasthuisberg, Leuven, Belgium; D Yocum, University of Arizona Health Sciences Center, Tucson, AZ, USA.

Study Center(s): This study was conducted at 106 centers: 52 in North America, 33 in Europe, 8 in Australia, 7 in Argentina, and 6 in New Zealand.

Publication (reference): not applicable

Studied Period (years): 26 Sep 2001 to 21 Nov 2003 **Phase of Development:** 3

Objectives: The primary objective was to assess the relative risk of serious infection within the first 22 weeks after the initiation of infliximab in combination with MTX in a population of subjects with RA reflective of the demographics (severity of RA, background disease-modifying antirheumatic drugs [DMARDs], concomitant disease) seen in clinical practice. The secondary objectives were to evaluate the overall safety of infliximab when given with MTX for 1 year; to assess the safety and efficacy of dose-escalation regimens above 3 mg/kg of infliximab given every 8 weeks in subjects with an incomplete response to 3 mg/kg; and to assess the efficacy of infliximab in combination with MTX in a population of subjects with RA reflective of the demographics seen in clinical practice.

Methodology: This was a randomized, multicenter, double-blind, 3-arm, parallel-group study of the safety of 3 mg/kg and 10 mg/kg infliximab in subjects with RA on background MTX. Subjects randomized to 1 of 3 treatment groups in a 1:1:1 ratio: Group I) placebo infusions through Week 14, followed by 3 mg/kg infusions every 8 weeks through Week 46; Group II) 3 mg/kg infliximab infusion through induction followed by infliximab infusions every 8 weeks through Week 46. At Week 22 and subsequent infusion visits, infliximab dose could have been escalated by 1.5 mg/kg increments depending on whether a subject exceeded the threshold of response or threshold of flare; and Group III) 10 mg/kg infliximab infusion through induction followed by infliximab infusions every 8 weeks through Week 46.

Number of Subjects (Planned and Analyzed): 1000 planned; 1084 randomized; 1082 analyzed for safety and clinical pharmacology; 1064 analyzed for efficacy

Diagnosis and Main Criteria for Inclusion: Eligible subjects had a diagnosis of active RA (ie, the presence of polyarticular disease [6 or more tender and swollen joints]) according to the revised (1987) criteria of the American Rheumatism Association (ARA) despite MTX with or without other concomitant DMARD therapy.

Test Product, Dose and Mode of Administration, Batch Number: infliximab, 3 to 10 mg/kg via infusion, multiple batches

Duration of Treatment: 46 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number: MTX ≤ 25 mg/week by mouth

Criteria for Evaluation: The primary safety endpoint and all safety evaluations were based on subjects who received at least 1 study infusion; subjects were analyzed according to the actual treatment they received. All randomized subjects were included and an intention-to-treat principle was applied for the secondary efficacy analysis according to the randomized treatment group.

Synopsis

Name of Sponsor/Company: Centocor, Inc.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: chimeric human-murine IgGκ (cA2)		

Primary Endpoint: The primary endpoint was the development of a serious infection at any time through Week 22. The primary endpoint analysis estimated a 95% confidence bound for the relative risk of serious infection in the combined infliximab groups (Groups II and III) compared with the placebo plus MTX group (Group I).

Pharmacokinetics/Pharmacodynamics: Serum concentrations of infliximab were summarized over time from Weeks 22 through 54. Preinfusion (trough) serum infliximab concentrations for subjects receiving 3 mg/kg or 10 mg/kg infliximab with concomitant MTX and 1 additional concomitant RA medication were summarized. Serum concentrations of infliximab during the dose-escalation phase for subjects in Group II were summarized by dose received. The relationship between preinfusion (trough) serum infliximab concentrations and clinical response (ie, tender and swollen joint counts) was examined for subjects in Group II and Group III.

Efficacy: All efficacy analyses were secondary. Analyses of data through Week 22 included: 1) the proportions of subjects achieving an ACR 20, ACR 50, and ACR 70 response over time; 2) the percent change from baseline in the individual efficacy response parameters over time; and 3) change from baseline in the mental and physical summary scores of the SF-36 at Weeks 6 and 22. Analyses of data collected during the dose-escalation portion of the study (Week 22 through Week 54) included: 1) the proportion of subjects at or below the threshold of response at Week 54 for Groups II and III; 2) the percent change from baseline in the number of tender joints and the number of swollen joints for Groups II and III at Week 54; 3) the percent change from predose in the individual efficacy response parameters following dose escalation for subjects in Group II; and 4) the dose received at Week 46 for subjects in Group II.

Safety: Safety was assessed by summarizing the incidences and types of adverse events (AEs), changes in laboratory parameters, and the duration of the most frequently reported infections through Week 22 by treatment group. The development of ANA or anti-dsDNA antibodies were summarized by treatment group. The incidence of antibodies to infliximab following infliximab therapy was summarized by treatment group and concomitant corticosteroids, NSAIDs, or DMARDs. The effects of antibodies to infliximab on the pharmacokinetic profile of infliximab were assessed.

Statistical Methods: Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for categorical variables were used to summarize most data. Mantel-Haenszel Chi-square test stratified by baseline corticosteroid dose was used in the analyses of serious infection data. Analyses suitable for categorical data (ie, chi-square) were used to compare the proportion of subjects achieving some endpoint . Continuous variables were compared using an analysis of variance (ANOVA) on the van der Waerden normal scores. All statistical tests were 2-sided (alpha = 0.05). Subjects' baseline disease characteristics and concomitant medication data were compared among the 3 treatment groups using an ANOVA test on the van der Waerden normal scores for continuous variables, or chi-square test for categorical variables.

SUMMARY – CONCLUSIONS:

Study Population: 1084 subjects were randomized; 2 of these subjects were never treated. Overall, 14.1% of subjects terminated study participation, with approximately equal proportions terminating from all 3 groups. No significant differences were observed among treatment groups in baseline demographic characteristics; 19.6% of subjects were men, 80.4% were women; the median age was 52 years and 78.7% were Caucasian. Similarly, the baseline disease characteristics were well-balanced across all treatment groups. For all subjects randomized, the median duration of RA disease was 7.5 years (range 0 to 56 years). A total of 58.2% of subjects had undergone a prior joint surgery or procedure at baseline. At baseline, subjects had a median HAQ value of 1.5, which indicates that most subjects had moderate to severe disability. Of the 1084 subjects

Synopsis

Name of Sponsor/Company: Centocor, Inc.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: chimeric human-murine IgGκ (cA2)		

randomized, 78 (7.2%) subjects had a concomitant illness or condition that could predispose them to infections. The prevalence of concomitant illnesses or conditions that could predispose subjects to infectious AEs was generally balanced across treatment groups. No significant differences were observed between treatment groups in the use of concomitant medications.

Primary Endpoint: At Week 22, the relative risk of serious infections was 2.125 (95% CI 0.864 to 5.229) for the combined infliximab (3 mg/kg and 10 mg/kg) plus MTX treatment group, 1.003 (0.321 to 3.138) for the 3 mg/kg infliximab treatment group, and 3.293 (1.299 to 8.346) for subjects in the 10 mg/kg infliximab treatment group; all were compared with placebo plus MTX treatment group. In addition, the relative risk of serious infection was similar across most subgroups based on demographic and disease characteristics. No increase in relative risk with infliximab was observed in any subgroup.

Pharmacokinetics/Pharmacodynamics Results: Reproducible patterns of median serum infliximab concentrations were observed in all infliximab-treated dose groups. In general, higher serum concentrations of infliximab were attained in subjects who received higher doses.

Efficacy Results: ACR 20, 50, and 70 response rates for the combined infliximab (3 mg/kg and 10 mg/kg) plus MTX treatment group were all significantly higher than those for the placebo plus MTX group ($p < 0.05$ all comparisons). Likewise, all ACR component scores showed significant improvement with infliximab treatment compared with placebo plus MTX. In the assessment of pain and global disease assessments, subjects in the combined infliximab group showed rapid and sustained improvement compared with subjects in the placebo plus MTX group. Similarly, the percent improvement from baseline in HAQ, CRP, and the change from baseline in the SF-36 component summary scores showed rapid and sustained improvement in subjects in the combined infliximab group compared with subjects in the placebo plus MTX group. The proportion of subjects above the threshold of response at Week 22 was nearly twice as high in the placebo plus MTX treatment group (Group I; 41.7%) compared with the combined infliximab treatment group (21.3%). By the Week 54 evaluation, however, 83.4% of subjects in Group I, who had been receiving 3 mg/kg infliximab since Week 22, were at or below the threshold of response compared with 87.3% of subjects in the combined infliximab treatment group.

Safety Results: Through Week 22, the average number of weeks of treatment and follow-up was similar in all treatment groups. The proportion of subjects experiencing an AE was slightly lower in the placebo plus MTX group (66.2%) than in the combined infliximab treatment groups (71.0%). The most frequently reported individual AE was upper respiratory tract infection, and the frequency was similar across all treatment groups. Through Week 54, the average number of weeks of treatment and follow-up was greater in Groups II and III than in Group I because infliximab treatment was initiated in Group I at Week 22. The proportion of subjects experiencing an AE was higher in Groups II and III (85.0% and 86.4%, respectively) compared with the Group I (72.8%) infliximab-treated subjects. The system-organ class with the most frequently reported AEs was the respiratory system, with upper respiratory tract infection, sinusitis, pharyngitis, and bronchitis reported most frequently. Through Week 22, 7.8% of all infliximab-treated subjects reported an SAE compared with 7.5% of subjects who received MTX only. The most common SAE reported in infliximab-treated subjects through Week 22 was pneumonia, which was reported in 0.8% of all infliximab-treated subjects compared with 0.0% of subjects receiving placebo plus MTX. Five subjects died and 11 noncutaneous malignancies were reported in 9 subjects. Active TB was reported in 7 subjects; all 7 subjects with active TB had negative PPD test results (according to local guidelines) at study entry. Six of 7 cases occurred in Europe while 1 case occurred in the South America. Five of the 7 subjects with active TB had evidence of extrapulmonary TB. Through Week 22, approximately 1400 infusions were administered to each of the infliximab treatment groups, with an infusion reaction rate of 3.0% and 2.5%, respectively. In contrast, the placebo plus MTX group included approximately 1400 placebo infusions, with an infusion reaction rate of 1.4%. Four subjects

Synopsis

Name of Sponsor/Company: Centocor, Inc.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: chimeric human-murine IgGκ (cA2)		

had notable autoimmune events: 1 subject in Group I (3 mg/kg infliximab) had worsening lichen planus and 3 subjects in Group III had lupus syndrome. All other autoimmune disorders were of an allergic-type in nature occurring in subjects who were not newly positive for ANA and/or anti-dsDNA antibodies.

Conclusions: The relative risk of serious infections in the combined infliximab (3 mg/kg and 10 mg/kg) plus MTX treatment group compared with the placebo plus MTX treatment group was 2.125 (95% CI 0.864 to 5.229). The relative risk of serious infections was generally similar among subgroups based on demographic and baseline characteristics. In addition:

- The relative risk of serious infections in subjects receiving the approved induction regimen of 3 mg/kg infliximab plus MTX was equivalent to that in subjects receiving placebo plus MTX.
- Subjects receiving the unapproved induction regimen of 10 mg/kg infliximab had a higher relative risk of serious infections. However, subjects receiving dose escalations up to 9 mg/kg infliximab did not have increased rates of serious infections or AEs.
- The rates and types of serious infection in the infliximab treatment groups were comparable to those seen in previous trials. Although active TB was observed in the infliximab-treated groups, none of the subjects who were PPD-positive by local guidelines and received INH prophylaxis developed active TB. Subjects who had a history of active TB and had received appropriate anti-TB therapy did not develop active TB.
- There were no reports of demyelinating disorders. Possible delayed hypersensitivity and anaphylactic reactions were infrequent. The occurrence of malignancies was similar across all 3 treatment groups, and the one case of lymphoma was observed after the subject had received only 3 infusions of infliximab.
- Subjects receiving infliximab treatment had a rapid, significant, and sustained reduction in disease activity, and had ACR 20, 50, and 70 responses that were similar to those seen in previous studies of infliximab in subjects with RA.
- Subjects receiving infliximab treatment showed a significant and sustained improvement in signs and symptoms, physical function, and quality of life compared with subjects receiving placebo plus MTX.
- Most subjects in START initially receiving 3 mg/kg infliximab plus MTX did not require dose escalation; when dose escalation was required, however, subjects receiving dose escalations did have improved efficacy with no increase in AEs, including serious infections.

Thus, the results from the START trial reaffirm the positive benefit/risk profile of infliximab in the treatment of RA.

Date of Report: 13 Sep 2004

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.