Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

Protocol: C0168T50
Title of the study: A Multicenter, Randomized, Double-blind Trial of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab) for the Treatment of Subjects with Psoriatic Arthritis (PsA) (24-week Report)

Coordinating Principal Investigator: Christian Antoni, MD – University Erlangen-Nurnberg, Erlangen, Germany

Study Centers: Subjects were enrolled at 36 centers: 19 in the US, 8 in Canada, 2 in the United Kingdom, 2 in Belgium, and 5 in Germany.

Publication (reference): None

Studied Period (years): 20 Dec 2002 to 22 Jan 2004 (through week 24) **Phase of Development:** 3

Objectives: The primary objective was to evaluate the efficacy of infliximab in subjects with active polyarticular PsA by assessing reduction in signs and symptoms of arthritis and prevention of structural damage. The major secondary objectives of this trial were to evaluate efficacy of infliximab in: 1) achieving the American College of Rheumatology (ACR) 20 sustained response, 2) achieving the Psoriatic Arthritis Response Criteria (PsARC), 3) clearing psoriatic skin lesions, and 4) improving quality of life in subjects with PsA.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled trial, with 2 parallel treatment groups (placebo and infliximab 5 mg/kg) of subjects with active polyarticular PsA. This was a study of induction dosing followed by maintenance dosing with infliximab 5 mg/kg. Subjects could enter early escape at week 16. The study continues through week 66 with the potential for dose escalation at week 38.

Number of Subjects (Planned and Analyzed): Two hundred subjects (planned) were randomized in a 1:1 ratio to infliximab 5 mg/kg (n = 100) or placebo (n = 100). All 200 subjects were analyzed for safety, efficacy, and health economics, and 83 (of 100 planned) subjects were analyzed for serum infliximab concentrations.

Diagnosis and Main Criteria for Inclusion: Subjects 18 years of age or older with a diagnosis of active, polyarticular (5 or more joints involved) peripheral PsA for at least 6 months prior to the first infusion, and with an inadequate response to current or previous disease-modifying antirheumatic drug (DMARD) or nonsteroidal anti-inflammatory drug (NSAID) therapy. Diagnosis of PsA must have included the presence of active psoriasis. Concomitant methotrexate (MTX) at stable doses was permitted, but not required.

Test Product, Dose and Mode of Administration, Batch Number: Infliximab drug substance (lot 01J084) was supplied as a sterile, white, lyophilized powder in a single-use 20 mL vial and was to be reconstituted with 10 mL of Sterile Water for Injection, resulting in a concentration of 10 mg/mL infliximab. Infliximab 5 mg/kg was infused at weeks 0, 2, 6, 14, and 22 (and at weeks 16, 18, and 22 for placebo subjects who entered early escape).

Duration of Treatment: 22 weeks (through week 24)

Reference Therapy, Dose and Mode of Administration, Batch Number: The placebo (lots 01G061 and 01G062) was supplied as a sterile, white, lyophilized powder in a single-use 20 mL vial and was to be reconstituted with 10 mL of Sterile Water for Injection. Placebo was infused at weeks 0, 2, 6, 14, and 22 (and at weeks 16 and 18 for infliximab subjects who entered early escape).

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Criteria for Evaluation: All randomized subjects were summarized in the description of the study population. All randomized subjects were included in the primary efficacy and selected secondary analyses. Secondary efficacy analyses were based on all randomized subjects or on the subset of subjects with available outcome measurements according to their randomized treatment group. Safety evaluations were based on subjects who received at least 1 study infusion; subjects were analyzed according to the actual treatment received. Included in the pharmacokinetic analysis were 83 subjects who had blood samples for the measurement of serum infliximab concentrations collected immediately prior to the infusion and 1 hour after the infusion at weeks 0, 14, and 22.

Pharmacokinetics: Preinfusion and postinfusion concentrations were summarized by visit, and the proportion of subjects with an undetectable concentration was plotted over time. The proportion of subjects achieving an ACR 20 response at week 14 was plotted by preinfusion concentration at week 14. Also, the proportion of subjects achieving an ACR 20 response at week 24 was plotted by preinfusion concentration at week 22.

Efficacy: The primary endpoint analyzed in this study report was the proportion of subjects with an ACR 20 response at week 14. Major secondary endpoints included the proportion of subjects with an ACR 20 response at week 24, the proportion of subjects achieving PsARC at week 14, the proportion of subjects with ≥ 75% improvement from baseline in PASI at week 14 (in a subset of subjects with ≥ 3% BSA psoriasis skin involvement at baseline), and the change from baseline in the physical component summary score of SF-36 at week 14. In addition, other secondary endpoints related to the signs and symptoms of arthritis, skin disease, and quality of life were evaluated.

Safety: Safety was assessed by summarizing the incidence and type of adverse events (AEs) by treatment group. The proportions of subjects with serious AEs (SAEs), reasonably related AEs, severe AEs, discontinuations due to AEs, and clinically significant AEs were summarized by treatment group. The proportions of subjects with markedly abnormal laboratory values was summarized by treatment group. The incidences of antibodies to infliximab and the development of antinuclear antibodies or anti-double-stranded DNA antibodies were also summarized by treatment groups.

Health Economics: Resource utilization was summarized by treatment group through week 24.

Statistical Methods: Data were summarized using descriptive summary statistics (ie, n, mean, standard deviation, median, interquartile range, minimum, and maximum) for continuous variables and counts and percentages for discrete variables. The Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline MTX usage was used to analyze the primary endpoint and secondary endpoints evaluating the proportion of subjects responding to treatment. Subgroup analyses assessing the consistency of treatment effect in the primary efficacy endpoint over various demographic and disease characteristics at baseline were performed using odds ratios and 95% confidence intervals on the proportion of subjects responding to treatment. Continuous response parameters were compared by analysis of variance with MTX as a factor on the van der Waerden normal scores. All statistical tests were performed at α=0.05. In addition to statistical analyses, graphical data displays (eg, box plots) and subject listings were also used to summarize and present the data.

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SUMMARY – CONCLUSIONS:

Study Population With the exception of gender, demographics were generally well balanced between treatment groups. Baseline disease characteristics indicated a population of subjects with active PsA disease, including psoriatic skin disease. The majority (61.0%) of subjects were men (71.0% in infliximab and 51.0% in placebo), most subjects were Caucasian (94.5%), and the median age was 47.0 years. The median PsA duration was 5.5 years and the median psoriasis duration was 12.9 years. At baseline, 46.0% of subjects were taking MTX, 12.5% were taking corticosteroids, and 72.0% were taking NSAIDs. Most subjects had 1 of the following predominant forms of PsA subtypes at baseline: polyarticular arthritis, arthritis involving DIPs, or asymmetric peripheral arthritis. ACR component severity at baseline: median number of swollen and tender joints were 12.0 and 23.0, respectively; median patient's assessment of pain was 6.1; median physician's and patient's global assessments of disease were 5.9 and 6.0, respectively; median HAQ score was 1.1; and median CRP was 1.1 mg/dL. The median duration of morning stiffness was 90.0 min. With regard to psoriasis involvement, 85.9% of subjects had a BSA ≥ 3%, and the median PASI at baseline for subjects with BSA ≥ 3% was 6.6. The majority (67.6%) of subjects had moderate to severe psoriasis as defined by a BSA ≥ 5%. Forty-seven (47.0%)and 9 (9.0%) subjects in the placebo and infliximab groups, respectively, entered early escape at week 16.

Pharmacokinetic Results: Subjects with PsA demonstrated predictable infliximab serum concentrations following multiple infusions of 5 mg/kg of infliximab at 8-week intervals following the induction regimen at weeks 0, 2, and 6. Median peak and trough concentrations were 131.1 µg /mL and 5.5 µg /mL, respectively, at steady state (at week 22). Achievement of ACR 20 response was associated with higher trough serum concentrations of infliximab.

Efficacy Results: For the primary endpoint (the proportion of ACR 20 responders at week 14), significant improvement in the infliximab group compared with the placebo group (58.0% versus 11.0%, $p < 0.001$) was demonstrated. A consistent treatment benefit was observed with infliximab over subgroups of demographic and baseline disease characteristics. All 4 major secondary endpoints were met, and showed a significant treatment effect for infliximab compared with placebo (ie, proportion of subjects with ACR 20 response at week 24 [54.0% versus 16.0%], proportion of subjects achieving PsARC response at week 14 [77.0% versus 27.0%], the proportion of subjects with ≥ 75% improvement in PASI from baseline at week 14 in a subset of subjects with ≥ 3% BSA at baseline [63.9% versus 2.3%], and change from baseline in the physical component summary score of the SF-36 at week 14 [8.7 versus 1.0]). The proportion of subjects who achieved ACR 20 response was significant in favor of the infliximab group as early as week 2 and persisted through week 24. Other secondary endpoints used to evaluate the signs and symptoms of arthritis (including dactylitis, enthesopathy, the ACR subcomponents, ACR 50 and ACR 70 responses, PsARC and its subcomponents, and duration of morning stiffness) were significant in favor of infliximab compared with placebo through week 24. A consistent treatment effect was observed for ACR 20 response over all subgroups including baseline MTX usage. Demonstrating improvement in skin disease, the proportion of subjects with ≥ 75% improvement in PASI from baseline was significant in the infliximab group compared with the placebo group at all timepoints (as early as week 2) through week 24. Improvement was observed regardless of ACR 20 response and was consistent over subgroups of subjects defined by baseline MTX usage. Improvement in physical function, as measured by improvement from baseline in HAQ at weeks 14 and 24, was significantly greater in the infliximab group compared with the placebo group. In addition, a ≥ 0.25 unit decrease in the median HAQ score was observed in a significantly greater proportion of subjects in the infliximab group compared with the placebo group. The infliximab group also showed significant improvement from baseline (compared with placebo) in quality of life at weeks 14 and 24 measured by the SF-36 physical and mental component summary scores.

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Safety Results: Treatment with infliximab 5 mg/kg was generally well tolerated through week 24 and similar proportions of subjects experienced AEs on infliximab (66.7%) and placebo (67.0%). Upper respiratory infection was the most frequently reported AE through week 24, 10.0% and 14.4% in combined infliximab- and placebo-treated subjects, respectively. The combined infliximab group of subjects receiving MTX at baseline had a slightly lower frequency of AEs (57.7%) compared with subjects not receiving MTX at baseline (74.7%). The incidence of SAEs was low, 8.7% of combined infliximab-treated subjects and 6.2% of placebo-treated subjects. Through week 24, there was 1 malignancy in a placebo-treated subject and no deaths, or demyelinating, autoimmune, CHF, or TB events. There were 5 serious infections (3 subjects in the combined infliximab group and 2 subjects in the placebo group). Infusion reactions occurred in 7.3% of combined infliximab-treated subjects and 6.2% of placebo-treated subjects, none were serious. With the exception of AST/SGOT and ALT/SGPT chemistry values, all markedly abnormal hematology and chemistry values occurred at very low rates and were comparable between infliximab- and placebo-treated subjects. Markedly abnormal AST/SGOT and/or ALT/SGOT values occurred in 5 (3.3%) combined infliximab-treated subjects compared with no placebo-treated subjects. Newly positive ANA results occurred in 28.1% of infliximab-treated subjects and 10.3% of placebo-treated subjects. The incidence of newly positive anti-dsDNA antibodies at week 24 was 4.1% in the combined infliximab group compared with no subjects in the placebo group. Among infliximab-treated subjects, 4.5% were positive for antibodies to infliximab.

Health Economics Results: The productivity scale (measured by VAS) showed significant improvement from baseline in favor of infliximab versus placebo at both weeks 14 and 24. However, no significant differences were observed between treatment groups in other PsA resource consumption variables.

Conclusions:
Infliximab, administered as 5 mg/kg infusions at weeks 0, 2, and 6, and every 8 weeks thereafter through week 24, demonstrated consistent evidence of efficacy and was well tolerated in the treatment of active PsA. Specifically, infliximab:

- Reduced signs and symptoms of arthritis as early as week 2 and demonstrated sustained effect through week 24. Similar efficacy was observed in subjects with or without baseline MTX usage.
- Improved PsA-specific features of dactylitis and enthesopathy and demonstrated sustained effect through week 24.
- Improved psoriatic skin disease as early as week 2 and demonstrated sustained effect through week 24. Similar efficacy was observed in subjects with or without baseline MTX usage.
- Improved physical function at week 14, and demonstrated sustained effect through week 24.
- Improved both physical and mental aspects of health-related quality of life at week 14 and demonstrated sustained effect through week 24.
- Was generally well tolerated with similar overall incidences and types of AEs as observed previously, with the exception of a slightly increased incidence of markedly abnormal transaminase levels.

Date of Report: 28 Jun 2004

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