Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module** 5.3.5 **of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

Protocol: C0168T51
Title of the study: A Randomized, Double-blind Trial of the Efficacy of REMICADE® (Infliximab) Compared with Placebo in Subjects with Ankylosing Spondylitis (AS) Receiving Standard Anti-inflammatory Drug Therapy: 24-week Report

Principal Investigators:
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Study Centers: 33 (12 in North America [10 in United States (US) and 2 in Canada] and 21 in Europe).

Publication (reference): None

Studied Period (years): 15 Nov 2002 to 05 Sep 2003 | **Phase of Development:** III

Objectives: The primary objective was to assess the reduction in signs and symptoms of AS with infliximab therapy at week 24. The secondary objectives were to assess: (1) the overall safety of infliximab in subjects with AS; (2) the effect of infliximab on physical function in subjects with AS; (3) the effect of infliximab on structural damage in subjects with AS; (4) the effect of infliximab on quality of life in subjects with AS; and (5) the pharmacokinetics of infliximab in subjects with AS.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled trial, with 2 parallel treatment groups (placebo and 5 mg/kg infliximab) of subjects with active AS.

Number of Subjects (Planned and Analyzed): The study was planned for the analysis of 275 subjects randomized in a 3:8 ratio to 1 of 2 treatment groups: placebo and 5 mg/kg infliximab, respectively. Of the 279 subjects randomized to treatment, 78 and 201 subjects were randomized to the placebo and infliximab groups, respectively. Two subjects randomized to placebo were not treated, and 1 subject was randomized to placebo but received infliximab at the week-6 visit. Therefore, data from all 279 subjects were analyzed for efficacy and health economics endpoints, while 277 subjects (75 in the placebo group and 202 in the infliximab group) were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were to be adults with a diagnosis of definite AS, as defined by the 1984 Modified New York Criteria (van der Linden et al, 1984), for at least 3 months prior to screening. Active disease at the time of screening was a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 and a visual analogue scale (VAS) score for spinal pain of ≥ 4, each on a scale of 0 to 10. Concurrent stable treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen (paracetamol), and tramadol was permitted during the study. Subjects were not permitted to be on methotrexate, systemic corticosteroids, cytotoxic drugs, or disease-modifying antirheumatic drugs (DMARDs) for various time periods before screening.

Test Product, Dose and Mode of Administration, Batch Number: REMICADE® (infliximab) was manufactured by Centocor in Leiden, The Netherlands or in Malvern, Pennsylvania, US, and filled at Parkedale, Rochester, Michigan, US. Infliximab 5 mg/kg was infused at weeks 0, 2, 6, 12, and 18; three lots of infliximab (01G031, 01G032, 01A091) were used.

Duration of Treatment: 18 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo was manufactured by Centocor in Leiden, The Netherlands. Placebo was infused at weeks 0, 2, 6, 12, and 18; one lot of placebo (01G061) was used.

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Criteria for Evaluation: All randomized subjects were included according to the assigned treatment, and an intention-to-treat principle was applied for the primary and selected secondary efficacy analyses. Other secondary efficacy analyses were based on evaluable subjects in the randomized population according to their assigned treatment. Safety evaluations were based on subjects who received at least 1 study infusion; subjects were analyzed according to the actual treatment they received.

Pharmacokinetics: Blood samples for the measurement of serum infliximab concentration were collected immediately prior to the infusion and 1 hour after the end of the infusion at weeks 0, 2, 6, 12, and 18 and prior to the week-24 infusion. Pre- and postinfusion concentrations of infliximab were summarized by visit. Derived pharmacokinetics (PK) parameters were also summarized. The proportion of subjects who achieved an Ankylosing Spondylitis Assessment (ASAS) 20 response by preinfusion serum infliximab concentration at week 24 was also assessed.

Efficacy: The primary endpoint was the proportion of ASAS 20 responders at week 24. Major secondary endpoints included in this report are the change from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at week 24; the proportion of subjects achieving an AS major clinical response at week 24; and the change from baseline in the physical component summary score of the short form-36 health survey questionnaire (SF-36) at week 24. Other secondary endpoints, related to reducing signs and symptoms of AS and improving range of motion and physical function, were also evaluated.

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

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

Statistical Methods: Most 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 C-reactive protein (CRP) level at screening was used to analyze the primary endpoint and major secondary endpoint of AS major clinical response. Subgroup analyses assessing the consistency of treatment effect in the primary efficacy endpoint at week 24 over various demographic and disease characteristics at baseline were performed using odds ratios and 95% confidence intervals. A Chi-square test was used to compare the secondary endpoints evaluating the proportion of subjects responding to treatment. Continuous response parameters were compared by analysis of variance on the van der Waerden normal scores. All statistical tests were 2-sided and performed at $\alpha = 0.05$. In addition to statistical analyses, graphical data displays (eg, box plots) and subject listings were also used to summarize/present the data.

SUMMARY – CONCLUSIONS:

Study Population: Demographic and baseline disease characteristics were well balanced between treatment groups. The majority (80.6%) of the subjects in this study were men, and most subjects (97.8%) were Caucasian. The median age of the subjects in this study was 40.0 years (range: 18.0 to 74.0 years). For all subjects enrolled, the median duration of AS was 8.8 years (range: 0.3 to

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41.1 years). Of the 278 subjects who were tested, 242 (87.1%) were positive for HLA-B27 genotype. Baseline CRP levels were comparable between treatment groups (median, 1.5 mg/dL). Baseline results for disease activity, as assessed on a 0-10 cm VAS, showed that subjects experienced a moderately high level of pain and inflammation: the median patient global assessment was 6.8, the median spinal pain was 7.7, and the median inflammation (morning stiffness) was 7.3. The median chest expansion was 3.0 cm. The mean number of swollen joints was 1.5 on a scale of 0 to 44. The median score was 6.6 for BASDAI, 5.8 for BASFI, and 4.0 for BASMI, each measured on a scale of 0 to 10. The median baseline SF-36 physical and mental component summary scores were 28.9 and 47.3, respectively. These data indicate that the subjects in this study were moderately to severely symptomatic.

Pharmacokinetic Results: Pharmacokinetic analyses through week 24 demonstrated predictable infliximab serum concentrations. Median trough concentrations were maintained above 10 μg/mL at steady state. The median maximum infliximab concentration in serum was 151.50 μg/mL for the 5 mg/kg dose in this population. The median clearance, volume of distribution at steady state, and half-life were 3.91 mL/kg/day, 80.11 mL/kg and 14.79 days, respectively. Through week 24, increased ASAS 20 response was associated with higher trough serum concentrations of infliximab. Through week 24, an increased ASAS 20 response was associated with higher trough serum concentrations of infliximab. AEs through week 24 were not associated with higher infliximab concentrations.

Efficacy Results: The primary endpoint (ie, the proportion of ASAS 20 responders at week 24) demonstrated significant improvements in the infliximab group compared with the placebo group (61.2% versus 19.2%; $p < 0.001$). Consistent treatment benefit was observed with infliximab versus placebo over subgroups of demographic and baseline disease characteristics. As early as week 2, the change from baseline in BASFI in the infliximab group was greater than that in the placebo group (median, –1.0 versus –0.1); at week 24, the between-group difference was significant ($p < 0.001$). At week 24, the proportion of subjects with a ≥ 2 improvement from baseline in BASFI in the infliximab group was significantly greater than that in the placebo group (47.5% versus 13.3%, $p < 0.001$). At week 24, the proportion of subjects achieving an ASAS major clinical response in the infliximab group was significantly greater than that in the placebo group (22.4% versus 1.3%; $p < 0.001$). Improvement from baseline in the SF-36 physical component summary score in the infliximab treatment group was significantly greater than that in the placebo group at week 24 ($p < 0.001$). At week 24, results in the infliximab group were significantly greater than those in the placebo group for the following other secondary endpoints: change from baseline in BASMI ($p = 0.019$), proportion of subjects with ≥ 1 improvement from baseline in BASMI ($p = 0.003$), and percent change from baseline in chest expansion ($p = 0.037$); these results indicate that infliximab improved range of motion. Results for other secondary efficacy endpoints, except for the enthesis index, showed that the difference between infliximab and placebo was statistically significant in favor of infliximab.

Safety Results: Treatment with infliximab 5 mg/kg through 24 weeks was safe and well tolerated in the subjects enrolled in this study. The most frequently reported individual AE was upper respiratory tract infection, which occurred at similar rates in the placebo group (14.7%) and the infliximab group (13.9%). The incidence of SAEs through 24 weeks was low (ie, 3.5% of subjects treated with infliximab had at least 1 SAE compared with 2.7% of subjects treated with placebo). Through week 24, no deaths, malignancies, central demyelinating events, or cases of tuberculosis were reported. Only 2 subjects in the infliximab group had a serious infection. Infusion reactions occurred in 10.9% of subjects treated with infliximab compared with 9.3% of subjects treated with placebo; no infusion reactions were serious.

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The proportion of subjects with markedly abnormal postbaseline hematology values through week 24 was low and comparable between treatment groups. The proportion of subjects with markedly abnormal changes for clinical chemistry values, with the exception of aspartate transaminase (AST) and alanine transaminase (ALT) values, were comparable between treatment groups. Although markedly abnormal increases in ALT and/or AST occurred in 14.9% and 6.4%, respectively, of subjects in the infliximab group and 0% in the placebo group, no subject discontinued or had clinical hepatitis as a result. The occurrence of autoimmune disorders was very low. Among the infliximab-treated subjects, only 3% were positive for antibodies to infliximab at week 24. The incidence of infusion reactions for subjects who were positive for antibodies to infliximab was comparable to that for subjects who were negative for antibodies to infliximab.

Health Economics Results: Resource utilization did not differ significantly between treatment groups, with the exception of the number of home health nursing visits, which was significantly lower in the infliximab group compared with the placebo group (0.04 versus 1.05, $p = 0.037$).

Conclusions: Infliximab, administered as 5 mg/kg infusions at weeks 0, 2, 6, and every 6 weeks thereafter through week 18, demonstrated consistent evidence of efficacy and was well tolerated in the treatment of active AS. Specifically, through week 24, in subjects with active AS, infliximab:

- Reduced clinical signs and symptoms of disease activity as early as week 2 and demonstrated sustained improvement.
- Improved physical function as early as week 2 and demonstrated sustained improvement.
- Improved range of motion.
- Improved quality of life.
- Demonstrated predictable serum infliximab concentrations.
- Was safe and well tolerated, with no changes in the overall patterns, incidences, and types of AEs observed previously.
- As monotherapy, provided sustained efficacy without an increase in infusion reactions, anaphylaxis, or delayed hypersensitivity reactions.

Date of Report: 16 Jan 2004

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