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- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

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## Synopsis

### Name of Sponsor/Company:
Centocor, Inc

### Name Of Finished Product:
REMICADE® (infliximab)

### Name Of Active Ingredient:
chimeric human–murine IgGκ (cA2)

### Protocol:
C0168T29

### Title of the study:
A Randomized, Double-blind, Trial of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab) in Combination with Methotrexate Compared with Methotrexate Alone for the Treatment of Patients with Early Rheumatoid Arthritis: Final Report.

### Study Centers:
This study was conducted at 122 centers: 71 in North America, 49 in Europe, and 2 in Israel. Substudy 1 was conducted at 27 centers in North America. Substudy 2 was conducted at 25 centers in North America.

### Publication (reference):
None.

### Studied Period (years):
10 July 2000 to 04 April 2003

### Phase of Development:
3

### Objectives:
The purpose of this trial was to examine the efficacy and safety of both 3 mg/kg and 6 mg/kg doses of infliximab in combination with methotrexate (MTX), versus MTX alone, in the treatment of early rheumatoid arthritis (RA). The primary objectives were to assess the efficacy of infliximab in reducing signs and symptoms, preventing structural damage, and preventing physical disability, and to assess the safety and tolerability of infliximab in subjects with early RA. The primary purpose of Substudy 1 was to determine the pharmacokinetics of infliximab, administered concomitantly with MTX, in subjects with early RA. The secondary purpose was to provide supportive evidence for prevention of structural damage as demonstrated by circulating levels of bone and cartilage synthesis and degradation products, as well as markers of inflammation. The purpose of Substudy 2 was to describe the response of subjects with early RA, receiving long-term infliximab therapy at either 3 or 6 mg/kg in combination with MTX, or MTX alone, to a therapeutic 23-valent pneumococcal vaccine.

### Methodology:
This was a randomized, multicenter, double-blind, active treatment-controlled, 3-arm, parallel study of chronic treatment with infliximab in 1040 MTX-naïve subjects with early RA (≥ 3 months and ≤ 3 years from date of diagnosis).

### Number of Subjects (Planned and Analyzed):
The study was planned for the analysis of 1050 subjects randomized to 1 of 3 treatment groups in a 5:5:4 ratio: 3 mg/kg infliximab + MTX, 6 mg/kg infliximab + MTX, and placebo + MTX. Of the 1049 subjects randomized to treatment, 372 subjects received 3 mg/kg infliximab + MTX, 377 subjects received 6 mg/kg infliximab + MTX, and 291 subjects received placebo + MTX. Nine subjects were randomized and not treated. A total of 1040 subjects were analyzed for safety and clinical pharmacology; 1004 subjects were analyzed for efficacy and health economics.

### Diagnosis and Main Criteria for Inclusion:
Subjects eligible for this study were to be MTX-naïve and to have a diagnosis of active RA according to the revised 1987 criteria of the American Rheumatism Association. Active disease was defined by the presence of polyarticular disease (10 or more swollen joints and 12 or more tender joints). Subjects were also to be rheumatoid factor (RF)-positive, show radiographic evidence of erosive RA, or have C-reactive protein (CRP) levels ≥ 2 mg/dL. Eligible subjects were required to have had a disease duration (defined as persistent synovitis) of ≥ 3 months and ≤ 3 years from date of diagnosis.

### Test Product, Dose and Mode of Administration, Batch Number:
REMICADE® (infliximab) was manufactured by Centocor, BV and supplied as a lyophilized solid in a 100 mg formulation (Lot No. 99J033, 99A074, 00H035, 00A085, and 00L042). Infliximab (3 or 6 mg/kg) was infused at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46. MTX was started at 7.5 mg/wk and gradually increased to 20 mg/wk by week 8. Subjects were to maintain the target MTX dose of 20 mg/wk for the duration of the trial whenever possible.
### Synopsis

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**Duration of Treatment:** 46 weeks

**Reference Therapy, Dose and Mode of Administration, Batch Number:** The placebo was manufactured by Centocor, BV and supplied as a lyophilized solid in a 20 mL vial for reconstitution with 10 mL of sterile water for injection (Lot No. 99K06 and 01G061). The placebo was infused at weeks 0, 2, and 6, and every 8 weeks thereafter through week 46. MTX was started at 7.5 mg/wk and gradually increased to 20 mg/wk by week 8. Subjects were to maintain the target MTX dose of 20 mg/wk for the duration of the trial whenever possible.

**Criteria for Evaluation:** All randomized subjects were included, and an intention-to-treat principle was applied, for the primary efficacy analyses according to the randomized treatment group, with the exception of data from sites and which were excluded. Safety evaluations were based on subjects who received at least 1 study infusion; subjects were analyzed according to the actual treatment they received.

**Pharmacokinetics/Pharmacodynamics:** Blood samples for measuring the concentrations of infliximab were drawn before each infusion at weeks 0 and 30, and at weeks 54 and 58. Pre- and postinfusion concentrations of infliximab were summarized by treatment group and visit. Serum concentrations of infliximab for subjects in Substudy 1 were collected from both pre- and postinfusion blood samples at weeks 2, 6, 14, 22, 30, 38, and 46, and single blood samples at weeks 26, 47, 48, and 50. Derived pharmacokinetic (PK) parameters were also summarized by treatment group. Serum concentrations of a variety of bone, cartilage, and inflammatory markers (ie, C telopeptide [CTX], COL2-3/4C long neoepitope, chondroitin sulfate epitope 846, TNFα, interleukin [IL]-1β, IL-8, matrix metalloproteinase [MMP]-1, MMP-3, and intracellular adhesion molecule [ICAM]-1), were analyzed and summarized from serum samples collected at weeks 0, 2, 6, 14, 30, and 54. Because only a small number of complete sets of samples were obtained from subjects enrolled in the substudy, analyses were performed for those subjects who were missing ≤ 1 sample either before week 46, or after the last infusion at week 46.

**Efficacy:** The 3 coprimary endpoints in this study were: 1) improvement from baseline in clinical signs and symptoms, as measured by percentage improvement in ACR (ACRn) at week 54; 2) prevention of structural damage, as measured by the change from baseline in total radiographic scores of the hands and feet (based on the vdH-S score) at week 54; and 3) prevention of physical disability, as measured by the change from baseline in health assessment questionnaire (HAQ) score versus time area under the concentration time curve (AUC), adjusted for length of follow-up, from week 30 to week 54 (ie, improvement in HAQ averaged over time from week 30 to week 54). Major secondary endpoints included assessments of overall clinical improvement during 54 weeks of treatment as measured by the percentage improvement from baseline in ACR AUC, the proportion of subjects achieving a 20% improvement from baseline in ACR criteria (ACR 20) at week 54, the proportion of subjects with no newly eroded joints at week 54, and the proportion of subjects achieving a major clinical response.

**Safety:** Safety was assessed by summarizing the incidence and type of adverse events (AEs), and changes in laboratory parameters and vital signs. The proportion of subjects experiencing serious adverse events (SAEs), and the proportion observed to have clinically noteworthy changes in laboratory parameters, were compared between the treatment groups. The incidences of antibodies to infliximab and the development of antinuclear antibodies or anti-double-stranded DNA antibodies were also summarized and compared between treatment groups.

**Other Evaluations:** Resource utilization, both direct and indirect, was summarized by treatment group. The immune responses to polyvalent pneumococcal vaccine were summarized in the vaccine substudy.
Synopsis

Name of Sponsor/Company: Centocor, Inc
Name Of Finished Product: REMICADE® (infliximab)
Name Of Active Ingredient: chimeric human–murine IgGκ (cA2)

Associated with Module 5.3.5 Early RA of the Dossier

**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. The chi-square test was used to compare the proportion of subjects responding to treatment. In cases of rare events, such as SAEs, Fisher’s Exact test was used for treatment comparisons. Continuous response parameters (eg, AUC-type analyses) were compared using a t-test on the van der Waerden normal scores. All statistical tests were 2-sided. In addition to statistical analyses, graphical data displays (eg, box plots) and subject listings were also used to summarize the data.

The baseline measurement was defined as the closest measurement taken before or at the time of the week 0 infusion. Subjects’ demographic data and baseline disease characteristics were compared among the 3 treatment groups using an analysis of variance on the van der Waerden normal scores for continuous variables, or chi-square test for categorical variables.

**SUMMARY – CONCLUSIONS:**

**Study Population:** The majority of the subjects (71%) in this study were women, which reflects the overall distribution of RA in men and women in the general population. Most subjects (86%) were white; their ages ranged between 18 and 76 years. There were no significant differences among the treatment groups with respect to demographic characteristics. The baseline disease characteristics of the study population were also well balanced across treatment groups. Subjects had early RA as indicated by the short median duration of disease at baseline (0.6 years); more than 90% of subjects had relatively mild joint destruction (ie, Anatomical Stage I or II), and approximately 20% of subjects had extra-articular manifestations of RA. Although subjects were diagnosed with early RA, at baseline, many had moderate to severe disease as indicated by the median numbers of swollen and tender joints (19 and 31, respectively), and by mild to moderate functional impairment (60% of subjects in functional Class II, 26.7% in functional Class III, and 2.3% in functional Class IV). Moderate to severe disease at baseline was also indicated by the elevated median erythrocyte sedimentation rate (ESR) and median CRP values (40 mm/hr and 1.5 mg/dL, respectively). In addition, 71.6% of subjects tested positive for RF at baseline. Thus, the study population had early RA with moderate to severe disease activity.

**Pharmacokinetics/Pharmacodynamics Results:** Pharmacokinetic analyses demonstrated predictable, consistent, and dose-proportional serum concentrations following multiple infusions of 3 or 6 mg/kg infliximab at 8-week intervals following the induction regimen at weeks 0, 2, and 6. The postinfusion serum concentrations indicated that infliximab is distributed primarily into the vascular space. Treatment through 46 weeks provides stable trough serum infliximab concentrations, and suggests that any potential effects of antibodies to infliximab on PK parameters did not increase with continued therapy. The derived pharmacokinetic parameters observed for infliximab-treated subjects in the early RA population were consistent with those observed in earlier studies of subjects with more advanced RA. The median t1/2 was approximately 11 days for both the 3 and 6 mg/kg infliximab treatment groups.

The results from the PK substudy suggest that infliximab plus MTX may be more effective at decreasing expression of markers COL 2-3/4C, ICAM-1, and MMP-3 at earlier timepoints than treatment with MTX alone in subjects with early RA. Subjects receiving MTX alone relative to those receiving infliximab plus MTX exhibited a comparable reduction in the expression of certain pharmacodynamic markers (ie, CTX and IL-1β).

**Efficacy Results:** ASPIRE had 3 coprimary endpoints. The median ACRn for the combined infliximab group was 44.3, compared with 26.4 in the placebo group. The global test of the combined infliximab treatment
group versus placebo treatment group was significant ($p < 0.001$). The mean change from baseline in total vdh-S score for the combined infliximab group at week 54 was 0.46, whereas the mean change for the placebo group was 3.70. The global test of the combined infliximab treatment group versus placebo treatment group was significant ($p < 0.001$). The median improvement in HAQ averaged over time from week 30 to week 54 in the combined infliximab group was 0.784; the comparable value for the placebo group was 0.750. The global test of the combined infliximab treatment group versus placebo treatment group was significant ($p = 0.001$). Sensitivity analyses indicated the results were robust.

For the secondary endpoints, the number of subjects who achieved an ACR 20 response at week 54 for the combined infliximab treatment group (64.3%) was greater than the placebo group (53.6%, $p = 0.002$). In 3 ad hoc analyses, subjects receiving infliximab treatment had greater improvement from baseline in ACR 50, 70, and 90 responses at week 54 than subjects receiving placebo. A total of 14.9% infliximab-treated subjects achieved a major clinical response compared with 7.7% subjects in the placebo group ($p = 0.003$).

The mean change from baseline in the erosion score at week 54 for the 3 mg/kg and 6 mg/kg infliximab groups were 0.31 and 0.07 ($p < 0.001$ for both groups), respectively, whereas the change for the placebo group was 2.97. A total of 52.8% infliximab-treated subjects, compared with 41.0% placebo-treated subjects had no new erosions in previously uninvolved joints throughout the study ($p = 0.002$). Among subjects who had an erosion score of 0 at baseline, 77 (78.6%) infliximab-treated subjects compared with 23 (57.5%) placebo-treated subjects also had an erosion score of 0 at week 54 ($p = 0.012$). The proportions of subjects with radiographic progression were 4.6% ($p < 0.001$) for the 3 mg/kg infliximab group and 2.3% for the 6 mg/kg group ($p < 0.001$), versus 13.7% for the placebo group. The proportions of subjects with no worsening in vdh-S scores at week 54 were 58.2% ($p = 0.003$) for the 3 mg/kg infliximab group and 59.2% ($p = 0.001$) for the 6 mg/kg group, versus 45.1% for the placebo group. Likewise, significantly more subjects in each of the infliximab treatment groups had no worsening in the erosion score.

A significantly greater proportion of subjects in the infliximab groups achieved a clinically significant improvement in HAQ ($\geq 0.25$) at week 54 than subjects in the placebo group ($p < 0.001$). Improvement from baseline in the SF-36 physical component summary score was significantly greater in the combined infliximab group compared with the placebo group at both week 30 and week 54 ($p \leq 0.009$). No worsening in the SF-36 mental component summary score was observed between the combined infliximab and placebo groups at week 54.

Overall, the results of the subgroup analyses showed consistent similarities across all subgroups in the differences between infliximab and placebo in each of the 3 coprimary endpoints. The confidence intervals overlap extensively and, therefore, no significant differences in treatment benefit of infliximab compared with placebo were evident among subgroups.

**Safety Results:** Treatment with 3 mg/kg and 6 mg/kg infliximab with concomitant MTX for up to 46 weeks was safe and well tolerated in this MTX-naïve, early RA subject population with no changes in the expected patterns, incidences, or types of AEs observed previously. The most frequently reported AEs for infliximab-treated subjects were upper respiratory tract infection (26.7%), nausea (18.4%), headache (11.3%), and sinusitis (11.2%). Four subjects died and 4 treated subjects reported noncutaneous malignancies. The incidence of SAEs was generally low and was similar across the 3 treatment groups. The most frequent SAEs were in the respiratory system, and the most frequent SAE was pneumonia, reported in 2.5% of all infliximab-treated subjects. Four cases of active tuberculosis (TB) were reported. Serious infections, including pneumonia and TB, were not unexpected in this early RA subject population. Overall, more infliximab-treated subjects than subjects in the placebo group, and more subjects treated with 6 mg/kg than
3 mg/kg, reported infections. While infliximab-treated subjects developed more autoantibodies than subjects who received placebo, clinical manifestations of autoimmune disease were infrequent. The development of antibodies to infliximab did not appear to substantively affect the benefits or increase the risks associated with infliximab treatment in this study.

**Conclusion:** After 3 or 6 mg/kg infusions at weeks 0, 2, 6, and then every 8 weeks, infliximab with concomitant MTX was well tolerated and demonstrated consistent evidence of efficacy in the treatment of moderate to severe early RA and the inhibition of further disease progression and disability, compared with MTX alone. Sensitivity analyses indicated the results were robust and benefit was consistent among subgroups. Specifically, in this year-long study, in MTX-naïve subjects with moderate to severe early RA, infliximab (3 or 6 mg/kg; administered every 8 weeks), in combination with MTX:

- Reduces the signs and symptoms of disease activity as early as 2 weeks after the initial infusion and sustains these reductions through 54 weeks of treatment.
- Prevents structural damage by as early as 30 weeks after the initial infusion and sustains this benefit through 54 weeks, prevents new erosions, prevents JSN in unaffected joints, and prevents radiographic progression and worsening of structural damage in affected joints.
- Provides clinically significant improvement in physical function.
- Demonstrates predictable, consistent, and dose-proportional serum concentrations.
- Through 54 weeks of follow-up, appears to be safe and well tolerated, with no changes in the overall patterns, incidences, and types of AEs observed previously.

**Date of Report:** 18 September 2003