Synopsis (C0168T51 ASSERT)

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

Protocol: C0168T51 **EudraCT No.:** 2004-001215-57

Title of the study: A Randomized, Double-blind Trial of the Efficacy of REMICADE® (infliximab) Compared With Placebo in Subjects With Ankylosing Spondylitis Receiving Standard Anti-inflammatory Drug Therapy

Principal/Coordinating Investigator(s):

- Professor D van der Heijde, Academisch Ziekenhuis Maastricht, Maastricht, The Netherlands
- Professor J Braun, Rheumazentrum Ruhrgebiet, Herne, Germany

Study Centers: 33 (10 in United States, 2 in Canada, and 21 in Europe)

Publication (reference): van der Heijde D, Dijkmans B, Geusens P, Sieper J, DeWoody K, Williamson P, et al., and Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy Study Group. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). Arthritis Rheum. 2005 Feb; 52(2):582-591.
Braun J, Landewe R, Hermann KA, Han J, Yan S, Williamson P, et al for the ASSERT study group. Major reduction in spinal inflammation in patients with ankylosing spondylitis after treatment with infliximab: results of a multicenter, randomized, double-blind, placebo-controlled magnetic resonance imaging study. Arthritis Rheum. 2006 May; 54(5): 1646-1652.

Studied Period: 15 Nov 2002 to 28 Feb 2005 **Phase of Development:** 3

Objectives: The primary objective was to assess the reduction in signs and symptoms of ankylosing spondylitis (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: The study was a randomized, double-blind, placebo-controlled clinical trial. Subjects were randomized to 2 treatment groups: subjects in Group 1 were to receive placebo for the first 18 weeks and 5 mg/kg infliximab from Week 24 to Week 96, and subjects in Group 2 were to receive 5 mg/kg infliximab with the option of increasing the dose to 7.5 mg/kg from Week 36 to Week 96 depending on clinical response. Subjects were followed for efficacy and safety evaluations for up to 102 weeks.

Number of Subjects (Planned and Analyzed): Planned: 275 subjects;
Randomized: 279 subjects (78 subjects in the placebo group and 201 in the infliximab group);
Analyzed for efficacy endpoints: 279 subjects;
Analyzed for safety: 277 subjects (76 in the placebo group and 201 in the infliximab group).

Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were adults with a diagnosis of definite AS, as defined by the 1984 Modified New York Criteria, for at least 3 months prior to screening. Active disease at the time of screening was defined as having 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.

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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 and 7.5 mg/kg were infused intravenously. Six lots of infliximab (01A091, 01G031, 01G032, 03J122, 03K102, and 04C127) were used.

Duration of Treatment: 96 weeks

Reference Therapy, Dose, and Mode of Administration, Batch Number: Placebo was manufactured by Centocor in Leiden, The Netherlands. Placebo was infused intravenously; 1 lot of placebo (01G061) was used.

Criteria for Evaluation: The primary efficacy and selected secondary efficacy analyses were based on all subjects who were randomized (ie, intent-to-treat population). Subjects were included according to their assigned treatment group regardless of whether or not they received the assigned treatment. Other secondary efficacy analyses were based on evaluable subjects in the randomized population according to their assigned treatment groups. Safety evaluations were based on subjects who received at least 1 study infusion. Safety analyses were based on actual treatment regimens received by the subjects but did not include subjects who were randomized but never received any study infusions.

Pharmacokinetics/Pharmacodynamics: Serum infliximab concentrations were summarized by visit. A base population PK model was constructed to estimate individual pharmacokinetic (PK) parameters. The derived PK parameters were also summarized for each treatment group.
The pharmacodynamic effects of infliximab on selected biologic markers of inflammation, bone formation, and bone and cartilage destruction were to be evaluated at Weeks 0, 2, 24, and 102. The pharmacodynamic biomarkers associated with bone turnover that were tested were bone alkaline phosphatase (BAP), osteocalcin, C-Telopeptide (CTx), N-Telopeptide (NTx), cartilage oligomeric matrix protein (COMP), and osteoprotegerin (OPG). In addition, the following markers associated with inflammation were also tested: IL-6, IL-10, vascular endothelial growth factor (VEGF), transforming growth factor β (TGFβ), and interferon γ (IFNγ).

Efficacy: The primary endpoint of this study was the proportion of subjects who achieved an ASAS 20 response at Week 24. The primary endpoint and some major secondary endpoints have been presented in the 24-week Clinical Study Report (CSR). The major secondary endpoint discussed in this report is the change from baseline in the MRI activity score at Week 24 compared between treatment groups. The correlation between the proportion of subjects who achieved an Ankylosing Spondylitis Assessment (ASAS) 20 response and the subjects' preinfusion serum infliximab concentration at Week 102 was also assessed.

Health Economics: Resource utilization, both direct and indirect, through Week 54 was summarized by treatment group. Direct resources include hospitalizations, physician visits, emergency room visits, specialist visits, physiotherapist visits, procedures and surgeries, home health nursing visits, and household assistance visits. Indirect resources include the number of work/study days missed by the subject and caregiver due to illness.

Safety: Safety was assessed by summarizing the incidence and type of AEs by treatment group. The number and proportion of subjects with AEs, reasonably related AEs, SAEs, reasonably related SAEs, and AEs leading to discontinuation of treatment were summarized by treatment group. The proportion of subjects with 1 or more infections, 1 or more infections requiring oral or parenteral antimicrobial treatment, 1 or more serious infections, 1 or more infusion reactions, and 1 or more possible anaphylactic reactions or possible delayed hypersensitivity (serum-sickness like) reactions were summarized by treatment group. The presence of antinuclear antibodies (ANA)/anti-double-stranded DNA (anti-dsDNA) was determined. Subjects' baseline ANA/anti-dsDNA antibody status and the proportion of subjects who experienced changes in ANA or

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anti-dsDNA antibody status during the trial were summarized by treatment group. The formation of antibodies to infliximab was evaluated on blood samples drawn prior to study infusion at baseline, and at Weeks 24, 54,78, 96, and 102. The proportion of subjects developing antibodies to infliximab was summarized by treatment group.

Statistical Methods:
Descriptive summary statistics, such as number (n), mean, SD, median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. The Cochran-Mantel-Haenszel (CMH) chi-square test stratified by C-reactive protein (CRP) levels at screening was used to analyze the primary endpoint and major secondary endpoint of AS major clinical response. 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. All statistical tests used 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 and present the data.

SUMMARY – CONCLUSIONS

Study Population Results: 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). The mean durations of AS in the study population were 11.9 and 10.1 years for the placebo group and the infliximab group, respectively, at baseline. Of the 278 subjects who were tested, 242 (87.1%) were positive for the HLA-B27 genotype. The proportions of subjects with positive HLA-B27 status or a history of joint surgery/procedure were well balanced between treatment groups. The most common comorbidities were uveitis, psoriasis, and inflammatory bowel disease. Baseline CRP levels were comparable between treatment groups (median, 1.5 mg/dL). Baseline results for disease activity, as assessed on a 0 to 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.

Pharmacokinetic/Pharmacodynamic Results:
Pharmacokinetic summary
The pharmacokinetic analyses demonstrated that:

- The median preinfusion and postinfusion serum infliximab concentrations were consistent with the dose administration pattern over time.
- The median trough infliximab concentrations were generally maintained above 10 μg/mL when either 5 mg/kg or 7.5 mg/kg infliximab was administered intravenously every 6 weeks. During maintenance treatment with 5 mg/kg infliximab every 6 weeks, the median preinfusion concentrations at different visits were maintained (range 10.2 μg/mL to 14.0 μg/mL). Dose escalation from 5 mg/kg→7.5 mg/kg infliximab led to a higher preinfusion concentration level (14.0 μg/mL to 20.0 μg/mL).
- The median serum concentration of infliximab 1 hour after the end of infusion (ie, postinfusion concentration) was 109.8 μg/mL following the first infusion of 5 mg/kg infliximab at Week 0. The median postinfusion concentration after repeated infliximab infusions of 5 mg/kg was only slightly

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increased (118.5 to 149.2 μg/mL) compared with that after the first infusion. Dose escalation resulted in a higher median postinfusion concentration of infliximab (176.8 to 224.1 μg/mL).

- There was no additional accumulation of serum infliximab concentration after achieving the steady state when either 5 mg/kg or 7.5 mg/kg infliximab was administered every 6 weeks.
- The median CL, Vss, and t1/2 were 3.44 mL/day/kg to 3.56 mL/day/kg, 74.57 mL/kg to 77.51 mL/kg, and 14.87 days to 15.50 days, respectively.

Pharmacodynamics summary
Treatment with infliximab resulted in:

- Substantial decreases from baseline in serum levels of markers associated with inflammation, IL-6 and VEGF, compared with treatment with placebo; this effect was maintained at Week 24 and Week 102.
- Increases from baseline in serum levels of markers of bone formation, osteocalcin and BAP at Weeks 2 and 24 compared with treatment with placebo. At Week 102, however, the increase in markers of bone formation was observed for BAP but not for osteocalcin.

Efficacy Results:

- Efficacy, as measured by ASAS 20, was maintained through Week 102 in subjects who received infliximab for approximately 2 years. Clinical response was also maintained through Week 102 for other signs and symptoms of AS, physical function, range of motion, and quality of life. Subjects who began receiving infliximab at Week 24 and received treatment with 5 mg/kg infliximab every 6 weeks for approximately 1.5 years also achieved similar ASAS 20 response and showed improvement in the signs and symptoms of AS, physical function, range of motion, and quality of life to a degree that was similar to the efficacy achieved and maintained in subjects who received infliximab for approximately 2 years.
- From Week 36 through Week 96, 106 (52.7%) subjects in the infliximab group started receiving a dose escalation from 5 mg/kg to 7.5 mg/kg when they had a BASDAI ≥ 3 for 2 consecutive visits. Although the percentage of subjects achieving an ASAS 20 response generally increased over time in this treatment group, a lower percentage of these subjects had an ASAS 20 response at any given time compared with subjects who received 5 mg/kg throughout the study.
- The median change from baseline in MRI activity score at Week 24 showed a statistically significant ($p < 0.001$) improvement in the infliximab group compared with the placebo group. The median change from baseline in chronicity score at Week 24 was not statistically significant between the 2 groups. At Week 102, the improvement from baseline in MRI activity score was maintained in the infliximab group, and the activity score in the placebo→infliximab group was comparable to the activity score in the infliximab group.
- The change from baseline in spine and hip DEXA T-scores and Z-scores at Week 24 showed a statistically significant improvement in the infliximab group compared with the placebo group. The median change from baseline in DEXA BMD of the spine and hip at Week 24 also showed a statistically significant improvement in the infliximab group compared with the placebo group. At Week 102, change from baseline in DEXA spine and hip T- and Z-scores were further improved compared with Week 24 scores for the infliximab group, and scores in the placebo→infliximab group were comparable to scores in the infliximab group.

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Safety Results: In this study, infliximab infusions at Weeks 0, 2, 6, and every 6 weeks thereafter through Week 96 were generally well tolerated in subjects with AS, with a favorable safety profile. No new safety trends were observed during approximately 2 years of infliximab infusions.

- No deaths, cases of active TB, serious possible opportunistic infections, CHF, or anaphylaxis were reported.
- Respiratory system disorders (76.0%) was the system-organ class with the most frequently reported AEs in all infliximab-treated subjects, followed by skin and appendages disorders (53.5%) and body as a whole - general disorders (51.6%). Upper respiratory tract infection was the most common AE (48.7%) in all infliximab-treated subjects. Other AEs commonly reported included pain (28.7%), rhinitis (21.5%), diarrhea (20.4%), and pharyngitis (20.0%).
- The overall frequency of SAEs through Week 102 was 17.8% in all infliximab-treated subjects. The musculoskeletal system and gastrointestinal system were the system-organ classes with the most frequently reported SAEs, with 14 (5.1%) and 9 (3.3%) subjects, respectively, in the combined infliximab group. Arthritis (1.8%), diverticulitis (1.1%), pain (1.1%), and pneumonia (1.1%) were the most common SAEs.
- Pneumonia was the most common serious infection, occurring in 3 (1.1%) infliximab-treated subjects.
- Malignancies were uncommon (a total of 3 malignancies were reported during the study), and no cases of lymphoma were reported.
- Infusion reactions were infrequent. No anaphylactic reactions were reported. One possible delayed hypersensitivity reaction was reported.
- Markedly abnormal laboratory values were generally infrequent. Markedly abnormal elevations in ALT, AST, and bilirubin occurred in 67 (24.5%), 31 (11.3%), and 6 (2.2%) subjects who were treated with infliximab, respectively. No subjects had both an ALT $\geq$ 3 x ULN and a total bilirubin $\geq 2 \times$ ULN.
- The majority of subjects had an inconclusive antibody-to-infliximab status at Week 102. A higher proportion of subjects who required dose escalation to 7.5 mg/kg infliximab were positive for antibodies to infliximab compared with subjects who remained on 5 mg/kg.
- A higher incidence of infusion reactions occurred in subjects who were antibody-to-infliximab positive compared with subjects who were antibody-to-infliximab negative or inconclusive.
- A greater proportion of subjects with inconclusive antibody-to-infliximab status achieved an ASAS 20 response compared with subjects classified as antibody-positive or antibody-negative. This could be attributed to these subjects maintaining detectable concentrations of infliximab longer than subjects who were either positive or negative for antibodies to infliximab.

Conclusions:

Infliximab, administered as 5 mg/kg infusions at Weeks 0, 2, 6, and every 6 weeks thereafter through Week 96, demonstrated consistent evidence of efficacy and was generally well tolerated in the treatment of active AS. Efficacy was maintained through Week 102 in subjects who received infliximab throughout the study. Subjects in the placebo group who began to receive infliximab at Week 24 and received treatment with 5 mg/kg infliximab every 6 weeks for approximately 1.5 years also achieved a response that was similar to the

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efficacy achieved and maintained in subjects who received infliximab for approximately 2 years. Specifically, 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.
- Improved the MRI activity score and spine and hip DEXA T- and Z-scores and BMD.
- Demonstrated predictable serum infliximab concentrations.
- Was generally safe and well tolerated, with no changes in the overall pattern and types of AEs observed previously with infliximab treatment through Week 24.

Date of Report: 22 Nov 2006

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