# Synopsis (C0168T50 IMPACT 2)

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

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| **Protocol:** C0168T50 | **EudraCT No.:** 2004-000435-28 |
| **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 | |
| **Principal/Coordinating Investigator(s):** Arthur Kavanaugh, MD, University of California San Diego, La Jolla, CA, US | |
| **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):** Antoni C, Krueger GG, de Vlam K, et al. Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. Ann Rheum Dis. 2005a. Available at: http://ard.bmjjournals.com/cgi/reprint/ard.2004.032268v2. Accessed 24 Feb 2005. | |
| **Studied Period:** 20 Dec 2002/29 Nov 2004 | **Phase of Development:** 3 |
| **Objectives:** The primary objective was to evaluate the efficacy of infliximab in subjects with active polyarticular psoriatic arthritis (PsA) by assessing reduction in signs and symptoms of arthritis and prevention of structural damage. The major secondary objectives were to evaluate the 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. The primary focus of this Clinical Study Report is the evaluation of radiograph data. | |
| **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 and 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, 109 (of 100 planned) subjects were analyzed for serum infliximab concentrations, and 107 (of 100 planned) were analyzed for pharmacodynamic serum biomarkers. | |
| **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 (Lots 01J084, 03K102) 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, 22, 30, 38, and 46; at Weeks 16, 18, 22, 30, 38, and 46 for placebo subjects who entered early escape, and at Weeks 24, 26, 30, 38, and 46 for placebo subjects who crossed over to infliximab. Infliximab 10 mg/kg was infused at Weeks 38 and 46 for subjects who dose escalated. | |
| **Duration of Treatment:** 46 weeks | |
| **Reference Therapy, Dose and Mode of Administration, Batch Number:** The placebo (Lots 01G061, 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 for | |

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subjects in the placebo group; at Weeks 16 and 18 for infliximab subjects who entered early escape; and at Weeks 22 and 24 for infliximab subjects who did not enter early escape.

**Criteria for Evaluation:** Baseline disease activity, efficacy measurements, and SF-36 scales were summarized by treatment received. All randomized subjects were included in the efficacy analyses for structural damage according to the randomized treatment group. Some secondary efficacy analyses for the structural damage were based on the subset of subjects with evaluable measurements according to their randomized treatment group. Follow-up information regarding signs and symptoms efficacy endpoints analyzed in the Week 24 report were summarized from Week 30 through Week 54 for those subjects who received at least 1 dose of infliximab at any time during the study according to the treatment received. 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 109 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, 22, and 38, and at Weeks 54 and 66. Included in the pharmacodynamic analysis were 107 subjects who had blood samples collected at Week 0. Samples were also to be collected at Weeks 2, 14, and 24.

**Pharmacokinetics/Pharmacodynamics:** Preinfusion and postinfusion serum infliximab concentrations were summarized by visit, and the proportion of subjects with an undetectable concentration was plotted over time. Pharmacodynamics were assessed by summarizing median changes in serum concentration for markers of inflammation and bone metabolism.

**Efficacy:** The primary endpoint was the change from baseline in the total modified van der Heijde modified Sharp (vdH-S) score at Week 24. In addition, other secondary endpoints and exploratory endpoints related to structural damage were evaluated. Maintenance of responses for signs and symptoms of arthritis, physical function, skin disease, and quality of life endpoints were summarized through Week 54.

**Health Economics:** Changes from baseline in productivity, PsA-related joint surgeries or procedures, and employment status were summarized by treatment group at Week 54.

**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 were 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.

**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. A 2-sided F-test using an ANOVA method with baseline MTX usage as a factor on the van der Waerden normal scores was used to analyze the primary endpoint and other secondary endpoints with continuous data. The Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline MTX usage was used to analyze other secondary endpoints with categorical data. Subgroup analyses assessing the consistency of treatment effect in the primary efficacy endpoint across various demographic and disease activities and characteristics at baseline were performed using median differences and 95% confidence intervals on the proportion of subjects responding to treatment. All statistical tests were 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.

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**SUMMARY – CONCLUSIONS**

**Study Population Results:** Median erosion scores and median JSN scores for both the hands and feet were similar between the infliximab group and the placebo group at baseline. The median total modified vdH-S score was 6.00 for the infliximab group and 4.50 for the placebo group.

**Pharmacokinetic/Pharmacodynamic Results:** PK analyses in subjects with PsA demonstrated that median peak concentrations of infliximab were dose proportional. The small group of subjects with PK samples who also dose escalated may have cleared infliximab faster than subjects who remained on the 5 mg/kg dose.

Baseline serum levels markers of inflammation and bone metabolism were generally comparable between treatment groups. Infliximab reduced serum levels of IL-1Ra, sIL-2R, IL-6, metalloproteinase-3 (MMP-3) and vascular endothelial growth factor (VEGF), inflammatory markers that have been associated with disease activity in PsA, as early as 2 weeks following the initiation of treatment. These changes were generally sustained through Week 24. In contrast, the serum levels of markers of bone metabolism, reflecting either the formation or resorption of bone, were not notably changed following treatment with infliximab.

**Efficacy Results:** For the primary endpoint (the change from baseline in the total modified vdH-S score at Week 24), infliximab treatment resulted in significant inhibition of structural damage in favor of the infliximab group compared with the placebo group (mean –0.70 versus 0.82, $p < 0.001$). A consistent treatment benefit with infliximab was demonstrated across subgroups of demographics, baseline disease activities and characteristics, and prior and concomitant medications. At Week 24, significant differences were observed in favor of infliximab (negative mean change from baseline in scores) compared with placebo (positive mean change from baseline in scores) in the modified vdH-S scores by region (hands or feet) and by type of damage (erosion or JSN). Based on the SDC, the proportion of subjects in the infliximab group with radiographic progression was significantly less than in the placebo group (3.0% versus 12.0%, $p = 0.017$). The mean change in the total modified vdH-S at Week 54 was –0.94 in the infliximab group compared with 0.53 in the placebo group ($p = 0.001$). Continued inhibition of structural damage was demonstrated in the infliximab group from Weeks 24 to 54 (mean change = -0.24), but less than that observed during the first 24 weeks of the trial (mean change = -0.70). The placebo crossover subjects (received infliximab from Weeks 24 to 54) demonstrated less mean changes (-0.29) compared with infliximab subjects from Weeks 0 to 24. The change from baseline in the total modified vdH-S score was significant in favor of infliximab for both central x-ray readers at both Weeks 24 and 54. The global assessment confirmed that changes in the total modified vdH-S score were clinically meaningful.

The infliximab treatment group maintained responses through Week 54 for endpoints evaluating the signs and symptoms of arthritis, physical function, skin disease, and quality of life. The proportion of subjects in the infliximab group who achieved an ACR 20 response at Week 54 was 53.0% compared with 54.0% at Week 24. The proportion of subjects in the infliximab group who achieved PsARC at Week 54 was 74.4% compared with 70.0% at Week 24. The proportion of subjects in the infliximab group (with BSA ≥ 3% at baseline) who achieved ≥ 75% improvement in Psoriasis Area and Severity Index (PASI) from baseline at Week 54 was 48.8% compared with 60.2% at Week 24. The median improvement from baseline in the SF-36 physical component summary score for the infliximab group was maintained from Week 24 (6.9) to Week 54 (7.4). The median improvement from baseline in the SF-36 mental component summary score for the infliximab group was also maintained from Week 24 (2.8) to Week 54 (2.8). A major clinical response (defined as achieving an ACR 70 response for 24 consecutive weeks) was achieved by 12.1% of infliximab-treated subjects at Week 54.

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At Weeks 14, 24, and 54, the proportion of subjects in the infliximab group who achieved ≥ 0.3 units decrease in HAQ was 58.0%, 54.0%, and 58.9%, respectively. In subjects who achieved ≥ 0.3 units decrease in HAQ at Week 14 or at Week 24, 74.1% and 88.9%, respectively, maintained this decrease at Week 54.

At Week 24, the change from baseline in the total modified vdH-S score correlated with infliximab concentration. However, at Week 54, infliximab concentrations were not as predictive of the change from baseline in total modified vdH-S score. Clinical response (ie, achievement of ACR 20 response) was associated with the need to obtain detectable serum infliximab levels (≥ 0.1 μg/mL).

**Safety Results:** The safety profile of infliximab through Week 54 was consistent with the safety profile observed through Week 24.

The proportion of subjects experiencing an AE was 84.8% in the combined infliximab group (average duration of follow-up of 42.8 weeks). The most frequently reported AE was upper respiratory tract infection, which occurred in 23.6% of subjects in the combined infliximab group. The frequency of AEs in the combined infliximab group was similar between subjects who received MTX and who those who did not receive MTX at baseline.

The number of subjects experiencing an SAE was 22 (11.5%) in the combined infliximab group. The most frequently reported SAEs in infliximab-treated subjects were arthritis and bone fracture (each reported by 3 subjects). One subject experienced an SAE following dose escalation (arterial stenosis).

Sixteen subjects in the combined infliximab group permanently discontinued study agent infusions due to an AE. Elevated liver function tests (LFTs) were the most frequent reasons for discontinuing infliximab treatment (7 subjects).

The proportion of subjects who had at least 1 infection was 55.0% in the combined infliximab group; upper respiratory tract infection was the most common infection. The frequency of infections in the combined infliximab group was similar in subjects who received MTX and who did not receive MTX at baseline.

Serious infections occurred in 2 (2.0%) subjects in the placebo group (cellulitis and bronchitis), and 3 (3.0%) subjects in the infliximab only group (infectious hepatitis, cellulitis and pneumonia). Despite the discrepancy in follow-up between the placebo groups, there was not an increased occurrence of serious infections in the infliximab group. There were no events of tuberculosis (TB) or potential opportunistic infections.

The infusion reaction rate with infliximab infusions was 2.1% for the combined infliximab group; 11.5% of subjects in this group had an infusion reaction. The majority of infusion reactions were mild in intensity; there were no serious infusion reactions. There were no possible anaphylactic reactions or possible delayed hypersensitivity reactions.

There were 2 malignancies: 1 basal cell carcinoma (placebo only subject) and 1 Stage I Hodgkin's lymphoma (infliximab only subject). There was 1 case of leukopenia, a hematologic event, and 3 neurologic events of interest. There were no autoimmune disorders, central demyelinating events, or occurrences of CHF.

Treatment with infliximab had no clinically significant adverse effects on hematologic values. With the exception of elevations in ALT/SGPT and AST/SGOT, the proportion of subjects with markedly abnormal postbaseline chemistry values was very low and comparable between treatment groups. Markedly abnormal ALT/SGPT and AST/SGOT values occurred in 8 (4.2%) and 4 (2.1%) subjects, respectively, in the combined infliximab group. A markedly abnormal GGT value was reported in 3.7% of subjects in the combined infliximab group. No subjects had a markedly abnormal total bilirubin. Infliximab treated subjects with elevations in ALT/SGPT or AST/SGOT did not develop liver failure. More infliximab-treated subjects not

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receiving MTX at baseline had a markedly abnormal ALT/SGPT or AST/SGOT as compared with infliximab-treated subjects receiving MTX at baseline. Similarly, more subjects in the combined infliximab group who were not receiving MTX at baseline had an ALT/SGPT or AST/SGOT value that shifted from normal to high.

The proportion of subjects who were newly positive for antinuclear antibodies (ANA; defined by ≥ 1:160 titer) through Week 66 was 41.3% in the combined infliximab group. The proportion of these subjects who became newly positive for anti-dsDNA antibodies was 8.6% in the combined infliximab group.

Among the combined infliximab group, 15.4% were positive for antibodies to infliximab through Week 66. In subjects receiving MTX at baseline, 3.6% tested positive for antibodies to infliximab compared with 26.1% who were not receiving MTX at baseline.

**Conclusions:** Infliximab administered as 5 mg/kg infusions at Weeks 0, 2, and 6 and every 8 weeks through Week 46, inhibited structural damage, improved physical function, and induced major clinical response in subjects with active PsA. Specifically, infliximab:

- Inhibited structural damage as early as Week 24 and continued to improve through Week 54.
- Demonstrated sustained effect of the reduction in the signs and symptoms of arthritis through Week 54. Similar efficacy was observed in subjects with or without baseline MTX usage.
- Demonstrated achievement of a major clinical response at Week 54
- Demonstrated sustained effect in PsA specific features of dactylitis and enthesopathy.
- Maintained physical function improvement through Week 54.
- Demonstrated sustained effect in psoriatic skin disease improvement through Week 54. Comparable efficacy was observed irrespective of baseline MTX usage.
- Demonstrated sustained effect of improvement in the physical and mental aspects of health-related quality of life through Week 54.
- Was generally well tolerated with an accepted safety profile in subjects treated up to 54 weeks. The slightly increased incidence of markedly abnormal transaminase levels observed through 24 weeks of treatment was not significantly increased with an additional 30 weeks of treatment.

**Date of Report:** 03 Aug 2005

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