Synopsis

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

Protocol: CR003136 **EudraCT No.:** Not Applicable

Title of the study: Open-label, Pilot Protocol of Patients with Rheumatoid Arthritis Who Switch to Infliximab after Incomplete Response to Etanercept: Final Report

Principal/Coordinating Investigator(s): Multicenter

Site #	Investigator	Site Name/Address	Number of Subjects Randomized
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002	Gary Feldman, M.D.	Arthritis Medical Center, Inc. 5230 Pacific Concourse Drive Suite 100 Los Angeles, CA 90045	0
003	Gary Williams, M.D.	Scripps Clinic and Research Foundation 10666 North Torrey Pines Road MD# MS113 La Jolla, CA 92037	0
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005	Norman Gaylis, M.D.	2845 Aventura Boulevard Suite 100 Aventura, FL 33180	7
006	Michael Weisman, M.D. Daniel Wallace, MD	Cedars-Sinai Medical Center 8700 Beverly Blvd., Suite B131 Los Angeles, CA 90048	2
007	Vance Bray, M.D.	Denver Arthritis Clinic 200 Spruce Street, #100 Denver, CO 80230	5
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009	Daniel Furst, M.D. Dinesh Khanna, MD	University of California Los Angeles Division of Rheumatology Department of Medicine 32-59 Rehabilitation Center 1000 Veteran Avenue Los Angeles, CA 90095-1670	2[a]

[a] One subject at this study site was randomized but withdrew consent before receiving first study agent administration.

Study Center(s): 9 US Study Centers, with 7 Enrolling Centers

Publication (reference): Furst et al, 2005; Rojas et al, 2005

Studied Period: 05-Sep-2003/12-Nov-2004 | **Phase of Development:** 3B

Objectives: 1. To evaluate safety and evidence of therapeutic benefit of infliximab plus methotrexate (MTX).
2. To evaluate the pharmacokinetics profiles of infliximab and etanercept.
3. To evaluate antibodies to infliximab and antibodies to etanercept.
4. To evaluate whether switching from etanercept to infliximab alters progression of structural damage over the study period.
5. To evaluate whether candidate serologic markers correlate with therapeutic response or benefit.

Methodology: The study was a multi-center, randomized, exploratory study, designed to evaluate safety and evidence of the therapeutic benefit of infliximab plus MTX in subjects with rheumatoid arthritis (RA) who had an incomplete response to etanercept plus MTX. The study was to be conducted at approximately 9 clinical study sites in the US. The randomized population was to consist of approximately 24 subjects with RA who had achieved some therapeutic benefit, but an incomplete response (as evidenced by a minimum of 9 tender and 6 swollen joints), after a minimum 3-month period of therapy with etanercept and concomitant MTX. Eligible subjects were randomized in a 1:1 ratio to the infliximab plus MTX treatment group (Group 1) or the etanercept plus MTX treatment group (Group 2). Subjects were evaluated on their randomized therapies for a period of 16 weeks. At the week 16 visit, subjects that had been randomized to the etanercept group at week 0 and that were experiencing an incomplete response, were able to initiate treatment with infliximab (Group 2b) for an additional four weeks; subjects that did not cross over, continued etanercept and MTX therapy to week 30. Subjects in the infliximab group were to continue the randomized treatment regimen through week 22. All subjects were followed for 30 weeks for efficacy. A safety follow up was conducted at week 35.

Number of Subjects (Planned and Analyzed): 24 subjects were planned, 28 subjects were analyzed

Diagnosis and Main Criteria for Inclusion: Subjects with RA who had a minimum of 9 tender and 6 swollen joints and who had been receiving stable doses of etanercept and MTX

Test Product, Dose and Mode of Administration, Batch Number: Subjects in the infliximab only group (Group 1) received intravenous infusions of 3 mg/kg of infliximab at weeks 0, 2, 6, 14, and 22. Subjects in the etanercept group (Group 2) who crossed over to infliximab (Group 2b) received intravenous infusions of 3 mg/kg of infliximab at weeks 16, 18, and 22. The following batches of infliximab were used during the study: 01J084 and 03A051.

Duration of Treatment: Up to 30 weeks for etanercept; 22 weeks for infliximab

Reference Therapy, Dose and Mode of Administration, Batch Number: Etanercept 25 mg subcutaneous injections twice weekly from week 0 to week 16 and, if continuing on Etanercept, from week 16 to week 30. See Appendix 8 (Appendix not attached) for batches of etanercept used during the study.

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Criteria for Evaluation: The Intent-to-Treat population (all subjects who were randomized and received one or more doses of study medication) was used for efficacy, pharmacology, and immunogenicity assessments. The Safety Population (ie, subjects who signed informed consent) was used for all safety analyses. Subjects who signed informed consent and did not receive study treatment after randomization were analyzed and summarized separately.

Pharmacokinetics/Pharmacodynamics: Serum concentrations and pharmacokinetic (pk) parameters (Cmax, tmax, and AUC0-t) for infliximab and etanercept; antibodies to infliximab and etanercept, anti-double stranded DNA, anti nuclear antibodies, and other markers of immune response and inflammation.

Efficacy: Tender joint counts (TJC), swollen joint counts (SJC), and total joint counts; duration of morning stiffness; subject pain, fatigue, and global disease assessments by visual analogue scale (VAS), physician's global disease assessment by VAS, treatment regimen assessment, Health Assessment Questionnaire (HAQ), Beck Depression Index (BDI), Short Form-36 Health Assessment Questionnaire (SF-36), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), ACR20, ACRn, Disease Activity Score based on 28 joints (DAS28), radiographic assessments of the hands and feet for computation of van der Heijde Modified Sharp scores (vdH-S), and magnetic resonance imaging (MRI) assessments of the most severely affected hand.

Safety: Adverse events (AEs), vital signs, and laboratory testing.

Statistical Methods: As this was an exploratory study, no formal hypothesis testing was planned and primary and secondary endpoints were not identified. Descriptive statistics, such as mean, median, standard deviation, minimum and maximum were prepared for continuous variables, and counts and percentages were prepared for categorical variables. For efficacy, pharmacology, and immunogenicity assessments data were analyzed according to the assigned treatment. For safety assessments, data were analyzed according to the treatment actually received.

SUMMARY – CONCLUSIONS

Study Population Results: The majority of the 27 subjects that were randomized and treated (infliximab: 13, etanercept: 14) were female (93%) and Caucasian (67%). Ages ranged from 24 to 77 years (median: 44 years) and weights ranged from 51 kg to 107 kg (median: 76 kg) with similar distributions for the 2 randomized treatment groups. The median duration of RA for the infliximab group was 4 years and the median duration for the etanercept group was 9 years. Other baseline clinical and radiographic characteristics for the 2 randomized treatments were similar, except that subjects treated with etanercept had a higher van de Heijde Modified Sharp sore at baseline than the subjects treated with infliximab. These disparities between the populations of the 2 randomized treatments were most likely due to the small sample size, but were not deemed to affect the overall interpretation of the results from the study.

Pharmacokinetic/Pharmacodynamic Results: Overall, the levels of infliximab found in the subjects in the different treatment groups reflected the infliximab treatment to which these subjects were exposed. The pharmacokinetic profiles of infliximab in this study were similar to other published pharmacokinetic profiles for this drug, and etanercept injection did not alter the pharmacokinetic profile of infliximab. Group 2a subjects maintained etanercept throughout week 30.

Pharmacodynamic analyses suggest that there are differential effects of infliximab and etanercept on markers of inflammation and bone resorption. After 14 weeks of treatment, levels of vascular endothelial growth factor (VEGF) decreased from baseline for all treatment groups. There were comparable reductions from baseline values of intracellular adhesion molecule-1 (ICAM-1) in Groups 1 (-11.1%) and 2b (-11.7%), whereas there was a slight increase in ICAM-1 (2.7%) in Group 2a. C-telopeptide-1 (CTX-1) increased in all groups. Col 2-3/4C long mono cartilage biomarker (C2C) decreased in Group 1, and the modulation of C2C and osteocalcin

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was very different between Group 2b and Group 2a at week 14.

By week 30, Group 1 subjects had a reduction from baseline in ICAM-1 (-7.0%), MMP-3 (-7.1%), VEGF (-7.4%), C2C (-4.7%), CTX-1 (-13.0%), and osteocalcin (-13.5%). Group 2a subjects at 30 weeks showed reduction in MMP-3 (-18.4%), C2C (-19.2%), CTX-1 (-3.1%), little change in VEGF (0.7%), and an increase in ICAM-1 (31.8%) and osteocalcin (21.7%). There were too few subjects with assay values above the lowest limit of quantification (LLOQ) to make any statements regarding the chemokine interleukin-8 (IL-8).

Efficacy Results: Efficacy assessments conducted in this study suggested that infliximab plus MTX provided clinical benefit to subjects who failed to respond to etanercept plus MTX. The improvements seen at week 16 in the infliximab group appeared to moderate somewhat after week 16, however, at week 30 assessed parameters generally continued to show improvement over baseline levels. Subjects switching to infliximab at week 16 (Group 2b) showed improvements in nearly all efficacy parameters at the week 30 visit.

Summary of Clinical Assessment Results: After 16 weeks of randomized treatment, the percentage of subjects in the infliximab group having an incomplete response to therapy (21%, 3/13) was less than half the percentage in the etanercept group who had an incomplete response (50%, 7/14).

The percentage of patients achieving an ACR20 response at week 16 was over 2-fold greater for the infliximab group (62%, 8/13 subjects) than for the etanercept group (29%, 4/14 subjects). At week 30, the percentage of patients achieving an ACR20 response for the infliximab group and Group 2b were 31% (4/13 subjects) and 50% (3/6 subjects), respectively. For Group 2a, the response rate was 60% (3/5 subjects) at week 30.

The median ACRn scores at week 16 indicated 28% improvement for the infliximab group compared to 12% deterioration for the etanercept group. At week 30, the median ACRn scores for the infliximab group and Group 2a were 10% improvement and 27% improvement, respectively. For Group 2b, the median week 16 ACRn score of 49% deterioration, increased by week 30 to an ACRn of 20% improvement.

The median reductions in DAS28 scores at week 16 showed a 2-fold improvement for the infliximab group (-1.6, -34%) than for the etanercept group (-0.8, -12%). Additionally, DAS28 scores indicated that there were 2 subjects in the infliximab group (2/13) and 1 patient in the etanercept group (1/14) who attained a DAS28 <2.6. At week 30, DAS28 results indicated that there were 0 subjects in the infliximab group (0/10) and infliximab cross-over group (0/5) and 2 subjects in the etanercept group (2/5) who attained a DAS28 <2.6. Median DAS28 baseline values for infliximab and etanercept were 5.9 and 6.5, respectively. At week 30, the DAS28 scores for the infliximab group and Group 2a indicated median reductions of 1.4 (-25%) and 1.5 (-25%), respectively. For Group 2b, the DAS28 reduced from a median value of 6.4 at week 16 to a median value of 5.3 at week 30, reflecting a median reduction from baseline of 1.6 (-26%). Median baseline values for Group 2a and Group 2b were 6.2 and 6.1, respectively.

The percentages of subjects preferring the current treatment regimen to the previous, as evidenced by responses at week 14 of "slightly better", "better", or "much better than the previous regimen", was 62% (8/13 subjects) in the infliximab group and 43% (6/14 subjects) in the etanercept group. At week 30, 100% (6/6) of subjects in Group 2b preferred the new infliximab regimen.

Clinical assessments of RA symptoms and markers of disease activity indicated greater median percent improvement at week 16 for the infliximab group than for the etanercept group for all clinical parameters. The improvements seen at week 16 in the infliximab group moderated after week 16, through week 30, but continued to show improvement over baseline levels. Group 2b also showed improvements in these parameters at the week 30 visit, with median percentage improvement ranging from 7% to 74% for these clinical assessments.

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HAQ Disability Index and SF-36 Physical Function/Domains: Greater improvements from baseline were observed for the infliximab group than for the etanercept group in the HAQ disability index at week 16 and SF-36 physical component summary (PCS) as well as most of the individual physical domains at week 14. Additionally, a greater percentage of infliximab subjects showed clinically meaningful reductions in HAQ scores (>0.22 reduction) at week 16 than did etanercept subjects.

The medians of the changes from baseline to week 16 indicated a 46% improvement in HAQ disability index for the infliximab group compared to no improvement for the etanercept group. Additionally, there were more subjects at week 16 with clinically meaningful HAQ index reductions in the infliximab group (8/13, 62%) than in the etanercept group (2/14, 14%). At week 30, the infliximab group maintained a 5% improvement over baseline HAQ score while Group 2a increased to a median improvement of 22%. At week 30, 31% (4/13) of the infliximab group and 60% (3/5) of Group 2a achieved clinically meaningful HAQ score reductions. For Group 2b, the HAQ score at week 30 indicated 11% improvement over the baseline value.

The medians of the changes from baseline to week 14 indicated a 13% improvement in SF-36 PCS score for the infliximab group compared to 9% improvement for the etanercept group. Similar or greater differences in medians of percent change from baseline to week 14 were observed between the infliximab and etanercept groups for the individual physical domains of role-physical, body pain, and general health. Neither group showed a change in median value at week 14 for the physical function domain.

Beck Depression Inventory and SF-36 Mental Function/Domains: Greater improvements from baseline to week 14 were observed for the infliximab group than for the etanercept group in the BDI and SF-36 mental component summary (MCS) as well as all of the individual mental health domains.

The medians of the changes from baseline to week 14 indicated a 50% improvement in BDI score for the infliximab group compared to a 10% improvement for the etanercept group. At week 30, the infliximab group maintained a 32% improvement over baseline BDI score while Group 2a increased to a median improvement of 29%. For Group 2b, the BDI at week 30 indicated a 6% improvement over the baseline value.

The medians of the changes from baseline to week 14 indicated a 13% improvement in SF-36 MCS score for the infliximab group compared to 1% deterioration for the etanercept group. Similar differences in medians of percent change from baseline to week 14 were observed between the infliximab and etanercept groups for all individual mental health domains. Comparisons between the infliximab group and Group 2a and Group 2b at week 30 were difficult to interpret due to the small sample size in these groups.

Summary of X-Ray and MRI Results: The medians of the changes from baseline x-rays of the hands and feet, or hands and feet combined, did not show clinically meaningful results in terms of erosions, joint space narrowing (JSN), or vdH-S score for any of the treatment groups at week 14 or week 30. However, a higher percentage of subjects in the infliximab group had no evidence of radiographic progression (ie, no increase in radiographic score) and no evidence or radiographic worsening (ie, >0.5 reduction) between weeks 0 and 14 than did the etanercept group for total vdH-S score (no progression: infliximab 67%, etanercept 50%; no worsening: infliximab 83%, etanercept 75%) and total JSN score (no progression: infliximab 75%, etanercept 58%; no worsening: infliximab 83%, etanercept 75%). For total erosions, a higher percentage of subjects in the infliximab group had no evidence of progression between weeks 0 and 14 (infliximab 67%, etanercept 58%), however the percentage of subjects with no radiographic worsening of total erosions between week 0 and week 14 was higher in the etanercept group (100%) than in the infliximab group (83%).

Additionally, the median annualized progression rate in total vdH-S score from week 0 to week 14 and from week 0 to week 30 was 0.0 for both time periods with the infliximab group. The median annualized progression rate in total vdH-S score from week 0 to week 14 was 0.9 for the etanercept group as a whole and 0.0 for Group 2a. Median annualized progression for Group 2b was 1.9 between week 0 and week 14 and 0.8 between week 14 and week 30. The median annualized progression rate for Group 2a from weeks 0 to 30

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was –0.9.

Results of MRI assessments, as reflected by the derived total MRI score, suggested less worsening in total MRI score for the infliximab group (7%) than for the etanercept group (10%) at week 14. Results with the derived total MRI collapsed score reflected the same pattern as those of the total MRI score.

The MRI assessed numbers of erosions, JSN, synovial thickening (ST), erosion volumes, erosion shapes, and signal intensities assessments using T1 and STIR methods did not provide a clear pattern for either the infliximab or the etanercept groups through the week 14 time point.

Summary of Correlations Between Clinical and Radiographic Assessments: Correlation tests of vdH-S scores at week 14 and total number of MRI-assessed erosions at week 14 showed strong positive correlations with coefficients of 0.6463 for infliximab and 0.8285 for etanercept. A strong positive correlation was also observed for Group 2a and Group 2b between the vdH-S score at week 30 and total erosions at week 30 (ie, over 80% correlation for Group 2a and nearly 60% correlation for Group 2b).

Correlation testing between the number of MRI-assessed erosions and ACR20, CRP, SJC, and TJC did not provide any clear patterns that were suggestive of correlation between these parameters.

Correlation analyses between total MRI score at baseline and the baseline vdH-S score suggested positive correlation between the metrics for both treatment groups (infliximab: 0.5746, etanercept: 0.7939). Similar results were obtained for the correlation between baseline total MRI score and baseline selected vdH-S score. Correlation between the baseline total MRI score and the median of percent change from baseline to week 14 in vdH-S score was not apparent nor was a correlation between the medians of percent change from baseline to week 14 for total MRI score and the medians of percent change from baseline to week 14 for total vdH-S score. Results with the derived total MRI collapsed score reflected the same pattern as those of the total MRI score.

Safety Results: During the first 15 weeks of the study, 7 of 13 (54%) infliximab subjects and 7 of 14 (50%) etanercept subjects reported 1 or more AEs. Between week 16 and week 35, 4 of 13 (31%) infliximab subjects and 2 of 6 (33%) Group 2b subjects reported 1 or more AEs. For the entire safety follow up period (ie, weeks 0 through 35) 11 of 13 (85%) infliximab subjects and 2 of the 5 (40%) Group 2a subjects reported 1 or more AEs. Nearly all reported AEs were mild or moderate in intensity.

AEs related to study treatment during the first 15 weeks of the study were reported for 2 of 13 (15%) infliximab subjects and 1 of 14 (7%) etanercept subjects. Between week 16 and week 35, none of the subjects in the infliximab group and 1 of 6 (17%) Group 2b subjects reported treatment-related AEs. For the entire safety follow up period, 2 of 13 (15%) infliximab subjects and 1 of 5 (20%) Group 2a subjects reported treatment related AEs.

The most commonly occurring AE was aggravated rheumatoid arthritis. This was the only AE that was reported by more than 1 subject in any of the treatment groups (infliximab 2/13, 15%; etanercept through week 15: 1/14, 7%; and Group 2a from week 16 through week 35: 2/6, 33%).

Treatment-emergent serious adverse events (SAEs) involved 1 of 13 (8%) subjects in the infliximab group, 2 of 14 (14%) subjects in the etanercept group prior to week 16, and 1 of 5 (20%) subjects in Group 2a after the week 16 visit. None of these SAEs were deemed to be related to study treatment.

AEs requiring discontinuation of study treatment involved 2 of 13 subjects (15%) in the infliximab group and 1 of 14 subjects (7%) in the etanercept group prior to week 16.

Infliximab infusion reactions involved 1 of 13 (8%) subjects in the infliximab group and 2 of 6 (33%) subjects in Group 2b on or after the week 16 visit. All infusion reactions were acute in nature (ie, occurred within 1 hour after the start of the infusion). Additionally, 1 of 13 (8%) subjects in the infliximab group experienced a possible anaphylactic reaction. No AEs meeting the definition of delayed hypersensitivity were reported.

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Etanercept injection reactions involved 1 of 14 etanercept subjects (7.1%) prior to week 16. No other injection reactions were reported.

No apparent trends in routine laboratory parameters or vital signs were noted for any of the treatment groups. There were a few subjects that had markedly abnormal sporadic hematologic cell counts; ie, 1 of 13 (8%) subjects in the infliximab group and 2 of 14 (14%) subjects in the etanercept group prior to week 16. Additionally a few subjects exhibited markedly abnormal sporadic systolic blood pressure: 3 of 13 (23%) subjects in the infliximab group; markedly abnormal diastolic blood pressure: 1 of 13 (8%) subjects in the infliximab group; or markedly abnormal pulse: 1 of 13 (8%) subjects in the infliximab group.

Development of antinuclear antibodies (ANAs) was observed for 2 of 13 (15%) subjects in the infliximab group. All other subjects in the infliximab group were either positive at baseline (n=4, 31%), negative at baseline and remained negative throughout the study (n=5, 39%), or not tested at baseline (n=2, 15%). For subjects in the etanercept group, 4/14 (29%) were positive at baseline but no other subjects were positive at any time during the trial.

Of the 11 subjects in the infliximab group that were tested for ds-DNA antibodies, all were negative at baseline and remained negative throughout the study. Of the 13 subjects in the etanercept group who were evaluated, one was positive for ds-DNA antibodies at baseline.

Antibodies to infliximab were observed for 1 of the 11 tested subjects (9%) in the infliximab group, and for 2 of 6 (33%) Group 2b subjects. The observed titers for these subjects were low and ranged from 1:10 to 1:40. No infusion reactions were observed in these subjects. For 2 of the 3 subjects testing positive for infliximab antibodies, a clinical response greater than ACR50 was achieved. The 3rd subject did not achieve ACR20.

Antibodies to etanercept were assayed, but none were found.

Conclusions: This randomized, active-controlled, exploratory study provides evidence of the beneficial clinical and radiographic effects of a switch to infliximab therapy for rheumatoid arthritis subjects who are etanercept incomplete responders.

• Subjects who switched from etanercept to infliximab showed an improvement in signs and symptoms of RA.

• For subjects that were treated with etanercept and demonstrated an incomplete response after 16 weeks of therapy, a switch to infliximab infusions reduced the median annualized total vdH-S score progression rate by 50% after 3 infusions. With 30 weeks of infliximab therapy (ie, 5 infusions) the median annualized progression rate was 0.

• Both infliximab and etanercept therapies were well tolerated, both had similar AE incidences, and no unexpected adverse effects from either treatment were observed.

• The pharmacokinetic profiles of both infliximab and etanercept were comparable to previously published results.

• Inflammatory and bone/cartilage metabolism markers are differentially affected by infliximab and etanercept.

Date of Report: 02 March 2006