Synopsis (C0168T44 EXPRESS II)

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: C0168T44	**EudraCT No.:** 2004-000553-30
Title of the study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of Infliximab Induction Therapy Followed by Multiple Regimens of Maintenance Infliximab Therapy in Subjects with Plaque-type Psoriasis – Final	
Principal/Coordinating Investigator: Alan Menter, MD – Texas Dermatology Research Institute, 5310 Harvest Hill Road, Suite 255, Dallas, TX 75230, US	
Study Center(s): 63 centers (41 in the US, 15 in Canada, 2 in Austria, 2 in Italy, 3 in France)	
Publication (reference): None	
Studied Period: 25 Sep 2003 to 06 Apr 2005	**Phase of Development:** 3
Objectives: The primary objective was to determine the efficacy of 3 mg/kg and 5 mg/kg infliximab induction therapy compared with placebo. The secondary objectives were to assess the efficacy of 4 regimens of maintenance infliximab therapy, the effects of infliximab on quality of life, and the safety of infliximab therapy.	
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study with 2 doses of infliximab (3 mg/kg or 5 mg/kg administered by intravenous [IV] infusion). The initial randomization allocated subjects to 1 of 3 treatment groups (3 mg/kg, 5 mg/kg infliximab, or placebo) for Weeks 0 through 10 (induction phase), stratified by investigational site. All treatment groups received a study infusion at Weeks 0, 2, and 6. Stratified by Psoriasis Area and Severity Index (PASI) response status at Week 10 and investigational site, subjects in the initial active treatment groups underwent a second randomization at Week 14 to either fixed therapy every 8 weeks (q8wks) or as needed (PRN) therapy. For both infliximab maintenance regimens (q8wks and PRN), placebo was administered at visits when subjects did not receive infliximab in order to maintain the blind. The placebo group was not randomized at Week 14, but crossed over to infliximab 5 mg/kg induction therapy at Week 16, receiving infliximab 5 mg/kg induction therapy in a double-blind fashion at Weeks 16, 18, and 22 followed by regularly scheduled maintenance therapy (infliximab 5 mg/kg q8wks). Subjects were treated through Week 46 and followed for routine efficacy and safety assessments through Week 50, with 1 additional visit at Week 66 to measure antibodies to infliximab.	
Number of Subjects (Planned and Analyzed): 800 (300 infliximab 3 mg/kg, 300 infliximab 5 mg/kg, and 200 placebo) planned; 835 randomized; 835 analyzed for efficacy**,** 834 analyzed for safety, and 178 analyzed for pharmacokinetics.	
Diagnosis and Main Criteria for Inclusion: Men or women 18 years of age or older with a diagnosis of plaque-type psoriasis at least 6 months prior to screening, and who were candidates for phototherapy or systemic therapy. Subjects must have had a PASI score ≥ 12, and at least 10% of their total body surface area (BSA) involved.	
Test Product, Dose and Mode of Administration, Batch Number: 3 mg/kg or 5 mg/kg administered by IV infusion at Weeks 0, 2, and 6 during the induction phase. Study agent was administered during the maintenance phase (beginning at Week 14) q8wks for infliximab subjects on regularly scheduled maintenance therapy; or at visits when subjects did not achieve ≥ 75% improvement in PASI from baseline for infliximab subjects randomized to infliximab PRN maintenance therapy. Subjects in the placebo group crossed over to infliximab 5 mg/kg therapy at Week 16, and received infliximab 5 mg/kg in a double-blind fashion at Weeks 16, 18, and 22, followed by infliximab 5 mg/kg q8wks. Batch numbers: 01J084, 03A051, 03E087, 03K101, and 03K102.	

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Duration of Treatment: 46 weeks of treatment, with final efficacy and safety evaluations performed at Week 50, and final antibody to infliximab evaluation performed at Week 66. Data through Week 50 are presented in this report. The antibody to infliximab data collected through Week 66 will be presented in a separate report.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo was administered by infusion at Weeks 0, 2, and 6 during the induction phase for subjects randomized to placebo. Placebo was administered in the maintenance phase to subjects randomized to placebo at Weeks 14, 26, 34, and 42. Subjects on infliximab q8wks maintenance were administered placebo at Weeks 16, 18, 26, 34, and 42; and subjects on infliximab PRN maintenance therapy were administered placebo at Week 16 and when not receiving infliximab at remaining visits (achieved ≥ 75% improvement in PASI). Batch numbers: 01G062, 03C157, 03D097.

Criteria for Evaluation: The primary efficacy and some of the secondary efficacy analyses were based on all subjects who were randomized. Subjects were included in the efficacy analyses according to their assigned treatment group regardless of whether or not they received the assigned treatment. Most of the efficacy analyses for the maintenance phase (Week 14 and onwards) were based on subjects who were randomized at Week 14 as responders and had evaluable outcome measurements. For subjects randomized to placebo, only subjects who crossed over to receive infliximab were included in the efficacy summaries after Week 16. Safety analyses included all subjects who received study treatment by the actual treatment received.

Pharmacokinetics/Pharmacodynamics: In a subset of subjects, blood samples were collected at specified timepoints for determination of infliximab concentration over time. Infliximab preinfusion serum concentration was summarized over time. Biopsies were collected at baseline, Day 3, and Week 10 to assess the pharmacodynamic effects of infliximab.

Efficacy: The primary endpoint was the proportion of subjects who achieved ≥ 75% improvement from baseline in PASI at Week 10. Efficacy assessments included PASI, Physician's Global Assessment of Disease (PGA), the Dermatology Life Quality Index (DLQI), the 36-item short form health survey (SF-36), and the Economic Questionnaire. In addition, the relationship between serum infliximab concentration and efficacy was examined, as well as between antibodies to infliximab and efficacy.

Safety: Safety was assessed by summarizing the incidence and type of adverse events (AEs) and serious adverse events (SAEs), the proportion of subjects with markedly abnormal laboratory values, the incidence of antibodies to infliximab, and development of antinuclear antibodies (ANA) or anti-double-stranded DNA (anti-dsDNA) antibodies by treatment group.

Statistical Methods: Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. Cochran-Mantel-Haenszel chi-square test or Pearson chi-square tests were used to compare the proportion of subjects responding to treatment. The row mean score chi-square test was used to compare ordinal categorical variables (eg, number of visits at which a subject achieved ≥ 75% improvement in PASI from baseline). Continuous response parameters were compared using an analysis of variance on the van der Waerden normal scores. For these comparisons, the mean squared error was calculated using data from all applicable treatment groups. The primary endpoint analyses were performed at the $\alpha = 0.025$ level for each comparison between individual infliximab dose and placebo. Nominal 2-sided p-values were reported for the secondary analyses.

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SUMMARY OF RESULTS

Study Population Results: The majority of subjects were male (66.3%), most subjects were Caucasian (92.6%), and the median age and weight of subjects were 44.0 years and 88.9 kg, respectively. Demographic characteristics were generally well balanced among treatment groups. The median psoriasis duration for subjects was 16.2 years, median BSA was 23.0%, and median PASI score was 17.8. Subjects showed considerable impairment in quality of life, with a median DLQI of 12.0.

Pharmacokinetic/Pharmacodynamic Results: Serum concentration data of infliximab were available through Week 50 for the 178 subjects who participated in the PK substudy. The infliximab 5 mg/kg group was superior to the infliximab 3 mg/kg group in maintaining detectable preinfusion serum levels of infliximab. Steady-state serum infliximab concentration was achieved by Week 30 for the infliximab 5 mg/kg q8wks group, with a trough level maintained at approximately 1.6 µg/mL to 2.1 µg/mL; the steady-state could not be determined for the infliximab 3 mg/kg q8wks group due to undetectable serum concentrations in most subjects. There was no evidence of accumulation in infliximab concentration over time during the q8wks maintenance regimens.

Infliximab treatment led to decreases in cellular proliferation and subsequent decreases in epidermal thickness and the inflammatory infiltrate within biopsied lesions. Infliximab treatment downregulated the expression of activated CD3+, CD4+ and CD8+ lymphocytes and increased epidermal CD1a-positive cells. There was no evidence of apoptosis.

Efficacy Results: Subjects with moderate to severe plaque-type psoriasis who received infliximab 3 mg/kg or 5 mg/kg induction therapy, followed by maintenance therapy given PRN or on a fixed schedule q8wks, showed significant improvement in psoriasis as measured by PASI score, PGA, and quality of life measures.

- The proportion of subjects achieving a ≥ 75% improvement in PASI from baseline to Week 10 was significantly greater in the infliximab groups (70.3% and 75.5% in the 3 mg/kg and 5 mg/kg groups, respectively) than in the placebo group (1.9%; $p < 0.001$ for each infliximab group versus placebo). Significant response was evident in infliximab-treated subjects as early as Week 2 in both infliximab groups. Significantly more subjects achieved a marked PASI response (≥ 90% improvement) at Week 10 in the infliximab 3 mg/kg group (37.1%) and infliximab 5 mg/kg group (45.2%) than placebo (0.5%; $p < 0.001$ for each infliximab group versus placebo).
- The proportion of subjects who achieved a PGA score of excellent or cleared at Week 10 was significantly greater in the infliximab 3 mg/kg (69.8%) and 5 mg/kg (76.0%) groups than the placebo group (1.0%; $p < 0.001$ for each infliximab group versus placebo).
- By Week 10, both infliximab groups had significant improvement from baseline in DLQI score compared with placebo: a median of -9.0 in the infliximab 3 mg/kg and 5 mg/kg groups, compared with a median of 0.0 (no improvement) in the placebo group ($p < 0.001$ for each infliximab group versus placebo).

During the maintenance phase from Week 16 through Week 50 for all subjects randomized at Week 14, response was better maintained in either of the infliximab q8wks groups compared with the respective infliximab PRN group, with the best response maintained by the infliximab 5 mg/kg q8wks group.

- The proportion of subjects randomized at Week 14 who achieved a ≥ 75% improvement in PASI at Week 50 was 43.8% and 54.5% in the infliximab 3 mg/kg q8wks and 5 mg/kg q8wks groups, respectively, compared with 25.4% and 38.1% in the infliximab 3 mg/kg PRN and 5 mg/kg PRN groups, respectively.

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Safety Results: Infliximab 3 mg/kg or 5 mg/kg administered by infusion to subjects with moderate to severe plaque-type psoriasis was generally well tolerated in the majority of subjects, with a safety profile consistent with previous infliximab studies.

Any AEs: The proportion of subjects who experienced at least 1 AE during the induction phase was higher in the infliximab 3 mg/kg and infliximab 5 mg/kg groups (62.6% and 68.8%, respectively) compared with placebo (56.0%), with comparable proportions of subjects among the 4 infliximab groups reporting AEs from Week 14 through Week 50.

SAEs: There were no deaths during the study through Week 50, and the overall incidence of SAEs was low. During the induction phase, SAEs were comparable between the placebo group (2.4%) and the infliximab 5 mg/kg group (2.9%), and lower in the infliximab 3 mg/kg group (1.0%). During the maintenance phase, SAEs were comparable among the 4 infliximab groups.

Infections: Infections occurred with similar incidence among treatment groups during the induction phase: 30.0% in placebo, 33.9% in infliximab 3 mg/kg, and 30.9% in infliximab 5 mg/kg. During the maintenance phase, incidence of infection was comparable among the 4 infliximab groups. Through Week 50, 2 (0.5%) subjects in the placebo group and 11 (1.4%) subjects in the combined infliximab group had a serious infection, including 2 cases of tuberculosis.

Infusion reactions: During the induction phase, the proportion of infusions with infusion reactions was higher in the infliximab 3 mg/kg group (5.3%) and infliximab 5 mg/kg group (3.4%) compared with the placebo group (2.2%). During the maintenance phase, the number of infliximab infusions with infusion reactions was higher in both infliximab 3 mg/kg groups compared with the infliximab 5 mg/kg groups.

Additional AEs of special interest: There were 12 malignancies reported in infliximab-treated subjects; 9 basal cell carcinomas, 1 squamous cell carcinoma, 1 breast cancer, and 1 adenocarcinoma. There were no central demyelinating disorders, 4 cases of lupus erythematosus (LE) syndrome in infliximab-treated subjects and 1 case in the placebo group, and 1 report of congestive heart failure secondary to volume overload in an infliximab-treated subject.

Laboratory test results: There were no significant differences among treatment groups regarding laboratory test results, except for alanine aminotransaminase/serum glutamate pyruvate transaminase (ALT/SGPT) and aspartate transaminase/serum glutamic oxaloacetic transaminase (AST/SGOT). Through Week 50, there were 40 (4.9%) subjects in the combined infliximab groups who had any markedly abnormal ALT/SGPT values, which were primarily transient; 25 (3.1%) subjects had any markedly abnormal AST/SGOT value. No subject had concomitant hyperbilirubinemia or evidence of liver failure.

Antinuclear Antibodies/Anti-double-stranded DNA Antibodies: The proportion of subjects who were newly positive for ANA through Week 50 was higher in the combined infliximab group (65.0%) compared with placebo (8.3%). The proportions of subjects newly positive for anti-dsDNA antibodies through Week 50 in the combined infliximab group, but who were negative for anti-dsDNA at baseline, was higher in the combined infliximab group (26.8%) compared with placebo (0%). Proportions of subjects who were newly positive for ANA or for anti-dsDNA antibodies were comparable among the 4 infliximab groups.

Antibodies to infliximab: Consistent with earlier studies in psoriasis as well as other indications, the incidence of subjects positive for antibodies to infliximab through Week 50 was higher for the infliximab 3 mg/kg group relative to the infliximab 5 mg/kg group, regardless of whether infusions occurred on a scheduled q8wks or PRN maintenance schedule. Among infliximab groups, the majority (55.1%) of antibody-positive subjects

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presented with titers ≤ 1:40.

CONCLUSIONS:

Infliximab, administered to subjects with moderate to severe plaque-type psoriasis as 3 mg/kg or 5 mg/kg infusions at Weeks 0, 2, and 6, followed by maintenance therapy q8wks or PRN, when compared with placebo administered on the same schedule for 14 weeks, demonstrated:

- Consistent evidence of initial high efficacy
  - Infliximab administration of 3 mg/kg or 5 mg/kg resulted in rapid, significant, and substantial improvement in psoriasis, with a maximum response measured by both PASI and PGA at Week 10. The improvement in PASI was consistent across all subgroups, including both the moderate and severe populations.
  - Infliximab rapidly and significantly improved quality of life as evaluated by both DLQI and the mental and physical components of SF-36 at Week 10, paralleling PASI response
- Through Week 50, response was best maintained by infliximab in the 5 mg/kg q8wks regimen as shown by PASI, PGA, and DLQI results.
- A relationship between clinical response and infliximab exposure was observed, with overall higher proportions of subjects achieving a response as the preinfusion serum levels of infliximab increased.
- Consistent with earlier studies in psoriasis as well as other indications, the incidence of subjects positive for antibodies to infliximab through Week 50 decreased as the dose of infliximab increased from 3 mg/kg to 5 mg/kg, regardless of whether infusions occurred on a scheduled q8wks or PRN maintenance schedule.
- Infliximab therapy at both 3 mg/kg and 5 mg/kg was generally well tolerated in the majority of subjects having moderate to severe psoriasis.
- The safety profile was generally consistent with infliximab use in other populations. The safety profile was consistent among the 4 maintenance groups, with the exception of increased infusion reactions with both infliximab 3 mg/kg regimens.
- Results indicated an increased incidence of aminotransferase elevations. No dose-related trend was observed in markedly abnormal ALT/SGPT values, and aminotransferase elevations were reversible and not associated with concomitant markedly abnormal elevations in bilirubin or liver failure.

Date of Report: 04 Aug 2005

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