Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module 5.3.5.1 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

Protocol: C0168T31
Title of the Study: A Phase II, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of Infliximab (REMICADE®) Induction Therapy in Patients with Plaque-type Psoriasis.

Principal Investigator: Alice Gottlieb, MD, PhD, UMDNJ Robert Wood Johnson University

Study Centers: This was a multicenter study with 24 sites across the United States.

Publication (reference): None to date.

Studied Period (years): 27 December 2001 to 06 May 2003 **Phase of Development:** II

Objectives: Primary objective - to determine the safety and efficacy of infliximab induction therapy. Secondary objectives - to assess the immune response to infliximab; to assess the safety of a single retreatment of infliximab at week 26; to characterize the pharmacokinetic profile of infliximab therapy; and to assess the maintenance of response to infliximab induction therapy through week 26.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled pharmacokinetic, efficacy, and safety study of infliximab given as single intravenous (IV) infusions as induction therapy followed by retreatment at week 26 in subjects with a Physician's Global Assessment (PGA) ≥ 3.

Number of Subjects (Planned and Analyzed): 200 planned; 249 analyzed for efficacy (randomized subjects); 248 analyzed for safety and pharmacokinetics (treated subjects).

Diagnosis and Main Criteria for Inclusion: Males or females at least 18 years of age with plaque psoriasis and a Psoriasis Area and Severity Index (PASI) score ≥ 12 with involvement of at least 10% of their total body surface area (BSA), having previously received psoralen plus ultraviolet A light (PUVA) or systemic therapy.

Test Product, Dose and Mode of Administration, Batch Number: Infliximab given in 250 mL infusions, containing either 3 mg/kg or 5 mg/kg, over not less than 2 hours. Two lots (00K052ZC and 00L041ZA) were used during the study.

Duration of Treatment: Subjects received either 3 mg/kg infliximab, 5 mg/kg of infliximab, or placebo infusions at weeks 0, 2, and 6. Subjects with a PGA score of ≥ 3 were eligible to receive an additional infusion of the same treatment at week 26.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo infusions. One lot of placebo (00D053) was used during the study.

Criteria for Evaluation: Pharmacokinetics: Derived pharmacokinetic parameters included the observed maximum serum concentration (Cmax), area under the concentration-time curve from time zero to infinity (AUC), AUC from time zero to the time t calculated according to the trapezoidal rule [AUC(0-t)], dose-normalized AUC (NAUC), and terminal half-life (t1/2 λz), for the 3 mg/kg and 5 mg/kg infliximab groups. Efficacy**:** Efficacy was evaluated by assessment of PASI and PGA at each visit through week 30, and Dermatology Life Quality Index (DLQI) at weeks 0 and 10. The primary endpoint was the proportion of subjects achieving a ≥ 75% improvement from baseline in PASI (PASI responders) at week 10. The major secondary efficacy endpoint was the proportion of PASI responders at week 26. Additional secondary efficacy endpoints were analyzed. Safety**:** Safety was evaluated by assessment of the following: adverse events (AEs); routine laboratory analyses (hematology and chemistry); antibodies to infliximab; immunoglobulin E (IgE) antibodies specific to infliximab;

Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module 5.3.5.1 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

antinuclear antibodies (ANA) and anti-double-stranded DNA (anti-dsDNA) antibodies; and tryptase and total IgE levels.

Statistical Methods: Descriptive statistics, graphical data displays, and subject listings were used to summarize the data. The Pearson chi-square test was used to compare the proportions of subjects achieving an endpoint, eg, the proportion of PASI responders at week 10. For the primary efficacy analysis, a screening test was first performed to compare the combined 3 mg/kg and 5 mg/kg infliximab groups versus the placebo group at a significance level of $\alpha = 0.05$ (2-sided). If the screening test was significant, comparisons were to be performed for each infliximab group versus the placebo group at the same significance level (2-sided). Analysis of variance on the van der Waerden normal scores was used to evaluate change from baseline in DLQI at week 10. Odds ratios and confidence intervals were calculated for the proportion of PASI responders at week 10 for different subgroups (based on demographics, baseline disease characteristics, and prior treatments for psoriasis). All statistical tests were 2-sided, with a significance level of $\alpha = 0.05$. Nominal p-values were reported for secondary efficacy endpoints. Non-compartmental analysis was employed to calculate pharmacokinetic parameters of infliximab using concentration-time data up to 26 weeks. Safety data were summarized using frequency tabulations or listed as appropriate; no inferential analyses were conducted.

SUMMARY – CONCLUSIONS:

Study Population: Of 249 subjects randomized (placebo: 51; 3 mg/kg: 99; 5 mg/kg: 99), 1 subject in the infliximab 3 mg/kg group was not treated due to violation of an inclusion criterion at baseline (BSA < 10%). Most subjects were male (69.9%) Caucasians (86.7%) with a median disease duration of 17.2 years and median baseline psoriasis BSA of 27.0%. The median baseline PASI score was 18.9; 62.2% of subjects had a baseline PGA score of "moderate" and 24.9% had a baseline score of "marked" or "severe." Baseline characteristics were comparable among treatment groups.

Pharmacokinetic Results: A 1.7-fold increase in dose from 3 mg/kg to 5 mg/kg resulted in an approximate 1.7- to 1.8-fold increase in peak serum concentration, indicating an approximate dose-proportional increase in Cpeak. A 1.7-fold increase in dose also resulted in an approximate 1.7- to 2.8-fold increase in the median trough concentrations prior to the second and third infusions, indicating a slightly higher than dose-proportional increase in Ctrough. Infliximab was slowly eliminated from the circulation with a median t1/2 λz of 7.7 days in the 3 mg/kg group and 9.1 days in the 5 mg/kg group. A 1.7-fold increase in dose from 3 mg/kg to 5 mg/kg resulted in an approximate 1.7-fold increase in Cmax (median Cmax of 105.7 and 175.1 µg/mL in the 3 mg/kg and 5 mg/kg groups, respectively), indicating that Cmax increased in an approximately dose-proportional manner. A 1.7-fold increase in dose resulted in an approximate 2.2-fold increase in AUC (median AUC of 2405.0 and 5178.8 µg.day/mL in the 3 mg/kg and 5 mg/kg groups, respectively) and a 2.1-fold increase in the partial AUC from time zero to week 14 [median AUC(0-t) of 2398.9 and 5148.4 µg.day/mL in the 3 mg/kg and 5 mg/kg groups, respectively]. These relationships are in agreement with the comparison of the NAUC, where the median NAUC value in the 5 mg/kg group was approximately 1.3-fold higher than the value in the 3 mg/kg group, indicating that the systemic exposure of infliximab increased in a slightly greater than dose-proportional manner.

Efficacy Results: Primary Endpoint: The proportion of subjects with ≥ 75% improvement in PASI from baseline at week 10 was 79.8% in the combined infliximab group, 71.7% in the 3 mg/kg infliximab group, 87.9% in the 5 mg/kg infliximab group, and 5.9% in the placebo group ($p < 0.001$ for each infliximab versus placebo comparison). Results of the primary efficacy analyses remained consistent in all subgroups. Major Secondary Endpoint: At week 26, the proportion of subjects with ≥ 75%

Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module 5.3.5.1 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

improvement in PASI from baseline decreased to 13.8% and 30.0% in the infliximab 3 mg/kg and 5 mg/kg groups, respectively, compared to 9.5% of placebo subjects. While the combined infliximab group versus placebo group contrast was not statistically significant (p=0.067), the 5 mg/kg group versus placebo group comparison was significant (p=0.010). Despite the statistically significant result, these data indicate that the majority of subjects in the active treatment groups fell below a ≥ 75% improvement in PASI at week 26, and therefore, most would have benefited from additional infliximab treatment prior to week 26 if their response were to be maintained. Other Efficacy Results: At week 4, 35.4% and 47.4% of subjects in the infliximab 3 mg/kg and 5 mg/kg groups, respectively, had achieved ≥ 75% improvement in PASI from baseline compared with none in the placebo group ($p < 0.001$ for each infliximab versus placebo comparison). Maximum response, as measured by a ≥ 75% improvement in PASI, was observed at week 10 among subjects in both infliximab groups. Subjects in the 3 mg/kg group began to lose response after week 10, although a majority of subjects were still PASI responders at week 14 (60.6%). In the 5 mg/kg group, subjects had a generally longer remission period, with loss of response beginning after week 14 in some subjects; although, a majority of subjects in the 5 mg/kg group were still PASI responders at week 18 (75.3%). Of those retreated at week 26, the proportion of subjects achieving ≥ 75% improvement in PASI from baseline at week 30 was 23.1% in the infliximab 3 mg/kg group, 34.0% in the infliximab 5 mg/kg group, and 18.2% in the placebo group. Results of the PGA over time were generally consistent with the PASI results over time. The median change from baseline in DLQI at week 10 was -8.0 and –10.0 for the infliximab 3 mg/kg and 5 mg/kg groups, respectively, compared with 0.0 in the placebo group ($p < 0.001$ for all infliximab versus placebo comparisons), demonstrating a substantial improvement in quality of life for subjects on infliximab therapy.

Safety Results: A total of 197 subjects in this study received at least 1 dose of infliximab (3 mg/kg: 98; 5 mg/kg: 99), and 51 subjects received at least 1 dose of placebo. The percentage of subjects with 1 or more AEs was slightly higher in the infliximab-treated groups (3 mg/kg: 77.6%; 5 mg/kg: 78.8%) compared with the placebo group (62.7%). AEs occurring in more than 10% of subjects in the combined infliximab group were upper respiratory tract infection (15.2%), headache (14.7%), pruritus (11.7%), and sinusitis (11.2%). With the exception of sinusitis, the proportion of subjects reporting these events was generally similar between the 3 mg/kg and 5 mg/kg infliximab groups with a lower incidence in the placebo group. Sinusitis occurred more frequently in the 5 mg/kg group (placebo: 7.8%; 3 mg/kg: 4.1%; 5 mg/kg: 18.2%). No subject died during the study. Twelve subjects reported serious adverse events (SAEs): 4 in the infliximab 3 mg/kg group and 8 in the 5 mg/kg group. Four subjects had SAEs that were considered reasonably related to study agent. In the infliximab 3 mg/kg group, 1 subject had squamous cell carcinoma and 1 had cholecystitis and cholelithiasis. In the infliximab 5 mg/kg group, 1 subject had diverticulitis and 1 had sepsis and pyelonephritis. Study infusions were permanently discontinued due to an AE for 11 subjects (7 in the infliximab 3 mg/kg group, 3 in the infliximab 5 mg/kg group, and 1 in the placebo group). A greater percentage of infliximab-treated subjects reported at least 1 infusion reaction (3 mg/kg: 14.3%; 5 mg/kg: 18.2%) during the weeks 0, 2, or 6 infusion compared with the placebo group (2.0%). At week 26, infusion reactions occurred more frequently in the 5 mg/kg group (13.7%) compared with the 3 mg/kg group (7.7%). Throughout the study, there were no events suggestive of a possible anaphylactic reaction. Three subjects had a possible delayed hypersensitivity (serum sickness-like) reaction (2 subjects in the infliximab 3 mg/kg group and 1 subject in the infliximab 5 mg/kg group).

No clinically meaningful adverse trends were identified in evaluations of hematology or clinical chemistry, with the possible exception of aspartate transaminase (AST) and alanine transaminase (ALT). For each of these parameters, a greater percentage of subjects treated with infliximab had increases that

Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module 5.3.5.1 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

met predefined thresholds for a clinically noteworthy shift (AST - placebo: 14.3%; 3 mg/kg: 24.5%; 5 mg/kg: 23.2%; ALT - placebo: 16.3%; 3 mg/kg: 32.7%; 5 mg/kg: 35.4%). Few of these subjects had increases that met the predefined criteria for markedly abnormal (> 150 U/L and ≥ 100% increase for AST or ALT). A total of 4 infliximab-treated subjects had ALT values that were markedly abnormal, 2 of whom had single, isolated values that met these criteria. Similarly, 4 infliximab-treated subjects had AST values that were markedly abnormal, 3 of whom had single, isolated values that were markedly abnormal.

Approximately one-quarter of subjects in each infliximab group were newly positive for ANA during the study; approximately one-half of these subjects were positive for ANA at the last evaluation. Only 1 subject in the placebo group was positive for anti-dsDNA antibodies at the last visit. Through week 26, the incidence of subjects positive for antibodies to infliximab was higher in the 3 mg/kg infliximab group (27.3%) compared with the 5 mg/kg treatment group (19.5%). Only 1 subject had a titer >1:40, presenting with a titer of 1:80. None of the detected antibodies to infliximab were determined to be of the IgE antibody class. The overall incidence of subjects positive for antibodies to infliximab after retreatment at week 26 was similar to the incidence observed in these subjects prior to retreatment (18.3% and 19.7%, respectively). The remaining subjects were antibody to infliximab negative (53, 74.6%) or had inconclusive status (4, 5.6%) after retreatment. Of the 14 subjects positive for antibodies to infliximab prior to retreatment, 8 (57.1%) remained positive following the week 26 retreatment, and this was comparable between the 3 mg/kg and 5 mg/kg groups. Of the 4 subjects identified as antibody to infliximab positive in the 3 mg/kg group, all demonstrated a 2- to 8-fold increase in antibody to infliximab titer. In contrast, in the 5 mg/kg group, only 1 of the 4 antibody to infliximab positive subjects had an increased titer following retreatment (1:10 to 1:40). The overall incidence of subjects who were antibody positive and experienced infusion reactions through week 30 was 23.7%. The 3 mg/kg infliximab dose was associated with a lower percentage of subjects with infusion reactions relative to the 5 mg/kg infliximab group (14.3% versus 35.3%, respectively). The incidence rate was not remarkably affected by antibody to infliximab status. No serious infusion or possible anaphylactic reactions were observed. Two subjects had infusion reactions that were judged by investigators to be severe and these were equally distributed between antibody to infliximab positive and negative subjects. Two of the 3 subjects with possible delayed hypersensitivity (serum-sickness like) reactions were also antibody to infliximab positive. Subjects who became positive for antibodies to infliximab following induction dosing (weeks 0, 2, and 6) with infliximab, had a 2- to 3-fold higher incidence of infusion reactions on retreatment with infliximab at week 26 relative to antibody negative subjects. No serious infusion reactions were observed at the week 26 retreatment, and only 1 subject positive for antibodies to infliximab reported a severe infusion reaction at retreatment. No possible delayed hypersensitivity reactions or possible anaphylactic reactions were reported following retreatment at week 26.

Conclusions:

1. An induction regimen of either 3 mg/kg or 5 mg/kg of infliximab administered at weeks 0, 2, and 6 resulted in statistically significant and substantial improvement in psoriasis compared with placebo at week 10.
2. The onset of efficacy as evaluated by ≥ 75% improvement in PASI from baseline was rapid and statistically significant by week 4.
3. Efficacy results were superior at all timepoints in the 5 mg/kg group when compared with the 3 mg/kg group.

Synopsis

Name of Sponsor/Company: Centocor	**Associated with Module 5.3.5.1 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: infliximab		

4. The maintenance of response after an induction regimen of either 3 mg/kg or 5 mg/kg infliximab was variable for individual subjects but in general was substantial. This supports exploration of maintenance dosing intervals of ≥ 8 weeks.
5. A single infusion of either 3 mg/kg or 5 mg/kg of infliximab at 20 weeks after the last induction dose was generally well tolerated but did not return the majority of subjects to 75% improvement in PASI 4 weeks after the infusion. This further supports exploration of maintenance dosing.
6. The peak, trough, and maximum serum concentration, and systemic exposure of infliximab following induction dosing increased in a dose-proportional or slightly greater than dose-proportional manner. The maximum serum concentration and t1/2 λz following induction dosing with infliximab in subjects with psoriasis was generally similar to that observed in subjects with Crohn's disease and in subjects with rheumatoid arthritis.
7. The incidence of antibodies to infliximab and the incidence of infusion reactions were generally within the ranges observed in other studies of Crohn's disease patients who received a comparable dosing regimen in the absence of concomitant immunosuppressants.
8. Infliximab was generally well tolerated.

Date of Report: 01 October 2003

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.