Synopsis (C0168T47 REACH)

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

Protocol: C0168T47	**EudraCT No.:** 2004-000761-35

Title of the study: A Randomized, Multicenter, Open-label Study to Evaluate the Safety and Efficacy of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in Pediatric Subjects with Moderate to Severe Crohn's Disease

Principal/Coordinating Investigator(s): Robert Baldassano, MD, Children's Hospital of Philadelphia, Philadelphia, PA, USA and Jeffrey Hyams, MD, Connecticut Children's Medical Center, Hartford, CT, USA

Study Center(s): 34 sites (North America [USA: 19 sites, CA: 4 sites], Western Europe [UK: 1 site, Belgium: 2 sites, Denmark: 3 sites, Netherlands: 2 sites], and Israel [3 sites]).

Publication (reference): None

Studied Period: 11-Feb-2003/13-Apr-2005	**Phase of Development:** 3

Objectives: The primary objective of this study was to evaluate the efficacy of a 3-dose induction regimen of infliximab in reducing signs and symptoms in pediatric subjects with moderately to severely active Crohn's disease. The clinical response achieved in the REACH study at Week 10 was compared with the historical clinical response observed in a subset of ACCENT I subjects (5 mg/kg infliximab group) at Week 10. The safety profile of infliximab during induction and maintenance treatment was also evaluated. The secondary objectives of the study were to evaluate the efficacy of 2 infliximab maintenance dosing regimens (q8 versus q12 weeks) in maintaining clinical response and inducing clinical remission in pediatric subjects with moderately to severely active Crohn's disease, to determine the pharmacokinetic profile in pediatric subjects following induction and maintenance dosing with 5 mg/kg infliximab, to determine the effect of dosing with infliximab on the use of corticosteroids, and to determine the effect of maintenance dosing with infliximab on growth over the course of 1 year. Additional evaluations of PCDAI (Pediatric Crohn's Disease Activity Index), ESR (erythrocyte sedimentation rate), and corticosteroids were conducted. The study included an open-label extension (OLE) beginning at Week 54 to offer continued infliximab therapy to subjects who participated in this study. The objectives of the OLE also included assessment of both the maintenance of clinical response and the safety of infliximab with long-term treatment of Crohn's disease in the pediatric subject population.

Methodology: This was a randomized, multicenter, open-label study for 54 weeks (maximum duration of 62 weeks; and a duration of 206 to 210 weeks [depending on the group] for subjects who participated in the OLE). Subjects who were in clinical response at Week 10 were randomized to treatment with 5 mg/kg infliximab q8 weeks or q12 weeks. Subjects were permitted to be on stable doses of corticosteroids upon entering the study, with tapering permitted following Week 2. Subjects completing treatment through Week 46 who, in the opinion of the investigator, could benefit from continued treatment, could enter an OLE beginning at Week 54. The OLE will continue until marketing authorization is obtained for the use of infliximab for the treatment of Crohn's disease in pediatric subjects, or for a maximum of 3 years. This report summarizes data through Week 54.

Number of Subjects (Planned and Analyzed): 110 subjects were planned; 112 subjects were enrolled and analyzed for efficacy and safety. At Week 10, 103 subjects were randomized and analyzed for efficacy and safety through Week 54.

Diagnosis and Main Criteria for Inclusion: Pediatric subjects ages 6 through 17 years with moderate to severe Crohn's disease (defined as PCDAI > 30 points at baseline). Subjects had active disease despite adequate current treatment with an immunomodulator (ie, azathioprine [AZA], 6 mercaptopurine [6-MP], or methotrexate [MTX]). Subjects were infliximab-naïve.

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Test Product, Dose and Mode of Administration, Batch Number: All subjects received an induction regimen of 5 mg/kg IV infliximab at Weeks 0, 2, and 6 (lot numbers: 02E052 and 03E087). Responders at Week 10 were randomized in a 1:1 ratio to receive 1 of 2 maintenance treatment regimens with IV infliximab. Subjects in Group I received 5 mg/kg infliximab at 8-week intervals (Weeks 14, 22, 30, 38, and 46) and subjects in Group II received 5 mg/kg infliximab at 12-week intervals (Weeks 18, 30, and 42). Subjects who were nonresponders to induction dosing at Week 10 did not receive further infusions of infliximab and were discontinued from the study (but followed for safety for 16 weeks). During the maintenance phase, subjects who lost response in Group I were eligible to receive 10 mg/kg infliximab every 8 weeks. Subjects in Group II who lost response ≤ 8 weeks from the previous infliximab infusion were eligible to receive 10 mg/kg infliximab every 8 weeks. Subjects in Group II who lost response > 8 weeks but ≤ 12 weeks were eligible to receive 5 mg/kg infliximab every 8 weeks. No other changes in dose or dosing interval were allowed during maintenance treatment.

Duration of Treatment: The maximum interval between first and last dose was 46 weeks for subjects who did not participate in the OLE. For subjects who participate in the OLE, the maximum interval between first and last dose will be 198 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

Criteria for Evaluation: All randomized subjects were included, and an intent-to-treat principle was applied for the primary efficacy analyses. Safety evaluations were based on subjects who received at least 1 study infusion; subjects were analyzed according to the actual treatment they received.

Pharmacokinetics/Pharmacodynamics: Serum concentration of infliximab, half-life (t1/2), clearance (CL), volume of distribution at steady state (Vdss), and AUC at steady state (AUCss) were summarized.

Efficacy: At Week 10, the clinical response to infliximab achieved in the REACH pediatric population with Crohn's disease (defined as a decrease from baseline in the PCDAI score of at least 15 points with a total score of no more than 30 points at Week 10) was compared to that reported in the adult population with Crohn's disease (ACCENT I). Secondary endpoints were clinical response at Week 54, clinical remission at Week 54, change from baseline in corticosteroid use at Week 54, and change from baseline in height status at Week 54. The change from baseline in bone metabolism (resorption and formation) was also evaluated at Week 2 and Week 10 and will be reported in a subsequent report.

Physician, parent/guardian, subject global assessments of disease activity (through Week 54) and change from baseline in quality of life (QOL; Weeks 10, 30, and 54) were also performed. Additional analyses included PCDAI, ESR, and clinical response following crossover through Week 54.

Safety: The safety of infliximab in pediatric subjects with Crohn's disease was assessed by examining summaries of AEs and clinical laboratory data (including antibodies to infliximab and antinuclear antibodies [ANA]/anti-dsDNA). Major safety parameters were summarized.

Statistical Methods: Demographic and baseline characteristic data were summarized. Analyses comparing the proportion of subjects in each maintenance treatment group who achieved a specified endpoint (eg, clinical response) used the chi-square test. Comparisons between the 2 maintenance treatment groups that involved continuous endpoints used analysis of variance on the van der Waerden normal scores. To test whether infliximab had an effect on a measurement, such as height status, paired t-tests were used to compare the change from baseline and final measurements of a subject. All statistical testing was 2-sided and used a 0.05 level of significance. In addition to tabular summaries, graphical displays were used to summarize the data.

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The analyses in this study were based on an intent-to-treat principle. Therefore, comparisons of the maintenance phase efficacy data for each subject randomly assigned to a group were analyzed according to the assigned group, regardless of the actual treatment received.

SUMMARY – CONCLUSIONS

Study Population Results: A total of 112 subjects (at 34 sites from North America [73.2%], Western Europe [22.3%], and Israel [4.5%]) were enrolled in the study to receive 5 mg/kg infliximab induction doses at Weeks 0, 2, and 6. Subjects not in clinical response at Week 10 were to be discontinued from the study. At Week 10, 9 subjects had discontinued from the study and were not randomized. At Week 10, 103 of the 112 enrolled subjects were evaluated by the principal investigators as being in clinical response and were randomized in a 1:1 ratio to receive 1 of 2 infliximab maintenance treatment regimens (5 mg/kg infliximab every 8 weeks or 5 mg/kg infliximab every 12 weeks). Of these 103 subjects, 5 subjects that were not in clinical response were randomized. One (1) subject was in clinical response but was inadvertently not randomized at Week 10 by the principal investigator. Therefore, 99 of the 112 treated subjects met Centocor criteria for being in clinical response.

Pharmacokinetic/Pharmacodynamic Results: ·The median infliximab serum level was maintained above detection limits and the median terminal half-life was 10.7 days in this study. The Cmax was 126.7 µg/mL, CL was 6.1 mL/day/kg, Vss was 86.4 mL/kg, and AUCss was 833.8 µg.day/mL. More frequent dosing resulted in a lower proportion of subjects with undetectable infliximab concentration. An increased dose of infliximab or a more frequent dosage regimen led to a sustained presence of infliximab in the serum of subjects who crossed over. Subjects who crossed over to 10 mg/kg had intrinsically higher infliximab clearance than subjects who remained on their original 5 mg/kg dose.

Efficacy Results: The clinical response to infliximab achieved in the REACH pediatric population with Crohn's disease at Week 10 (88.4%) was greater than that achieved in the ACCENT I adult population with Crohn's disease at the same timepoint (66.7%). The confidence intervals for the proportion of subjects in clinical response at Week 10 for the pediatric population in the REACH study lay completely above the confidence interval for the adult population in the ACCENT I study, and on this basis, the REACH study met its primary endpoint. In addition:

- Clinical remission was induced by Week 10 in a greater proportion of pediatric subjects with Crohn's disease compared with the proportion of adult subjects with Crohn's disease in ACCENT I (58.9% versus 39.1%, respectively).
- The q8 week maintenance treatment regimen was more effective than the q12 week maintenance treatment regimen in maintaining clinical response and remission at Weeks 30 and 54.
  - At Week 30, a significantly greater proportion of subjects randomized to the q8 week than the q12 week maintenance treatment group were in clinical remission (59.6% vs. 35.3%; $p = 0.013$).
  - At Week 54, a significantly greater proportion of subjects randomized to the q8 week than the q12 week maintenance treatment group were in clinical remission (55.8% vs. 23.5%; $p < 0.001$).
- Subjects with active Crohn's disease who were on corticosteroids at baseline were able to reduce corticosteroid use. A substantial reduction in median corticosteroid use was observed by Week 10. Both maintenance treatment groups maintained reduced corticosteroid use through Week 54. No significant difference in the change from baseline in corticosteroid dose was noted between the q8 week and q12 week maintenance treatment groups through Week 54.
- A consistently greater proportion of subjects on corticosteroids at baseline were in remission and off corticosteroids in the q8 week maintenance treatment group (45.8%) compared with the q12 week maintenance treatment group (16.7%) at Week 54.

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- The height status (measured as z-score) for pediatric subjects with Crohn's disease was significantly improved at both Weeks 30 and 54.
- Subject, physician, and parent/guardian global assessment scores were numerically improved after treatment with infliximab when compared with baseline.
- The QOL for pediatric subjects with Crohn's disease was significantly improved at Weeks 10, 30, and 54 in the subgroup evaluated.
- The improvement in PCDAI score was seen as early as 2 weeks after the first study agent administration and continued through Week 10. When the q8 week and q12 week maintenance treatment groups were combined, the significant improvement from baseline in PCDAI score observed at Week 10 was maintained at both Weeks 30 and 54.
- The improvement in ESR was evident when first examined at Week 10 and continued improvement was observed through Week 54 ($p < 0.001$ for all comparisons).
- The majority of subjects (75%) who lost response and crossed over to a more frequent dosing interval (5 mg/kg q8 weeks) or to a higher dose (10 mg/kg q8 weeks), regained response.

Safety Results: A difference of approximately 10 weeks in the average duration of follow-up between the 2 maintenance treatment groups was noted. This was due to the higher proportion of subjects who discontinued study agent infusions and crossed over in the q12 week compared with the q8 week maintenance treatment group.

- There were no deaths, malignancies, serious neurologic events (eg, optic neuritis, demyelinations), serious hematological events (eg, pancytopenia, aplastic anemia), tuberculosis (TB), or CHF.
- In the 103 randomized subjects, SAEs were reported in 14.6% of subjects, with similar proportions of subjects in the q8 week and the q12 week maintenance treatment groups (15.1% and 14.0%, respectively).
- The system-organ class with the highest incidence of SAEs was the GI system, with SAEs reported in 10.7% of subjects (9.4% and 12.0% of subjects in the q8 week and q12 week maintenance treatment groups).
- Greater than 90.0% of all treated subjects had 1 or more AEs, with similar proportions in the 2 maintenance treatment groups (96.2% and 92.0% in the q8 week and q12 week maintenance treatment groups, respectively).
- The GI system organ class had the highest incidence of AEs, which were reported in 73.8% of subjects; vomiting, nausea, abdominal pain, and Crohn's disease were the most frequently reported AEs.
- The respiratory system-organ class had the next highest proportions of subjects with AEs, which were reported in 63.1% of subjects (60.4% and 66.0% in the q8 week and q12 week maintenance treatment groups, respectively).
- Two (2) of 53 (3.8%) and 4 of 50 (8.0%) randomized subjects discontinued study infusions because of an AE in the q8 week and the q12 week maintenance treatment groups, respectively.
- Overall, 17.5% of randomized subjects experienced 1 or more nonserious infusion reactions. The proportion of infusions associated with infusion reactions was lower (2.9%) in the q8 week than in the q12 week maintenance treatment group (5.3%).
- There were no subjects who had a possible delayed hypersensitivity reaction. Two (2) subjects had nonserious anaphylactic reactions.
- Overall, AEs were classified by the investigators as infections in 73.6% and 38.0% of subjects in the q8 week and the q12 week maintenance treatment groups, respectively, with respiratory infection reported as the most common AE.

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- AEs were classified by the investigators as serious infections in 2 subjects who were not randomized (sepsis and fever each in 1 subject), 3 subjects in the q8 week maintenance treatment group (pneumonia, abscess/furunculosis and infection bacterial/lymphadenopathy, and colitis), and 4 subjects in the q12 week maintenance treatment group (abdominal pain/fever/vomiting, enterocolitis, abscess, and worsening of Crohn's disease).
- Three (3; 6.0%) subjects in the q12 week maintenance treatment group and no subject in the q8 week maintenance treatment group had a markedly elevated ALT value. In addition, liver function abnormalities occurred during the induction phase of the study and normalized with continued infliximab treatment.
- Newly positive anti-dsDNA was detected in 5.9% of subjects in the q8 week maintenance treatment group compared with 8.3% in the q12 week maintenance treatment group. There were no reports of new autoimmune disease.
- The overall incidence of subjects positive for antibodies to infliximab through Week 54 was 2.9% (3/105) and did not distinguish subjects who crossed over to higher or more frequent doses of infliximab from those who maintained their randomized maintenance treatment schedule. Positive antibody to infliximab status was associated with a slightly higher incidence of mild to moderate infusion reactions compared with antibody negative and inconclusive subjects. One (1) antibody negative subject experienced a single event of a possible anaphylactic reaction. Clinical response and remission were comparable between the few subjects who were antibody positive and the majority of subjects who were inconclusive through Week 54.
- In subgroup analyses, there were no clear patterns supporting a potential safety concern related to the use of infliximab and concomitant corticosteroids and/or immunomodulating agents.

Conclusions: The REACH study provided clinically important evidence that infliximab was efficacious in pediatric subjects with Crohn's disease, with efficacy at least as good as that seen in adults. Specifically, in this 54 week study of infliximab in pediatric subjects with moderate to severe Crohn's disease (PCDAI > 30), infliximab administered at 5 mg/kg at Weeks 0, 2, and 6 and then every 8 or 12 weeks:

- Reduced the signs and symptoms of disease activity at Week 10 and sustained these reductions through Week 54. At Week 10, the proportion of pediatric subjects with Crohn's disease in clinical response and remission were at least as good as that seen in adult subjects with Crohn's disease (ACCENT I study).
- Demonstrated that the q8 week maintenance treatment regimen was significantly more effective than the q12 week maintenance treatment regimen in maintaining clinical response and remission at Weeks 30 and 54.
- Allowed for a substantial reduction in median corticosteroid use by Week 10 that was maintained through Week 54, with at least 50% of subjects discontinuing corticosteroids by their first maintenance treatment visit.
- Demonstrated improved height status, global assessment scores (subject, physician, parent/guardian), and QOL scores through Week 54. Improvement of PCDAI score was seen as early as 2 weeks after the first study agent administration and was maintained through Week 54.
- Demonstrated a similar half-life for the q8 week and the q12 week maintenance treatment groups. More frequent dosing resulted in a lower proportion of subjects with undetectable trough infliximab concentration. An increased dose of infliximab or a more frequent dosage regimen led to a sustained presence of infliximab in the serum of subjects who crossed over. Subjects who crossed over to 10 mg/kg intrinsically had higher infliximab clearance than subjects who remained on their original 5 mg/kg dose.

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- Infliximab was generally well tolerated. AEs and infections were seen in patterns similar to those seen in ACCENT I. A lower proportion of randomized subjects in the REACH study experienced 1 or more infusion reaction when compared with subjects in the ACCENT I study. No subjects had a possible delayed hypersensitivity reaction and 2 subjects had nonserious anaphylactic reactions in the REACH study.
- Demonstrated an overall incidence of subjects positive for antibodies to infliximab through Week 54 of 2.9% (3/105). Positive antibody to infliximab status was associated with a somewhat higher incidence of mild to moderate infusion reactions compared with antibody negative and inconclusive subjects.
- Although the proportion of subjects with AEs reported by investigators as infections was higher in the q8 week than the q12 week maintenance treatment groups, and a higher proportion of subjects in the q8 week maintenance treatment group with infections required antimicrobial treatment, a similar proportion of subjects in the q8 and q12 week maintenance treatment groups reported AEs, SAEs, and AEs leading to discontinuation.

Date of Report: 20 Oct 2005

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