# Synopsis (C0168T47 REACH)

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Centocor, R & D, Inc | **Associated with Module 5.3 of the Dossier** | |
| **Name of Finished Product:** REMICADE® | | |
| **Name of Active Ingredient:** REMICADE® | | |

| | |
|---|---|
| **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 US and Jeffrey Hyams, MD, Connecticut Children's Medical Center, Hartford, CT US

**Study Center(s):** Sixteen of the original 34 sites (North America [USA: 8 sites, CA: 4 sites], Western Europe [UK: 1 site, Belgium: 1 sites, Netherland: 1 sites], and Israel [1 sites]) participated in the open-label extension.

**Publication (reference):** Hyams J, Crandall W, Kugathasan S, et al. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132:863-873.

| | |
|---|---|
| **Studied Period:** 16 Mar 2004/23 Aug 2007 | **Phase of Development:** 3 |

**Objectives:** The main objective of the open-label extension was to offer continued infliximab therapy to the subjects who participated through Week 54 of the main study as well as to examine the safety and efficacy of long-term treatment with infliximab in pediatric subjects with moderate to severe Crohn's disease.

**Methodology:** Subjects completing treatment through Week 46, who, in the opinion of the investigator, could benefit from continued treatment, could enter an open-label extension beginning at Week 54.

**Number of Subjects Analyzed:** 60 analyzed in the open-label extension.

**Diagnosis and Main Criteria for Inclusion:** Subjects completing treatment through Week 46 and who, in the opinion of the investigator could benefit from continued treatment.

**Test Product, Dose and Mode of Administration, Lot Number:** Subjects entering the open-label extension received 5 mg/kg infliximab q8 or q12 weeks, or 10 mg/kg infliximab q8 weeks infusion, according to the maintenance schedule and dose they were receiving at the end of the main study. Subjects who lost response during the open-label extension were eligible to have their dose of infliximab increased or their frequency decreased. (Lot Numbers: 02E052, 03A051, 03E087, 04C127, 04K072, 6DD0506101, DD0506101, 06E05101, 06J02101.)

**Duration of Treatment:** A maximum of 3 years or until marketing authorization was obtained for the use of REMICADE® infliximab for the treatment of pediatric subjects with moderate to severe Crohn's disease.

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

**Criteria for Evaluation:** All PK, safety, and efficacy analyses included subjects entering the open-label extension. Subjects were analyzed according to the treatment they were receiving at visit 1 of the open-label extension. PK and safety evaluations were based on subjects who received at least 1 infusion during the open-label extension, including partial infusions of study agent.

# Synopsis (C0168T47 REACH)

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Centocor, R & D, Inc | **Associated with Module 5.3 of the Dossier** | |
| **Name of Finished Product:** REMICADE® | | |
| **Name of Active Ingredient:** REMICADE® | | |

**Pharmacokinetics/Pharmacodynamics:** Blood samples for determining the serum concentration of infliximab were to be drawn in all subjects at the final visit (during the open-label extension) or for subjects who withdrew from the study early, samples were to be collected at the time of withdrawal and 8 weeks following the last study infusion. Serum concentrations of infliximab were determined with an enzyme-linked immunosorbent assay. This assay was capable of quantifying a serum infliximab concentration of at least 0.1 μg/mL.

**Efficacy:** Global assessment scores (physician, parent/guardian, and subject) were summarized at intervals of approximately every 6 months from the beginning of the study extension.

The change from baseline in age and gender-specific height status was summarized yearly from the beginning of the study extension. These data were summarized for subjects with a 1-year delay in bone age at the beginning of the main study.

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

**Statistical Methods:** Descriptive statistics, such as the mean, median, standard deviation, range, and the interquartile range for continuous variables and counts and percentages for categorical variables were used to summarize all the data. No hypothesis testing was performed.

**SUMMARY – CONCLUSIONS**

**Study Population Results:** Of the 60 subjects who participated in the open-label extension, 33 were in the 5 mg/kg q8 weeks treatment group, 12 were in the 5 mg/kg q12 weeks treatment group, and 15 were in the 10 mg/kg q8 weeks treatment group at the beginning of the open-label extension. Twelve subjects crossed over at least once during the open-label extension. Overall, 18 (30.0%) subjects discontinued study participation in the open-label extension.

**Pharmacokinetic/Pharmacodynamic Results:**

- Overall, median infliximab concentrations were maintained above the lower limit of quantification (LLOQ) (0.1 μg/mL) in all dosing groups at the time of the final PK sampling for the subjects who did not change their dosing regimen.
- The median serum infliximab concentration for subjects at the end of the open-label extension was proportional to the infliximab dose administered during the open-label extension.
- A total of 4.8% (2/42) subjects were positive for antibodies to infliximab, 1 each in the 5 mg/kg and 10 mg/kg q8 weeks dose groups.

**Efficacy Results:**

- During the open-label extension, the global assessment scores were maintained at levels indicating very good health in the past 2 weeks (for subject and parent/guardian global assessments) and no disease activity (for physician global assessment).
- The height status (as measured by age and gender-specific z-scores) for pediatric subjects with Crohn's disease (and a 1-year delay in bone age at the beginning of the main study) showed a trend toward improvement during the open label extension.

# Synopsis (C0168T47 REACH)

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Centocor, R & D, Inc | **Associated with Module 5.3 of the Dossier** | |
| **Name of Finished Product:** REMICADE® | | |
| **Name of Active Ingredient:** REMICADE® | | |

**Safety Results:**

- The system-organ class with the highest proportion of AEs (≥ 10%) reported in the combined infliximab treatment group was respiratory system disorders (80.0%). More events were observed in the 5 mg/kg q8 weeks treatment group (87.9%) compared with the 5 mg/kg q12 weeks group (75.0%), and the 10 mg/kg q8 weeks group (66.7%).
- A total of 90.0% of subjects had at least 1 AE during the open-label extension; the proportion of subjects with an AE was similar among all treatment groups. The WHOART preferred term in which the highest proportion of AEs was reported was upper respiratory infection (41.7%) followed by pharyngitis (38.3%). A higher proportion of subjects experienced upper respiratory infections in the 5mg/kg q 12 weeks treatment group (66.7%) compared with the 5 mg/kg q8 weeks treatment group (45.5%) and 10 mg/kg q8 weeks treatment group (13.3%).
- SAEs were reported in 33.3% of subjects in the combined infliximab treatment group. Pneumonia was reported in 1 subject from the 10 mg/kg q8 weeks treatment group.
- No TB, deaths or malignancies were reported during the open-label extension.
- One subject in the 5 mg/kg q8 weeks treatment group, discontinued study agent because of a treatment emergent AE of worsening of Crohn's disease.
- Infections were reported in 76.7% of subjects in the combined infliximab treatment group. The WHOART preferred terms in which the highest proportion of infections reported (≥ 10%) in order of frequency were upper respiratory tract infection (36.7%), pharyngitis (30.0%), and fever (10%). One subject from the 5 mg/kg q12 weeks treatment group was reported to have a potential nonserious opportunistic infection of herpes zoster (shingles).
- A total of 9 serious infections were reported in 6 subjects. With the exception of the SAE of pseudomembranous colitis which lasted 86 days and a report of intra-abdominal abscess, which had an unknown duration, most serious infections had a duration of 2 to 9 days and all reportedly resolved. None of the events resulted in study agent discontinuation.
- Overall, 23.3% subjects in the open-label extension experienced 1 or more infusion reactions. There were no serious infusion reactions. There were no possible delayed hypersensitivity reactions or anaphylactic reactions.
- The highest proportion of markedly abnormal hematology values was decreased neutrophil count with 20.3% subjects in the combined infliximab treatment group.
- One subject from the 10 mg/kg q8 weeks treatment group presented with an abnormally high ALT value (195 IU/L) on Day 525. ALT returned to normal (50 IU/L) at the next visit (Day 579). No abnormal AST values were noted in the open-label extension.

# Synopsis (C0168T47 REACH)

| | | |
|---|---|---|
| **Name of Sponsor/Company:** Centocor, R & D, Inc | **Associated with Module 5.3 of the Dossier** | |
| **Name of Finished Product:** REMICADE® | | |
| **Name of Active Ingredient:** REMICADE® | | |

**Conclusions:**

In pediatric subjects with moderate to severe Crohn's disease who participated in the open-label extension, infliximab, administered as 5 mg/kg q8 weeks, 5 mg/kg q12 weeks, and 10 mg/kg q8 weeks:

- Subject, parent/guardian and physician global assessment scores were maintained during the open-label extension.
- Height status (as measured as age and gender-specific z-scores) for pediatric subjects with Crohn's disease showed a trend toward improvement during the open label extension.
- Median infliximab concentrations were maintained above the LLOQ (0.1 μg/mL) in all dosing groups at the time of the final PK sampling for the subjects who did not change their dosing regimen.
- Median serum infliximab concentration for subjects at the end of the open-label extension was proportional to the infliximab dose administered during the open-label extension.
- A total of 90.0% of subjects had at least 1 AE during the open-label extension; the proportion of subjects with an AE was similar among all treatment groups.
- A total of 9 serious infections were reported in 6 subjects. The serious infection preferred terms included abscess, infection bacterial, upper respiratory tract infection, colitis pseudomembranous, gastroenteritis, pneumonia, appendicitis, and Crohn's disease.
- A potential nonserious opportunistic infection of herpes zoster (shingles) of moderate intensity was reported in 1 subject.
- No TB, deaths or malignancies were reported during the open-label extension.
- Infections were reported in 76.7% of subjects in all combined infliximab treatment group.
- A total of 23.3% subjects in the open-label extension experienced 1 or more infusion reactions.

**Date of Report:** 11 Aug 2008

**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.*