Synopsis (C0168T32)

Name of Sponsor/Company: Centocor, Inc./B.V.	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE®		
Name of Active Ingredient: Infliximab		

Protocol: C0168T32	**EudraCT No.:** 2004-000758-22

Title of the study: A Randomized, Double-blind Study of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab) in Combination with Methotrexate for the Treatment of Subjects with Polyarticular Juvenile Rheumatoid Arthritis/Open-label Extension 3-year Follow-up

Principal/Coordinating Investigator(s): Martini A, MD – IRCCS, Ruperto N, MD, MPH, Istituto G. Gaslini, Divisione di Pediatria II, Largo G. Gaslini, 5, 16148 Genova, Italy

Study Center(s): The open-label extension (OLE) was conducted at 24 sites: 4 sites in North America (2 in the US and 2 in Canada), 3 in Argentina, and 17 sites in Europe.

Publication (reference): Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis A*rthritis & Rheum.* 2007;56(9):3096-3106.

Studied Period: 18 Oct 2002 to 15 Mar 2007	**Phase of Development:** 3

Objectives: The objectives of the OLE were to assess both the maintenance of clinical response and the safety of infliximab with long-term treatment in the juvenile rheumatoid arthritis (JRA) subject population.

Methodology: In the double-blind portion of the study, subjects in Group 1 received placebo at Weeks 0, 2, and 6; 6 mg/kg infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Subjects in Group 2 received 3 mg/kg infliximab at Weeks 0, 2, 6, 14, and placebo at Week 16; then 3 mg/kg infliximab at Week 20 and every 8 weeks through Week 44. All subjects who completed the double-blind portion of the study and entered the OLE were to receive 3 mg/kg infliximab beginning at Week 52 and then every 8 weeks through Week 196, and were to continue concomitant methotrexate (MTX) therapy. The dose may have been adjusted by ≤ 1.5 mg/kg every 8 weeks to a maximum dose of 6 mg/kg every 8 weeks or to a minimum dose of 3 mg/kg every 8 weeks. During the OLE, MTX dose and route were adjusted at the discretion of the physician, but, when possible, the dose was to remain > 7.5 mg/m^2 per week.

Number of Subjects (Planned and Analyzed): In the double-blind portion of the study, 122 subjects were randomized to treatment; 62 subjects received placebo→6 mg/kg infliximab plus MTX therapy and 60 subjects received 3 mg/kg infliximab plus MTX therapy (2 subjects were randomized and not treated). Ninety-three randomized subjects completed the double-blind portion of the study and were eligible to enter the OLE. A total of 78 subjects entered the OLE and received at least 1 infusion of study agent; 36 subjects received infusions though Week 196.

Diagnosis and Main Criteria for Inclusion: Subjects who completed treatment in study C0168T32 through Week 44 who, in the opinion of the investigator, could benefit from continued treatment, were eligible to enter the OLE beginning at Week 52.

Test Product, Dose and Mode of Administration, Batch Number: REMICADE® (infliximab) was supplied as a sterile, white, lyophilized powder in a single-use 20 mL vial and was reconstituted with 10 mL Sterile Water for Injection, resulting in a concentration of 10 mg/mL infliximab for administration. The batch numbers used in the OLE were 00H035, 01H072, 03A052, and 04C127.

Duration of Treatment: Maximum of 196 weeks for subjects participating in the OLE. Data from 3 years of the OLE (Week 52 to Week 216) are included in this study report.

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

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Criteria for Evaluation: Safety evaluations were based on subjects who received at least 1 study infusion in the OLE. Efficacy analyses were based on the observed data.

Pharmacokinetics/Pharmacodynamics: Serum concentrations of infliximab over time were summarized.

Efficacy: The proportion of subjects who achieved a JRA core set positive response (also referred to as American College of Rheumatology Pediatric [ACR Pedi] 30; defined as an improvement from baseline of at least 30% in at least 3 of any 6 core variables, with no more than 1 of the remaining variables worsened by more than 30%) was summarized over time. The other efficacy endpoint, improvement from baseline for efficacy components, was also summarized over time.

Safety: Safety was assessed by summarizing the incidence and types of adverse event (AEs) and changes in laboratory parameters. Vital signs and physical findings were monitored by the investigator. Any significant changes in vital signs were recorded as AEs. The proportion of subjects with serious adverse events (SAEs), discontinuations due to AEs, and other significant AEs of of heightened clinical importance with infliximab therapy, were summarized. The incidence of antibodies to infliximab and the development of antinuclear antibodies or anti-double-stranded deoxyribonucleic acid antibodies were also summarized.

Statistical Methods: Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for categorical variables, were used to summarize most data.

SUMMARY – CONCLUSIONS

Study Population Results: The majority of OLE subjects were female (85.9%) and Caucasian (92.1%). Over one-third of the subjects were at least 12 years of age (43.6%). In general, the demographic characteristics at baseline were similar to those reported in the double-blind portion of study.

Pharmacokinetic/Pharmacodynamic Results: Interpretation of the pharmacokinetic (PK) data is limited by the design of the OLE. In the infliximab groups, trough concentrations 8 weeks after the most recent dose were generally low, and in most cases lower than the limit of quantification; however, there were too few subjects with available PK data approaching Week 204 to infer a relationship between infliximab dose and trough serum concentration.

Efficacy Results:

- In general, the ACR Pedi 30, ACR Pedi 50 and ACR Pedi 70 responses were consistent over time and with the results from the double-blind portion of the study, and efficacy was maintained during the OLE. It should be noted that the number of OLE subjects decreased because of a combination of loss of efficacy, discontinuation of subjects because of AEs, voluntary study withdrawals considered nonresponders, and subjects who were in remission and no longer required administration of study agent. Therefore, the conclusions that can be drawn from these data are limited.
- In general, efficacy was maintained for each of the JRA core set components through Week 204 for subjects who remained in the OLE. The sustained efficacy may have been influenced positively by allowing physicians to dose escalate from the 3 mg/kg starting dose at Week 52 according to individual subject's needs.
- It was difficult to discern any apparent relationship between infliximab serum concentration and efficacy as measured by ACR Pedi response because of the limited data available.

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Safety Results: In general, the proportions and types of AEs observed in the OLE were consistent with those reported in the double-blind portion of the study.

- There were 91.0% of OLE subjects who reported at least 1 AE from Week 52 to Week 204.
- No deaths were reported for subjects who participated in the OLE.
- There were 21.8% of OLE subjects who reported at least 1 SAE from Week 52 to Week 204. Nine of these 17 subjects received a > 3 mg/kg dose, 7 received 3 mg/kg or less, and 1 subject reported at least 1 SAE while receiving a 3 mg/kg dose and later a 6 m/kg dose.
- There were 14.1% of OLE subjects who permanently discontinued study infusions because of an AE from Week 52 to Week 204.
- No OLE subjects reported a solid malignancy, lymphoma, or congestive heart failure (CHF) from Week 52 to Week 204.
- There were 73.1% of OLE subjects who had at least 1 infection from Week 52 to Week 204. Similar to the double-blind portion of the study, the most commonly reported infection was upper respiratory tract infection; however, more respiratory tract infections occurred during the OLE, possibly because of the longer OLE period.
- There were 9.0% of OLE subjects who reported a total of 12 serious infections from Week 52 to Week 204.
- The proportion of OLE subjects positive for antibodies to infliximab from Week 52 to Week 216 was 36.6%. Thirteen OLE subjects had titers of ≥ 1:320, with the highest titers of 1:20480 and 1:40960 observed in 1 subject each. The incidence of antibodies to infliximab in the combined infliximab groups in the double-blind portion of the study was lower (25.5%), with a titer of 1:20480 observed for 3 subjects.
- Comparable to the overall proportion of subjects who reported an infusion reaction in the double-blind portion of the study (26.5%), 32.1% of OLE subjects had an infusion reaction from Week 52 through Week 204. Two OLE subjects had a serious infusion reaction and 1 OLE subject had a possible anaphylactic reaction. There were increased rates of infusion reactions in subjects with antibodies to infliximab as was observed in the first 52 weeks of the study. Among antibody to infliximab positive OLE subjects, 57.7% had an infusion reaction, compared with 22.7% of antibody-negative subjects, and 13.0% of antibody-inconclusive subjects.

Conclusions: The conclusions from the 3-year OLE of JRA Study C0168T32, which assessed both the maintenance of clinical response and the safety of infliximab with long-term treatment in the JRA population, support the findings from the double-blind portion of the study:

- Efficacy was maintained during the OLE, regardless of the dose received. Interpretation of the data is limited due to the small number of subjects who completed the Week 204 visit.
- The overall safety profile from the 3-year OLE was consistent with that from the 52-week double-blind portion of the study, with no new or emergent safety signals, despite the longer exposure time to infliximab in the OLE. A correlation between antibody to infliximab positivity and infusion reactions was still observed; however, the relationship between higher rates of antibody formation and lower dose of infliximab noted through Week 52 cannot be established given the method of dosing during the 3-year OLE.

Date of Report: 13 Dec 2007

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