Synopsis (C0168T32 JRA)

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 1 Year Follow-up)		
Principal/Coordinating Investigator: Martini A, MD – IRCCS, Istituto G. Gaslini, Divisione di Pediatria II, Largo G. Gaslini, 5, 16148 Genova, Italy		
Study Center(s): This study was conducted at 24 sites: 4 sites in North America (2 in the US and 2 in Canada), 3 in South America, and 17 sites in Europe.		
Publication (reference):		
Studied Period (years): Oct 2002 to Mar 2005	**Phase of Development:** 3	
Objectives: The objectives of the open-label extension 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 I received placebo at Weeks 0, 2, and 6; 6 mg/kg of infliximab at Weeks 14, 16, and 20, and then every 8 weeks through Week 44. Subjects in Group II received infliximab 3 mg/kg at Weeks 0, 2, 6, 14, and placebo at Week 16; then 3 mg/kg of 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 open-label extension (OLE) were to receive 3 mg/kg infliximab beginning at Week 52 and then every 8 weeks through Week 196, and were to continue on 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/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. Two subjects were randomized and not treated. There were 93 randomized subjects who completed the double-blind study and were eligible to enter the OLE. At the Week 52 visit, 83 subjects initially registered for the OLE (5 discontinued prior to their first OLE infusion); 78 subjects entered the OLE and received at least one infusion of study agent.		
Diagnosis and Main Criteria for Inclusion: Diagnosis and inclusion criteria for the OLE were the same as for the double-blind study. 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 open-label extension study beginning at Week 52.		
Test Product, Dose and Mode of Administration, Batch Number: REMICADE® (infliximab). The study agent was supplied as a sterile, white, lyophilized powder in a single-use 20 mL vial and was reconstituted with 10 mL of Sterile Water for Injection, resulting in a concentration of 10 mg/mL infliximab for administration. The batch numbers used in the OLE were 01H072 and 03A052.		
Duration of Treatment: Maximum of 196 weeks for subjects participating in the OLE. Only data from the first year of the OLE (Week 52 to Week 108) are included in this study report update.		
Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable		
Criteria for Evaluation: An intent-to-treat principle was applied for the efficacy analyses. Safety evaluations were based on subjects who received at least 1 study infusion in the first year OLE.		

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

Efficacy: The proportion of subjects who achieved a JRA core set positive response (heretofore referred to as 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 one of the remaining variables worsened by more than 30%) were 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 type of adverse events (AEs) and changes in laboratory parameters. Vital signs and physical findings were monitored by the investigator. These items were not entered into the database. Any significant changes were recorded as AEs. The proportion of subjects with serious AEs (SAEs), discontinuations due to AEs, and clinically significant AEs, were summarized. The incidences of antibodies to infliximab and the development of antinuclear antibodies or double-stranded DNA 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: The majority of the subjects (85.9%) in the OLE study were female. Most subjects (92.1%) were Caucasian; ranging in age between 4 and 17 years. The demographic characteristics and baseline disease characteristics of the OLE study population were similar to those reported in the 122 subjects randomized in the double-blind portion of the study. The median duration of JRA in all subjects was 2.7 years. The majority of OLE subjects (64.1%, 50/78) presented with Polyarticular onset JRA. Systemic onset JRA was present in 11.5% (9/78) of the subjects, and Pauciarticular onset JRA was present in 24.4% (19/78) of OLE subjects. A positive rheumatoid factor was seen in 26.3% (20/76) of the OLE subjects.

Pharmacokinetics/Pharmacodynamics Results: · Though the OLE was not designed to further study PK parameters in detail beyond the double-blind portion of the study, limited PK analyses demonstrated there was limited correlation in the OLE between serum trough infliximab concentrations and efficacy. · Subjects in the OLE maintained a serum infliximab concentration at Week 100 that closely resembled that of the 3 mg/kg in the blinded phase of the study. The preinfusion infliximab levels at Week 100 were consistent with the expected profile based on the PK information from the blinded phase of the study, and the doses administered at Week 92 in the OLE. Though efficacy in general did not appear to significantly correlate with serum drug concentration, there was reduced efficacy and increased rates of infusion reactions (which are correlated with antibodies to infliximab and undetectable serum infliximab concentrations) in subjects with antibodies to infliximab.

Efficacy Results: ·In the double-blind portion of the study the relative proportion of subjects who demonstrated an improvement at Week 14 in JRA core set response was greater in the 3 mg/kg group than in the placebo group at each level of improvement (30%, 50%, and 70%). However, following cross-over to active study drug at Week 14, subjects in the 6 mg/kg group had an ACR-pedi 30 response rate at Week 16 that exceeded the response rate of subjects in the 3 mg/kg group, which was maintained through Week 52. The proportions of OLE subjects who achieved ACR-pedi 30 at Weeks 52, 76 and 100 were 83.3% (65/78), 80.8% (63/78), and 75.6% (59/78). The proportions of OLE subjects who achieved ACR-pedi 50 at Weeks 52, 76 and 100 were 79.5% (62/78), 76.9% (60/78), and 67.9% (53/78). The proportions of OLE subjects who achieved ACR-pedi 70 at Weeks 52, 76 and 100 were 57.7% (45/78), 62.8% (49/78), and 60.3% (47/78). From baseline (Week 0) to Week 100 of the OLE, there was a consistent trend for improvement in most of the ACR-pedi 30 components for the OLE subjects.

Safety Results: There were 87.2% (68/78) of subjects in the first year OLE who reported at least one AE. The most commonly reported AEs were: upper respiratory tract infection (30.8%, 24/78), pharyngitis (23.1%, 18/78), rhinitis (16.7%, 13/78), and headache (15.4%, 12/78); coughing, infusion syndrome, and vomiting were reported in 14.1% (11/78) of subjects, each. No subjects reported pneumonia. In general, the proportions and types of AEs observed in

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the first year OLE were consistent with those reported in the double-blind portion of the study. There were 6.4% of subjects (5/78) who discontinued study infusions due to an AE. Four of the subjects discontinued due to infusion syndrome, one of which was serious. The remaining subject discontinued due to coughing, pharyngitis, and urticaria. There were no deaths reported in subjects who participated in the first year of the OLE. Eight subjects (10.3%) experienced at least one SAE during the Week 52 to 108 portion of the OLE. With the exception of exacerbation of juvenile rheumatoid arthritis, reported in 2 subjects, all remaining serious AEs were reported in 1 subject for each event. Three subjects (3.8%) reported a total of 4 serious infections: cellulitis, pulmonary fibrosis (due to TB), intradermal reaction, and pyelonephritis. There were 24.4% (19/78) of subjects who experienced an infusion reaction from Week 52 through Week 108. The percentage of subjects with antibodies to infliximab was 35.5% (27/76). High titers of 1:20480 and 1:40960 were observed for 4 subjects in total. Among the antibody positive subjects, 66.7% (18/27) experienced an infusion reaction. One antibody positive OLE subject experienced a serious infusion reaction.

Conclusion: The following conclusions from this one-year report of the open label extension for JRA Study C0168T32 support the findings from the double-blind portion of the study:

- A high rate of sustained efficacy was maintained during the first year of the OLE, regardless of dose received.
- The safety profile from the OLE was consistent with that from the double-blind portion of study, with no new or emergent safety signals.

Date of Report: 30 Aug 2005

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