Synopsis (C0168T32 JRA)
Amended 24 Feb 2006 to revise efficacy results

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	
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 34 centers. 9 in North America (7 in the United States and 2 in Canada), 3 in South America, and 22 in Europe.	
Publication (reference):	
Studied Period (years): 19 Oct 2001 to 01 Apr 2004	**Phase of Development:** 3

Objectives: The primary objective of this study was to evaluate the efficacy and safety of infliximab in subjects with active JRA who were receiving concomitant MTX therapy, either with or without NSAIDs and/or low-dose corticosteroids. The secondary objective of this study was to evaluate the pharmacokinetic (PK) profile of infliximab in subjects with JRA with active disease despite background therapy. The main objective of the open-label extension (OLE) was to offer continued infliximab therapy to the subjects who participated in this study, since infliximab was not approved for the treatment of JRA. Additionally, 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 JRA subject population.

Methodology: This was a multicenter randomized, placebo-controlled, double-blind, study for 14 weeks, followed by a double-blind, all-active treatment extension, for a maximum of 44 weeks with following assessments at Weeks 52 and 64. Randomization was stratified by investigational site and age group (≥ 4 years and < 8 years, ≥ 8 years and < 12 years, ≥ 12 years and < 18 years). Subjects completing treatment through Week 44 who, in the opinion of the investigator, could benefit from continued treatment, may enter an open-label extension beginning at Week 52.

Number of Subjects (Planned and Analyzed): This study was planned for the analysis of 120 subjects randomized in a 1:1 ratio to either placebo/6 mg/kg infliximab plus MTX therapy (Group I; n = 60) or 3 mg/kg infliximab plus MTX therapy (Group II; n = 60). Subjects initially randomized to placebo were subsequently permitted to receive (after Week 14) 6 mg/kg infliximab plus MTX therapy. Of the 122 subjects 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. A total of 120 subjects were analyzed for safety, 117 subjects were analyzed for clinical pharmacology, and 121 subjects were analyzed for efficacy.

As part of the internal process for preparing for regulatory inspections/audits, Centocor became aware of potential inconsistencies in study conduct at one of the JRA (C0168T32) study investigational sites, specifically Site 392. These inconsistencies placed the integrity of the efficacy data collected at the site into question. After completion of the Centocor evaluation, it was determined that unblinded site personnel at Site 392, were involved in the assessment and collection of primary efficacy data. Centocor concluded that the efficacy data from this site (4 subjects) must be excluded from all efficacy analyses since the unbiased nature of the efficacy data could not be assured.

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Diagnosis and Main Criteria for Inclusion: Subjects with active JRA aged 4 to < 18 years, treated with oral, intramuscular, or subcutaneous methotrexate (MTX) for 3 months prior to study entry with a sub-optimal response and no serious MTX-related toxicity. For inclusion, subjects must have onset of disease prior to 16th birthday and 1 of the following:

1. Diagnosis of polyarticular JRA at least 6 months prior to study entry; or,
2. Systemic onset of JRA with a polyarticular course and no systemic symptoms (eg, fever, splenomegaly) for at least 1 year prior to study entry; or,
3. Pauciarticular onset of JRA with a polyarticular course for at least 6 months prior to study entry.

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. Subjects in Group I: 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: 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. Three lots of infliximab (00H035, 01H072, 03A052) were used.

Duration of Treatment: Maximum of 44 weeks for subjects not participating in the OLE; maximum of 196 weeks for subjects participating in the OLE. Data from the OLE are not included in this study report.

Reference Therapy, Dose and Mode of Administration, Batch Number: The placebo 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. Placebo was infused at Weeks 0, 2, and 6 for subjects in Group I (and at Week 16 for subjects in Group II). Three lots of placebo (99K06, 00D053, 00K072) were used.

Criteria for Evaluation: All randomized subjects were included, and an intent-to-treat principle was applied for the primary efficacy analyses. The efficacy data from Site 392 (4 subjects) has been excluded from all efficacy analyses since the unbiased nature of the efficacy data could not be assured. 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 concentrations of infliximab over time along with derived PK parameters were summarized. The PK parameters include: Cmax, mean residence time, Cl, volume of distribution at steady state, and t1/2. Pharmacodynamic inflammatory markers (including TNFα, IL-8, MMP-3, ICAM-1, IL-1β, IL-12P40, and VEGF) were measured from serum samples, along with plasma concentrations of IL-6. These markers were summarized over time by treatment group.

Efficacy: The JRA core set defined by Giannini (1997) consists of 6 variables that are described in detail in Section 5.5.5.1 of this study report. The primary endpoint of this study was the proportion of subjects who achieved a JRA core set positive response (also 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%) at Week 14 in the 3 mg/kg group (Group II) and the placebo/6 mg/kg group (Group I). Secondary endpoints included the average change from baseline in CHAQ over time; the proportions of subjects with ACR-pedi 30 through Week 52 by treatment group; percent improvement from baseline in CRP concentrations by treatment group.

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Safety: Safety was assessed by summarizing the incidence and type of adverse events (AEs) and changes in laboratory parameters by treatment group. 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), including deaths, discontinuations due to AEs, and clinically significant AEs, were summarized by treatment group. The incidences of antibodies to infliximab and the development of antinuclear antibodies or double-stranded DNA antibodies were also summarized by treatment groups.

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. Most data were presented with graphical displays, including box plots and line graphs of results versus time, and appropriate summary statistics. The proportion of subjects who respond to treatment (eg, achieve ACR-pedi 30 at Week 14) was assessed by the chi-square test at an alpha level of 0.05 (two-sided). Continuous response parameters (eg, average CHAQ) will be compared using a t-test on van der Waerden normal scores. Categorical response variables (eg, proportion of subjects with ACR-pedi 30) were analyzed using the Cochran-Mantel-Haenszel (CMH) chi-square test. Rare events (eg, SAEs) were assessed using Fisher's exact test. A matched pair statistical analysis based on McNemar's test was performed to compare the response rate in placebo after 14 weeks of treatment and the response rate in infliximab 6 mg/kg after 14 weeks of treatment.

SUMMARY – CONCLUSIONS:

Study Population: The majority of the subjects (83.6%) in this study were female. This reflects the overall distribution of JRA in the general population. Most subjects (87.3%) were Caucasian; ranging in age between 4 and 17 years. The demographic characteristics and baseline disease characteristics of the study population were well balanced across treatment groups. The median duration of JRA in all subjects was 2.5 years. The majority of randomized subjects (74 of 121; 61.2%) presented with Polyarticular onset JRA. Systemic onset JRA was present in 15.7% (19 of 121) of the subjects, and Pauciarticular onset JRA was present in 23.1% (28 of 121) of the subjects. The most common joint procedure/surgery in this population at baseline was steroid injection that was performed in 51.2% (62 of 121) of the subjects. Growth disturbance was the most common extra-articular manifestation at baseline, occurring in 15.7% (19 of 121) of the subjects, and a positive rheumatoid factor was seen in 22.7% (27 of 119) of the randomized subjects.

Pharmacokinetics/Pharmacodynamics Results: ·Pharmacokinetic analyses demonstrated dose-proportional postinfusion serum concentrations following multiple infusions of 3 or 6 mg/kg infliximab. The 3 mg/kg dose of infliximab was associated with slightly higher clearance and shorter half-life of infliximab compared with the 6 mg/kg dose. In general, by the end of the Week 36 and Week 44 treatments, more than half of the subjects in the 3 mg/kg group did not maintain detectable infliximab in their blood through the 8 weeks up to the next scheduled assessment.
The results from the PD marker analyses indicate that treatment with 3 mg/kg of infliximab produced a greater median percent decrease from baseline in IL-6, MMP-3, VEGF, and ICAM-1 compared with placebo up to Week 14. A dose response effect was shown after Week 14 in the 6 mg/kg group, with larger reductions from baseline in markers IL-6, MMP-3 and VEGF at most timepoints, compared with the 3 mg/kg group.

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Efficacy Results: Centocor concluded that the efficacy data from Site 392 must be excluded from all efficacy analyses since the unbiased nature of the efficacy data could not be assured. A CSR Addendum was written with revised efficacy results. As presented in the Week-64 CSR (which included Site 392 data), the proportion of subjects achieving ACR-pedi 30 in the 3 mg/kg group was greater than in the placebo group at Week 14 and approached statistical significance [65.0%, (39/60) versus 47.5%, (29/61), p = 0.055].
The primary endpoint was reanalyzed with all of the subjects from Site 392 excluded (4 subjects total; 2 in the 3 mg/kg group, 2 in the placebo group). Similar to the result of the original analysis, the revised results also demonstrate that a greater proportion of the 3 mg/kg infliximab-treated subjects achieved the primary endpoint compared with placebo-treated subjects [63.8% (37/58) versus 49.2% (29/59)]. However, the p-value changed from one that approached statistical significance (p = 0.055) to a nonsignificant p-value (p = 0.117). Given the results of the revised primary endpoint analysis, revised secondary efficacy endpoint analyses were not deemed necessary.

Safety Results: The proportion of subjects with adverse events was comparable between placebo (81.7%) and 3 mg/kg (76.7%) groups during the initial 14 weeks of the study. Through Week 14, the most common (and greater than placebo) AEs in the 3 mg/kg group were: fever (16.7%), headache (15.0%), pharyngitis (11.7%), SGPT increased (10.0%), and vomiting (10.0%). The proportion of subjects with adverse events was comparable between the 3 mg/kg (96.7%) and 6 mg/kg (94.7%) groups over 52 and 38 weeks of observation, respectively. The number of treatment emergent adverse events per 100 years of subject follow-up were comparable between the 3 mg/kg (769.9) and 6 mg/kg (768.7) groups. The average number of weeks of treatment were 39.6 and 26.2, respectively.
More than twice as many subjects with serious adverse events were observed in the 3 mg/kg (13.3%) group compared with placebo group (5.0%) during the first 14 weeks of the study. The 3 mg/kg group had a higher overall proportion (31.7%) of subjects with serious adverse events and of SAEs of an allergic nature, than subjects in the 6 mg/kg group (8.8%).
A greater proportion of discontinuation of study infusions due to adverse events was noted in the placebo/6 mg/kg group (8.8%) during active treatment (Weeks 14-52) compared with the 3 mg/kg group (3.3%, Weeks 0-52) or the placebo/6 mg/kg group (1.7%) during placebo administration (Weeks 0-14).
A total of 8 subjects were reported with at least 1 serious infection. There were 6 subjects in the combined group and 2 subjects in the placebo group. The most commonly reported serious infection was pneumonia with a frequency of 3.4% in the combined group. One subject, randomly assigned to the placebo group, was hospitalized and treated for septic shock. Cardiac function deteriorated followed by cardiac arrest. Multiple resuscitations were unsuccessful. A second subject, randomly assigned to the 3 mg/kg group, died post-study. The subject withdrew from the study and approximately 3 months later, died in the hospital while awaiting a stem cell transplant. The cause of death was severe flare of JRA and cardiac arrest.
A higher proportion of subjects with an infusion reaction was observed in the 3 mg/kg group (35.0%) compared with the placebo/6 mg/kg group during active treatment (17.5%).
The proportion of subjects with antibodies to infliximab was higher for the 3 mg/kg group (37.7%) relative to the placebo/6 mg/kg group (12.2%), and the titers were higher for the 3 mg/kg group compared with the 6 mg/kg group. The observed incidence across the treatment groups in the ASPIRE study was, approximately 10.7%.

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Conclusion:

- Due to the small sample size of the study, the result of the primary endpoint analysis is not robust to the removal of the 4 subjects from Site 392. As with the primary endpoint result in the Week-64 CSR, a greater proportion of infliximab-treated subjects achieved the primary endpoint compared with placebo-treated subjects; however, removal of the 4 subjects from the primary endpoint analysis resulted in the p-value changing from 0.055 to 0.117.
- On the basis of the results of this study, Centocor is unable to establish the efficacy of infliximab in JRA.
- This Addendum provides no changes to the analyses and conclusions of safety and clinical pharmacology data from the Week-64 CSR.
- Dose-proportional serum concentrations following multiple infusions of 3 mg/kg or 6 mg/kg of infliximab at 8 week intervals following the induction regimen (at Weeks 0, 2, and 6 or Weeks 14, 16, and 20, respectively) were shown. The 3 mg/kg dose of infliximab was associated with slightly higher clearance and shorter half-life of infliximab compared with the 6 mg/kg dose.
- Through 38 weeks and 52 weeks of follow-up, respectively, the 6 mg/kg dose appears to have a better safety profile than the 3 mg/kg dose. There were no changes in the overall patterns, or types of AEs compared with those observed in previous studies with infliximab.
- A higher incidence of antibodies to infliximab was observed for the 3 mg/kg group compared with the 6 mg/kg group. Across treatment groups, there was also a higher incidence of infusion reactions for the subjects with antibodies to infliximab compared with the subjects who were negative for antibodies to infliximab or inconclusive.

Date of Report: Week-64: 16 May 2005; Addendum 24 Feb 2006

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