Synopsis (C0168T65)

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: C0168T65	**EudraCT No.:** 2004-000681-12
Title of the study: A Randomized, Double-masked, Placebo-controlled, Multicenter Study of the Safety and Efficacy of Infliximab in Subjects with Giant Cell Arteritis	
Principal/Coordinating Investigator(s): Gary Hoffman, MD, Cleveland Clinic Foundation, Cleveland, Ohio, USA	
Study Center(s): 22 study centers: 11 in the USA, 3 in the United Kingdom, 6 in Belgium, 1 in Italy, and 1 in Spain.	
Publication (reference): None	
Studied Period: 22 Oct 2003/29 Jul 2005	**Phase of Development:** 2
Objectives: The primary objective was to assess the preliminary evidence of the safety and efficacy of infliximab in subjects with giant cell arteritis (GCA), as measured by the proportion of relapse-free subjects through Week 22 and the incidence of AEs. The secondary objective was to further evaluate the preliminary evidence of the efficacy of infliximab therapy in subjects with GCA as measured by the following: the proportion of relapse-free subjects through Week 54, the time to first relapse, the levels of biochemical markers of inflammation and disease activity, and the cumulative dose of prednisone (or prednisone equivalent).	
Methodology: This was a Phase 2, multicenter, randomized, double-masked, placebo-controlled, parallel-group study in subjects with GCA. For at least 1 week prior to randomization, subjects were receiving a stable dose of 40 mg/day to 60 mg/day of prednisone/prednisolone, had a normal erythrocyte sedimentation rate (ESR) (< 40 mm in the first hour by Westergren method), and had no symptoms/signs of GCA. At Week 0, subjects were randomized in a 1:2 ratio to receive either placebo or infliximab 5 mg/kg infusions. Subjects were assigned using an adaptive treatment allocation with the subject's baseline prednisone/prednisolone dose as the stratum (receiving 40 mg/day to 50 mg/day; receiving 51 mg/day to 60 mg/day). Study agent infusions were to have been administered at Weeks 0, 2, 6, 14, 22, 30, 38, and 46. Subjects were to be followed through 54 weeks for the assessment of safety and clinical effects. Subjects were also to return at Week 66 for a blood draw to evaluate infliximab concentration, antibodies to infliximab, and biochemical markers of inflammation and disease activity, and for a brief assessment of subject status.	
Number of Subjects (Planned and Analyzed): 42 planned, 44 analyzed	
Diagnosis and Main Criteria for Inclusion: Eligible study subjects were adult males and females who had a diagnosis of GCA (as defined by American College of Rheumatology [ACR] classification criteria for GCA) of ≤ 4 weeks' duration and had an ESR ≥ 40 mm in the first hour by Westergren method at the time of diagnosis of GCA.	
Test Product, Dose and Mode of Administration, Batch Number: Infliximab was supplied as a sterile, white, lyophilized powder in a 10 mg/mL formulation. The 10 mg/mL formulation of infliximab contained 50 mg of sucrose, 0.61 mg of dibasic sodium phosphate dihydrate, 0.22 mg of monobasic sodium phosphate monohydrate, and 0.05 mg of polysorbate 80 in a 20 mL vial for reconstitution with 10 mL of Sterile Water for Injection. Subjects received intravenous infusions of 5 mg/kg infliximab at Weeks 0, 2, 6, 14, 22, 30, 38, and 46. One lot of infliximab (Lot 03A052) was used during the study.	
Duration of Treatment: 46 weeks	

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Reference Therapy, Dose and Mode of Administration, Batch Number: The placebo was supplied as a sterile, white, lyophilized powder containing 50 mg of sucrose, 0.61 mg of dibasic sodium phosphate dihydrate, 0.22 mg of monobasic sodium phosphate monohydrate, and 0.05 mg of polysorbate 80 in a 20 mL vial for reconstitution with 10 mL of Sterile Water for Injection. Subjects received intravenous infusions of placebo at Weeks 0, 2, 6, 14, 22, 30, 38, and 46. Two lots of placebo (Lot 01G061 and Lot 03C157) were used during the study.

Criteria for Evaluation:

Pharmacokinetics: Serum infliximab concentrations were summarized by visit for subjects who received infliximab.

Efficacy: Efficacy analyses included all randomized subjects. The primary efficacy endpoint was the proportion of relapse-free subjects through Week 22. Major secondary efficacy endpoints included the proportion of relapse-free subjects through Week 54, the time to first relapse, and the cumulative dose of prednisone (or prednisone equivalent).

Safety: Safety data (incidence and type of AEs, markedly abnormal changes in laboratory values and vital signs, immune response, and complications of glucocorticosteroids) of all treated subjects were analyzed by treatment received.

Statistical Methods: The Cochran-Mantel-Haenszel (CMH) chi-square test stratified by baseline prednisone/prednisolone dose (40 to 50 mg/day or 51 to 60 mg/day) was used to analyze the primary efficacy endpoint (the proportion of relapse-free subjects through Week 22). The van der Waerden scores on the cumulative glucocorticosteroid or prednisone dose were compared using an analysis of variance. All statistical tests were 2-sided and performed at $\alpha = 0.05$.

SUMMARY – CONCLUSIONS

In order to aid in directing the clinical development program, an interim analysis of the primary and selected secondary endpoints was conducted in Feb 2005, after all subjects had completed the Week 22 visit. The results of this analysis demonstrated that infliximab was generally well tolerated, but it did not reduce the number of first relapses in GCA or the cumulative glucocorticosteroid dosage through Week 22 when compared with placebo. Therefore, further study infusions for all subjects were prematurely discontinued; the last study agent infusion was administered on 11 Mar 2005. Subjects returned for follow-up visits to evaluate safety at 4 weeks and at 20 weeks after their last infusion of study agent. No further clinical development of infliximab for use in the treatment of GCA is planned at this time.

Study Population Results: Treatment groups were generally well balanced for baseline demographic and disease characteristics.

Pharmacokinetic/Pharmacodynamic Results: Median preinfusion serum infliximab concentrations during maintenance treatment (Week 22 to Week 46) ranged from 0.0 µg/mL to 1.7 µg/mL. Median postinfusion serum infliximab concentrations during maintenance treatment ranged from 115.1 µg/mL to 146.7 µg/mL.

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Efficacy Results: Analysis of the primary endpoint and major secondary endpoints showed no statistically significant or clinically meaningful differences between the infliximab treatment group and the placebo treatment group in subjects with GCA. The efficacy results are described briefly as follows:

- The proportion of subjects who remained relapse-free through Week 22 was similar between the infliximab and placebo treatment groups (42.9% of infliximab-treated subjects and 50.0% of placebo-treated subjects; p = 0.651).
- A total of 23 of 28 infliximab-treated subjects and 12 of 16 placebo-treated subjects had at least 1 relapse during the study.
- There was no statistically significant difference between treatment groups in the time to first relapse (p = 0.561).
- The median cumulative prednisone dose through Week 22 was similar between treatment groups (2982.0 P.Eq mg for the infliximab group and 2909.3 P.Eq mg for the placebo group; p = 0.946).

Safety Results:

- Overall, infliximab was generally well tolerated in this small population of elderly subjects with newly diagnosed GCA, with a safety profile consistent with the infliximab prescribing information.
- A total of 92.9% of infliximab-treated subjects and 93.8% of placebo-treated subjects had at least 1 AE during the study. The AEs most commonly reported in infliximab-treated subjects were weight increase (infliximab group 39.3%; placebo group 25.0%), peripheral edema (infliximab group 28.6%; placebo group 6.3%), hypertension (infliximab group 28.6%; placebo group 12.5%), pain (infliximab group 28.6%; placebo group 12.5%), and upper respiratory tract infection (infliximab group 25.0%; placebo group 18.8%). Three infliximab-treated subjects and 2 placebo-treated subjects discontinued study agent because of 1 or more treatment-emergent AEs.
- No subjects died during the study. One or more SAEs were reported in a similar proportion of subjects in each treatment group (28.6% of infliximab-treated subjects and 25.0% of placebo-treated subjects).
- One or more infusion reactions were reported in 21.4% of infliximab-treated subjects. No infusion reactions were reported in placebo-treated subjects. The most commonly reported infusion reactions were infusion syndrome, fever, and urticaria, each reported in 2 (7.1%) infliximab-treated subjects. One infliximab-treated subject permanently discontinued study agent due to infusion reactions of dyspnea and infusion syndrome. There were no reports of possible anaphylactic reactions or possible delayed hypersensitivity (serum sickness-like) reactions during the study.
- A greater proportion of infliximab-treated subjects had 1 or more infections (71.4%) than placebo-treated subjects (56.3%). The most common infection was upper respiratory tract infection. There were no cases of sepsis or TB.
- The proportion of infliximab-treated subjects who tested positive for antibodies to infliximab at any time during the study was 26.9%.

Conclusions: Infliximab administered as 5 mg/kg intravenously every 8 weeks after an induction regimen in this small cohort of subjects with newly diagnosed GCA did not appear to provide a clinically meaningful therapeutic effect. Infliximab was generally well tolerated and had a safety profile consistent with the infliximab prescribing information.

Date of Report: 09 Jun 2006

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