Synopsis (C0743T06)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 1275		
Name of Active Ingredient: CNTO 1275		

Protocol: C0743T06	**EudraCT No.:** 2004-000145-38

Title of the study: A Phase 2, Double-blind, Placebo-controlled, Randomized, Dose-ranging Study of Multiple Subcutaneous Injections of Human Monoclonal Antibody to IL-12p40 (CNTO 1275) in Subjects with Relapsing-remitting Multiple Sclerosis

Principal/Coordinating Investigator(s): Benjamin Segal, MD, [redacted], US

Study Center(s): 38 investigative sites: 12 in the United States (US), 7 in Hungary, 6 in Poland, 5 in the United Kingdom (UK), 3 in the Czech Republic, 4 in Australia, and 1 in Canada.

Publication (reference): None

Studied Period: 03 Aug 2004 / 11 Dec 2006	**Phase of Development:** 2

Objectives: The primary objective was to assess the dose-response effect of multiple SC injections of CNTO 1275 in subjects with relapsing-remitting multiple sclerosis (RRMS) based on the cumulative number of newly gadolinium (Gd)-enhancing T_1-weighted lesions on cranial MRIs through Week 23. The secondary objectives were to assess the clinical response and safety of multiple SC injections of CNTO 1275 and to describe the pharmacokinetics after repeated doses of CNTO 1275 in subjects with RRMS.

Methodology: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adults with a diagnosis of RRMS.
At Week 0, subjects were randomly assigned to 1 of the following 5 treatment groups using an adaptive treatment allocation with investigative site and presence or absence of a Gd-enhancing T_1-weighted lesion on cranial MRI at baseline as the strata:
Group 1: Placebo at Weeks 0, 1, 2, 3, 7, 11, 15, and 19.
Group 2: 27 mg CNTO 1275 at Weeks 0, 1, 2, 3, 7, 11, 15, and 19 (27 mg q4w).
Group 3: 90 mg CNTO 1275 at Weeks 0, 1, 2, 3, 11, and 19; Placebo at Weeks 7 and 15 (90 mg q8w).
Group 4: 90 mg CNTO 1275 at Weeks 0, 1, 2, 3, 7, 11, 15, and 19 (90 mg q4w).
Group 5: 180 mg CNTO 1275 at Weeks 0, 1, 2, 3, 7, 11, 15, and 19 (180 mg q4w).
The study was conducted in 2 study cohorts. A total of 26 subjects were enrolled in Safety Cohort 1 and 223 subjects in Cohort 2. An independent Safety Monitoring Committee (SMC) reviewed the safety data after the last subject in Safety Cohort 1 had received the fifth study agent injection (Week 7) and before the first subject was treated in Cohort 2. After the SMC's review of safety data in Safety Cohort 1, subjects who were eligible for Cohort 2 were randomized to 1 of the 5 treatment groups. Subjects were followed through 37 weeks for the assessment of safety and clinical effect. Data from Safety Cohort 1 and Cohort 2 were combined for analysis purposes. From Week 37 through Week 71, targeted safety information was to be collected.

Number of Subjects (Planned and Analyzed): 250 subjects planned; 249 subjects analyzed.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were adult males and females who had a diagnosis of RRMS as defined by the criteria recommended by the International Panel on multiple sclerosis (MS) Diagnosis, Kurtzke's Expanded Disability Status Scale (EDSS) score of 0 to 6.5, and a history of at least 1 of the following: a minimum of 2 relapses of MS within the previous 2 years but not within the 1-month period prior to screening, or a relapse of MS within the previous 6 months but not within the 1-month period prior to screening.

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Test Product, Dose and Mode of Administration, Batch Number: CNTO 1275 was supplied in a 2 mL single-use vial as a sterile, white, lyophilized powder containing 90 mg CNTO 1275 for reconstitution with 1 mL of sterile water for SC injection; lot numbers D03PM7322 and D05PF7433.

Duration of Treatment: 19 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number: The placebo was supplied in a 2 mL single-use vial as a sterile, white, lyophilized powder for reconstitution with 1 mL of sterile water for SC injection; lot numbers D02PJ7192 and D04PJ7381.

Criteria for Evaluation:
Pharmacokinetics: The pharmacokinetics of CNTO 1275 were determined from CNTO 1275 serum samples that were collected at protocol-specified timepoints from Week 0 through Week 37 for a subset of treated subjects who received CNTO 1275. Samples were also evaluated for antibodies to CNTO 1275.
Efficacy: The efficacy analyses included all randomized subjects (ie, intention-to-treat population). The primary efficacy endpoint was the cumulative number of newly Gd-enhancing T_1-weighted lesions on cranial MRIs in any CNTO 1275 treatment group compared with the placebo treatment group through Week 23. Major secondary endpoints included total number of relapses of MS through Week 23, and change from baseline in EDSS score at Week 23.
Safety: Safety analyses included all subjects who received study treatment. Safety evaluations included assessment of adverse events (AEs), injection site reactions, antibodies to CNTO 1275, changes in vital signs, and changes in routine laboratory values. After Week 37, targeted safety information was collected to evaluate for AEs of special interest with anti-IL-12 or anti-IL-23 therapies (eg, autoimmune and hematological events; malignancies; pregnancies; events of tuberculosis [TB]; and serious adverse events [SAEs]) or any AE associated with the final blood draw.

Statistical Methods: In order to address the primary hypothesis of a dose-response effect of CNTO 1275, the Jonckheere-Terpstra nonparametric trend test procedure with 5% level of significance was used to test for a monotonic trend in the cumulative number of newly Gd-enhancing T_1-weighted lesions on cranial MRIs from baseline through Week 23. Tukey's no statistical significance of trend procedure was used to identify the highest dose of CNTO 1275 for which a dose-response effect occurred. Additionally, the total number of relapses of MS from baseline to Week 23 was compared by treatment group using the nonparametric Wilcoxon-Mann-Whitney rank-sum statistic. The change from baseline in EDSS at Week 23 was analyzed using an analysis of variance on the van der Waerden normal scores.
Categorical data were summarized using counts and percentages. Continuous variables were summarized using descriptive statistics (ie, mean, median, standard deviation, interquartile range, range).
All statistical tests (except the trend test for the primary endpoint) were 2-sided with 5% level of significance.

SUMMARY – CONCLUSIONS: In order to aid the direction of the clinical development program, an interim analysis evaluating safety and efficacy was conducted in June 2006, after all subjects had completed the Week 23 visit. The results of this analysis demonstrated that CNTO 1275 was well tolerated, but did not reduce the cumulative number of newly Gd-enhancing T_1-weighted lesions on cranial MRIs or the total number of relapses of MS through Week 23 when compared with the placebo treatment group. Secondary efficacy analyses conducted on data through Week 37 confirmed the lack of therapeutic effect of CNTO 1275 in subjects with RRMS. Therefore, the study was prematurely terminated on 8 Nov 2006.

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Study Population Results: Overall, baseline demographics and disease characteristics were similar across treatment groups. Approximately half of the subjects in both the combined CNTO 1275 treatment group and the placebo treatment group had at least 1 Gd-enhancing T_1-weighted lesion at baseline. Additionally, 162 (81.0%) of 200 subjects in the combined CNTO 1275 treatment group and 37 (75.5%) of 49 subjects in the placebo treatment group had at least 2 clinical relapses within the previous 2 years.

Pharmacokinetic Results: There was a dose-dependent increase in CNTO 1275 serum concentration with the 4 different CNTO 1275 dose regimens, each consisting of 4 weekly loading doses followed by maintenance doses given at either 8-week or 4-week intervals. Weekly administration of CNTO 1275 resulted in substantial drug accumulation during the loading phase (ie, the first 4 weeks) as a result of the long half-life of CNTO 1275. The highest measured trough serum CNTO 1275 concentrations were observed at Week 3 prior to the 4th loading dose. After instituting maintenance therapy with less frequent doses (ie, q4w or q8w), trough serum CNTO 1275 concentrations gradually decreased accordingly. Trough serum CNTO 1275 concentrations at Week 19 were regarded as representative of trough concentrations during maintenance therapy. It was noted that the median trough serum CNTO 1275 concentration at Week 19 for the 90 mg q8w dose regimen at Week 19 was approximately half of that for the 90 mg q4w maintenance regimen.
Samples from a subset of 39 subjects were evaluated for the presence of antibodies to CNTO 1275 through Week 37. Of those, 2 subjects (both in the 27 mg q4w group) were classified as positive for antibodies to CNTO 1275. The titers of antibodies to CNTO 1275 ranged from 1:40 to 1:80.

Efficacy Results: Analyses of the primary and major secondary endpoints showed no statistically significant or clinically meaningful differences between any of the CNTO 1275 treatment groups and the placebo treatment group in subjects with RRMS.
The primary endpoint analysis conducted at Week 23 showed no evidence that the cumulative number of newly Gd-enhancing lesions in any CNTO 1275 treatment group was statistically significant compared with the placebo treatment group. The 1-sided p-value for the Jonckheere-Terpstra trend test with the placebo treatment group and all CNTO 1275 treatment groups was not estimated because the observed trend was in the opposite direction of that stated in the alternative hypothesis.
The total number of clinical relapses was not significantly different in any CNTO 1275 treatment group compared with the placebo treatment group. The number of subjects with clinical relapses and the number of subjects with objective relapses was similar among all the dose groups.
Analysis of the change from baseline in EDSS at Week 23 showed no statistically significant difference between any CNTO 1275 treatment group compared with the placebo treatment group. The median change from baseline in EDSS for each treatment group was zero.

Safety Results: In general, the number of subjects with AEs was comparable across all CNTO 1275 treatment groups when compared with the placebo treatment group. A total of 170 (85.0%) of 200 subjects in the CNTO 1275 treatment group and 38 (77.6%) of 49 subjects in the placebo treatment group had at least 1 AE during the study. Four subjects treated with CNTO 1275 and no subjects treated with placebo discontinued study agent as a result of an AE. Injection site erythema was the most frequently reported AE, experienced by 45 (22.5%) subjects in the combined CNTO 1275 treatment group and 4 (8.2%) subjects in the placebo treatment group. No subjects discontinued study treatment as a result of injection site reactions. There were no serious infections, and no cases of TB were reported during the study. There was no notable difference in the number of subjects with infections between the combined CNTO 1275 treatment group and the placebo treatment group. No deaths occurred during the study. Six (3.0%) subjects in the combined CNTO 1275 treatment group and 1 (2.0%) subject in the placebo treatment group had an SAE. The number of subjects with markedly abnormal chemistry and hematology laboratory values during the study was similar across treatment groups.

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Conclusions: Although CNTO 1275 was well tolerated, none of the studied doses of CNTO 1275 demonstrated efficacy in the primary or secondary efficacy endpoints. There was no dose-response effect seen in this population of subjects with RRMS treated with any dose of CNTO 1275 based on the cumulative number of newly Gd-enhancing T_1-weighted lesions on cranial MRIs through Week 23. Also, there was no statistically significant difference between subjects treated with placebo and subjects treated with any dose regimen of CNTO 1275 (27 mg q4w, 90 mg q8w, 90 mg q4w, or 180 mg q4w). Based on the lack of efficacy, no further clinical development of CNTO 1275 for use in the treatment of RRMS is planned at this time.		
Date of Revised Report: 24 Jul 2007		

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