Synopsis (C0743T10)

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: C0743T10	**EudraCT No.: 2005-003525-92**
Title of the study: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of CNTO 1275, a Fully Human Anti-IL-12 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis	
Principal/Coordinating Investigator: Alice Gottlieb, MD, PhD – Tufts University Medical Center, Boston, MA, US	
Study Center(s): 24 sites in the US, Canada, Finland, Denmark, and Switzerland	
Publication (reference): None	
Studied Period: 21 Dec 2005/20 Sep 2007	**Phase of Development:** 2
Objectives: The primary objective of this study was to evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with active psoriatic arthritis (PsA). The secondary objectives were to evaluate: (1) The efficacy of CNTO 1275 in achieving a high level of improvement in arthritis. (2) The impact of CNTO 1275 on quality of life. (3) The efficacy of CNTO 1275 on psoriatic skin lesions. (4) The pharmacokinetic and pharmacodynamic characteristics of CNTO 1275 in subjects with PsA.	
Methodology: This was a Phase 2, multicenter, randomized, double-blind, placebo-controlled, 2 arm study of CNTO 1275 90 mg in subjects with active PsA who had an inadequate response to current standard therapies (eg, methotrexate [MTX], corticosteroids, NSAIDs, anti-tumor necrosis factor [anti-TNF] agents).	
Number of Subjects (Planned and Analyzed): 140 planned (70 subjects per group); 146 subjects were randomized to treatment and analyzed for efficacy and for safety; 133 were analyzed for pharmacokinetics and 124 were analyzed for antibodies to CNTO 1275.	
Diagnosis and Main Criteria for Inclusion: Men and women aged 18 years or older with active PsA (defined as disease for at least 6 months prior to study drug administration) who had an inadequate response to standard disease modifying antirheumatic drug (DMARD), and/or NSAID, and/or prior exposure to anti-TNF therapies.	
Test Product, Dose and Mode of Administration, Batch Number: 90 mg CNTO 1275 (or 63 mg after filtration) was administered by SC injection. Subjects randomized to CNTO 1275 x 4 were to receive CNTO 1275 at Weeks 0, 1, 2, and 3. At Week 12, subjects randomized to placebo were to receive CNTO 1275 63 mg at Weeks 12 and 16. One lot of CNTO 1275 was used (D05PF7433).	
Duration of Treatment: The first to last administration of study agent was 16 weeks; pharmacokinetics, efficacy, safety, and antibodies to CNTO 1275 were evaluated through Week 36.	
Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo was administered by SC injection. Subjects randomized to placebo were to receive placebo injections Weeks 0, 1, 2, and 3. To maintain the blind , subjects randomized to CNTO 1275 x 4 were to receive placebo injections at Weeks 12 and 16. One lot of placebo was used (D04PJ7381).	

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Criteria for Evaluation: All randomized subjects were summarized in the description of the study population. All randomized subjects were included in the primary efficacy analysis. Secondary efficacy analyses were based on all randomized subjects or on the subset of subjects with available outcome measurements. Safety analyses included all subjects who were randomly assigned and received at least 1 administration of study agent. Subjects were analyzed according to their randomized treatment group.

Pharmacokinetics/Pharmacodynamics: Blood samples were collected from all subjects at each visit through Week 36 for the determination of serum CNTO 1275 concentration over time and t1/2. Antibodies to CNTO 1275 were determined from serum samples collected at Weeks 0, 12, and 36. Biomarkers were assessed at Weeks 0, 4, 12, and 36.

Efficacy: The primary efficacy endpoint was American College of Rheumatology (ACR) 20 response at Week 12. Major secondary endpoints were ACR 50 and ACR 70 responses, improvement from baseline in HAQ score and Dermatology Life Quality Index (DLQI), and Psoriasis Area and Severity Index (PASI) response at Week 12. Other efficacy assessments included assessments of dactylitis, enthesopathy, morning stiffness, Disease Activity Index (DAS) 28, and target lesions assessments. In addition, the relationship between serum CNTO 1275 concentration and efficacy was examined, as well as between antibodies to CNTO 1275 and efficacy.

Safety: Safety was assessed by 1) measurement of vital signs; 2) AEs assessment and injection site reaction evaluation; and 3) routine laboratory analyses (ie, complete blood count, blood chemistry).

Statistical Methods: Simple descriptive statistics, such as mean, median, SD, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables were used to summarize most data. For categorical data, the Cochran-Mantel-Haenszel (CMH) chi-square test was used to compare the proportion of subjects achieving selected endpoints (eg, proportion of subjects with an ACR 20 response). Continuous response parameters were compared using an analysis of covariance (ANCOVA) on the van der Waerden normal scores (Conover, 1980). Analyses were adjusted for subjects' status of anti-TNF exposure for PsA or psoriasis. All statistical procedures were performed 2-sided at a significance level of 0.05. The study was designed to maintain a Type I error of 0.05 or less for the primary analysis. Nominal p-values were to be reported for secondary analyses.

SUMMARY – CONCLUSIONS

Study Population Results: Baseline demographics and disease characteristics were generally comparable between the study groups. The majority of subjects were men (56.2%) and Caucasian (94.5%). The median age was 49.0 years, and the median weight was 90.91 kg. The median duration of PsA was 5.22 years while the median duration of psoriasis was 16.92 years. The total median numbers of swollen and tender joints at baseline were 9.0 and 18.0, respectively. The total median HAQ disability index was 0.8 and total median C-reactive protein (CRP) was 0.5 mg/dL. In subjects with ≥ 3% body surface area (BSA) involvement at baseline, the median PASI score was 8.70 and the median DLQI score was 10.5.

Pharmacokinetic/Pharmacodynamic Results: At each sampling timepoint from Week 1 through Week 4, serum CNTO 1275 concentrations were higher in subjects who received 90 mg x 4 than in subjects who received 63 mg x 4, with the difference between the 2 dosages showing an approximate dose-proportionality. CNTO 1275 was eliminated from the circulation with a median t1/2 of 22.4 days. Subjects classified as positive for antibodies to CNTO 1275 exhibited median serum levels of CNTO 1275 that trended lower than those in subjects either negative or undetectable for antibodies to CNTO 1275. Antibodies to CNTO 1275

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were generally low titer and occurred in 11.3% of subjects treated with CNTO 1275. No significant changes were seen in vascular endothelial growth factor (VEGF), soluble IL-2 receptor (sIL-2R), matrix metalloproteinase-3 (MMP-3), or osteocalcin in CNTO 1275-treated subjects when compared with placebo-treated subjects.

Efficacy Results: Subjects with active PsA who received injections of CNTO 1275 at Weeks 0, 1, 2, and 3 (CNTO 1275 x 4 group) showed significant improvement in PsA as measured by endpoints designed to assess arthritis and psoriasis when compared with subjects randomized to placebo. At Week 12, for subjects randomized to CNTO 1275:

- A significantly greater proportion achieved ACR 20 (42.1% vs 14.3%, $p < 0.001$), ACR 50 (25.0% vs 7.1%, $p = 0.004$) and ACR 70 responses (10.5% vs 0%, $p = 0.005$) compared with subjects randomized to placebo.
- Similar trends were generally seen in each of the individual ACR component scores.
- There was a significantly greater change in HAQ disability score (median: –0.25 vs –0.0, $p < 0.001$) and a greater proportion demonstrated a decrease from baseline HAQ score of ≥ 0.3 units (46.7% vs 21.9%, $p = 0.002$).
- In the subset of subjects with 1 or more dactylitis digits at baseline ($n = 33$), there was a significant change in the dactylitis score (median: 2.00 vs 0.00, $p = 0.011$), but there was no significant reduction in the proportion of subjects with dactylitis digits.
- There was a significantly lower proportion of subjects with active enthesopathy (23.0% vs 42.2%, $p = 0.016$).
- There was a significant percent reduction in duration of morning stiffness (median: 50.00% vs 0.00%, $p = 0.003$).
- There was a significantly greater percent improvement from baseline in psoriasis target lesion score (median: 60.00% vs 0.00%, $p < 0.001$).
- In the subset of subjects with psoriasis BSA $\geq 3\%$ at baseline:
  - A greater percentage achieved a PASI 50 (73.0% vs 14.5%), PASI 75 (52.4% vs 5.5%, $p < 0.001$) and PASI 90 (33.3% vs 3.6%, $p < 0.001$) response;
  - There was a greater change from baseline in DLQI score (median: –6.0 vs 0.0, $p < 0.001$).

Response trends for PsA peaked at Week 16 for subjects randomized to CNTO 1275.

- The proportion who achieved an ACR 20 response was 49.3%
- The change in the HAQ disability index was a median –0.38.

At Week 36, for subjects randomized to CNTO 1275:

- ACR 20 responses at Week 36 (32 weeks after the last dose of CNTO 1275) were nearly 80% of those reported at Week 12.
- Similar trends were generally seen in each of the individual ACR component scores with the exception of median CRP. This might reflect that both groups had low baseline CRP levels.
- The level of PASI 75 response peaked at Week 12 and decreased by Week 36.

Subjects in the placebo → CNTO 1275 x 2 group, who received CNTO 1275 at Weeks 12 and 16, achieved improvements in arthritis and psoriasis similar to those of subjects in the CNTO 1275 x 4 group. At Week 24, 12 weeks after initiation of CNTO 1275:

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- The proportions of subjects who achieved ACR 20, ACR 50, and ACR 70 responses were 50.9%, 27.3%, and 9.1%, respectively.
- In the subset of subjects with psoriasis BSA ≥ 3% at baseline, the proportions of subjects with PASI 75 and PASI 90 responses were 52.2% and 34.8%, respectively.
- The change from baseline in HAQ disability score was a median of –0.25.

Though the number of subjects positive for antibodies to CNTO 1275 was small, there was no apparent effect of antibodies on ACR response. However, these subjects were less likely to achieve an improvement in skin disease as measured by PASI response.

Safety Results: Through Week 12:

- CNTO 1275 was generally well tolerated. The proportions of subjects reporting at least 1 AE were comparable in the placebo and CNTO 1275 x 4 groups, at 62.9% and 60.5%, respectively.
- The most commonly reported AEs in the CNTO 1275 x 4 and placebo groups were upper respiratory tract infection (13.2% and 8.6%, respectively), nasopharyngitis (10.5% and 2.9%, respectively), and diarrhea (6.6% and 2.9%, respectively).
- No CNTO 1275-treated subjects and 3 placebo-treated subjects reported SAEs. One subject in the placebo group had an MI.

Through Week 36:

- The average durations of follow-up for subjects randomized to the CNTO 1275 x 4 and placebo → CNTO 1275 x 2 (after Week 12) groups were approximately 35 weeks and 23 weeks, respectively.
- AEs were reported by 76.3% of subjects in the CNTO 1275 x 4 group and 63.2% of subjects in the placebo → CNTO 1275 x 2 group.
- The pattern of AEs after placebo crossover was similar to the pattern observed during the placebo controlled period. As through Week 12, the most commonly reported AEs in the CNTO 1275 combined group were upper respiratory tract infection (14.3%), nasopharyngitis (9.8%), and diarrhea (6.8%). A disproportionate increase in AE rates was not observed after Week 12 through Week 36.
- After Week 12 and through Week 36, 7 additional subjects reported SAEs, 1 subject in the placebo group who did not cross over to receive CNTO 1275 and 6 subjects in the CNTO 1275 combined group.
  - One CNTO 1275-treated subject had an MI and 1 CNTO 1275-treated subject had a haemorrhagic stroke.
  - One serious infection (respiratory tract infection) occurred in a CNTO 1275-treated subject.
- One malignancy was reported, a basal cell carcinoma in a CNTO 1275-treated subject with a prior history of basal cell carcinoma.
- There were no cases of TB or serious opportunistic infections.
- There were no deaths.
- Injection-site reactions were infrequent, mild to moderate in severity, and occurred only in subjects who received CNTO 1275 injections. There was no association between antibodies to CNTO 1275 and injection-site reactions.
- Markedly abnormal laboratory values were infrequent.

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Conclusions:

- Treatment with 4 weekly doses of CNTO 1275 led to significantly greater proportions of ACR 20 responses at Week 12, and responses reported at Week 36 (32 weeks after the last dose of CNTO 1275) were nearly 80% of those reported at Week 12.
- In the subset of subjects with BSA ≥ 3% at baseline, a greater percentage of CNTO-1275 treated subjects achieved significant improvement in PASI and DLQI at Week 12.
- In subjects who initially received placebo and crossed over to receive 2 doses of CNTO 1275 at Weeks 12 and 16, responses were similar to those seen in the subjects originally randomized to 4 weekly doses of CNTO 1275.
- Overall AE rates were comparable between placebo- and CNTO 1275-treated subjects. Numerically, there were more events of upper respiratory tract infections, nasopharyngitis, and diarrhea in CNTO 1275-treated versus placebo-treated subjects, though event numbers were small precluding conclusions about an impact of CNTO 1275.
- The t1/2 values for CNTO 1275 in this study were similar to a typical t1/2 for an endogenous IgG. CNTO 1275 t1/2 values in this study were also consistent with those reported in other Phase 1 to Phase 3 studies in subjects treated with single or multiple doses of SC CNTO 1275.

Date of Report: 22 May 2008

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