

Synopsis (C0743T09 PHOENIX 2)

Name of Sponsor/Company: Centocor, Inc	Associated with Module 5.3 of the Dossier	
Name of Finished Product: CNTO 1275		
Name of Active Ingredient: Monoclonal antibody (CNTO 1275) to IL-12p40		
Protocol: C0743T09		EudraCT No.: 2005-003530-17
Title of the study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial Evaluating the Efficacy and Safety of CNTO 1275 in the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis		
Principal/Coordinating Investigator: Prof. Kristian Reich – SCIderm GmbH, [REDACTED], Germany		
Study Centers: 71 investigative sites: 4 sites in Austria, 19 sites in Canada, 1 site in France, 10 sites in Germany, 2 sites in Switzerland, 3 sites in the United Kingdom, and 32 sites in the United States		
Publication (reference): Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). <i>Lancet</i> . 2008;371(9625):1675-84.		
Studied Period: 03 Mar 2006/14 Sep 2007		Phase of Development: 3
Objectives: The primary objective of this study was to evaluate the efficacy and safety of CNTO 1275 in the treatment of subjects with moderate to severe plaque psoriasis. Secondary objectives were to: (1) Evaluate dosing interval adjustment in subjects who inadequately respond to their starting dose regimen and (2) Evaluate the impact of CNTO 1275 on quality of life. The primary focus of this Clinical Study Report is the evaluation of data from the randomized dose interval adjustment period.		
Methodology: This is a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of CNTO 1275 45 mg (Group 1), CNTO 1275 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis.		
Number of Subjects (Planned and Analyzed): 1200 planned (400 subjects per group); 1230 subjects were randomized to treatment and analyzed for efficacy and for safety; 1212 subjects were analyzed for pharmacokinetics of CNTO 1275		
Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy and had a Psoriasis Area and Severity Index (PASI) \geq 12, and at least 10% of their total body surface area (BSA) involved.		
Test Product, Dose and Mode of Administration, Batch Number: 45 or 90 mg CNTO 1275 (0.5 or 1.0 mL, respectively) was administered by SC injection. Subjects randomized to the 45 or 90 mg CNTO 1275 groups were to receive CNTO 1275 at Weeks 0, 4, and 16. At Week 12, subjects randomized to placebo, were to receive 45 mg or 90 mg CNTO 1275 at Weeks 12 and 16. Two lots of CNTO 1275 (D05PE7427 and D05PE7428) were used.		
Duration of Treatment: First to last administration of study agent was either 40 weeks (subjects maintained on q12w dosing), 44 weeks (subjects adjusted to q8w dosing at Week 28), or 48 weeks (subjects adjusted to q8w dosing at Week 40); pharmacokinetic, antibodies to CNTO 1275, efficacy, and safety data evaluated through Week 52.		

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Name of Active Ingredient: Monoclonal antibody (CNTO 1275) to IL-12p40		
Criteria for Evaluation: All randomized subjects were summarized in the description of the study population. All randomized subjects were included in the primary efficacy, and selected secondary analyses; subjects were analyzed according to the assigned treatment group. Secondary efficacy analyses were based on all randomized subjects or on the subset of subjects with available outcome measurements according to their randomized group. Safety evaluations were based on subjects who received at least 1 administration of study agent; subjects were analyzed according to the actual treatment received.		
Pharmacokinetics/Antibodies to CNTO 1275: Blood samples were collected from all subjects at selected timepoints through Week 52, for the determination of serum CNTO 1275 concentration overtime and the incidence of antibodies to CNTO 1275. In addition, a CNTO 1275-specific cell based Neutralizing antibody (NAb) bioassay was used to identify NAb positive subjects among those who tested positive for antibodies to CNTO 1275 in a bridging Enzyme Immunoassay (EIA).		
Efficacy: Efficacy evaluations in this CSR included the Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA). In addition, the relationship between efficacy and antibodies to CNTO 1275 was examined.		
Safety: Safety evaluations included the following: 1) AEs and serious AEs (SAEs) that may have occurred at and between each of the evaluation visits; 2) collection of vital signs, including weight 3) TB evaluation; 4) changes in routine laboratory analyses (hematology and chemistry); 5) evaluation of hemoglobin A1c at selected timepoints; and 6) post-hoc evaluation of baseline and Week 12 lipids.		
Statistical Methods: A Cochran-Mantel-Haenszel (CMH) chi-square test was used to compare the proportion of subjects responding to treatment. Continuous response parameters were compared using an analysis of variance (ANOVA) on the van der Waerden normal scores with weight as a binary covariate. The CMH chi-square test stratified by site (pooled) and weight (≤ 90 kg, > 90 kg) were used to determine the p-values for comparing the primary endpoint between the CNTO 1275 treatment groups and the placebo group. The row mean score chi-square statistic stratified by weight was used to compare the ordinal category variable. To maintain the overall Type I error rate at 0.05 for the primary endpoint analysis and the major secondary endpoint analyses, the primary endpoint and the major secondary endpoints were tested sequentially in a prespecified order and for each endpoint, the Holm's procedure was used if 2 doses were tested.		

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SUMMARY – CONCLUSIONS		
<p>Study Population Results: Demographic characteristics were generally well balanced among randomized groups. The majority (68.3%) of subjects were men and most subjects were Caucasian (91.7%). The population included substantial proportions of subjects with moderate as well as severe psoriasis, based on a BSA threshold of 20%, a PASI threshold of 20, and a PGA score of mild or moderate (< 4) versus marked or severe (≥ 4). Approximately one-fourth of subjects reported a medical history of psoriatic arthritis (PsA), and approximately 16% of subjects had an inadequate response to, were intolerant to, or had a contraindication to ≥ 3 conventional systemic antipsoriatic therapies. Baseline clinical disease characteristics for the subset of subjects who underwent a second randomization at Week 28 (ie, partial responder subpopulations) were generally comparable to the overall population randomized at Week 0. The baseline clinical disease characteristics differed for subjects who were partial responders versus subjects who were PASI 75 responders at Week 28; partial responders tended to have higher body weight, more marked or severe disease as measured by PGA, a higher incidence of PsA, and were more likely than PASI 75 responders to have failed treatment with at least 1 conventional systemic or biologic agent.</p>		
<p>Pharmacokinetic/Antibodies to CNTO 1275 Results:</p>		
<ul style="list-style-type: none"> • In long-term PASI 75 responders who continued q12w dosing through Week 52, median serum CNTO 1275 concentrations were higher in the 90 mg group than the 45 mg group, with the differences between the 2 groups showing an approximate dose-proportionality. • Serum CNTO 1275 concentrations were maintained at steady state from Week 28 through Week 52 in PASI 75 responders who continued q12w dosing; there was no evidence of accumulation in serum CNTO 1275 concentrations over time when given subcutaneously q12w. • In partial responders, median trough serum concentrations of CNTO 1275 increased substantially when the dosing interval was adjusted to q8w. • The overall incidence of antibodies to CNTO 1275 through Week 52 was low. Sixty-five (5.4%) subjects developed antibodies to CNTO 1275. Antibody responses were predominantly low titer. Observations based on the antibodyanalyses are: <ul style="list-style-type: none"> – The overall incidence of antibodies in the combined 45 mg group, regardless of subjects’ weight, trended higher than the combined 90 mg group (40 [6.7%] subjects vs 25 [4.2%] subjects). – The overall incidence of antibodies in subjects ≤ 100 kg was lower than those in weighing > 100 kg (4.3% vs 8.1%). – Subjects positive for antibodies to CNTO 1275 exhibited median serum levels of CNTO 1275 that were generally lower than those in subjects negative or undetectable for antibodies to CNTO 1275. – Analysis of the neutralizing capacity of antibodies to CNTO 1275 showed that most of the antibodies were able to neutralize the bioactivity of CNTO 1275 in vitro. 		

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<p>Efficacy Results:</p> <ul style="list-style-type: none"> The major secondary endpoint of the number of visits at which Week 28 partial responders achieved a PASI 75 response between Weeks 40 and 52 was not higher in the overall population of subjects randomized to q8w versus q12w (p = 0.468). In the 90 mg group, partial responders randomized to 90 mg q8w achieved a PASI 75 at more visits between Weeks 40 and 52 than those randomized to continue 90 mg q12w dosing (p = 0.014). However, in the 45 mg group, the number of visits at which a PASI 75 response was achieved between Weeks 40 and 52 was not different in subjects randomized to 45 mg q8w versus 45 mg q12w (p = 0.210). Among Week 28 partial responders in the 90 mg group, efficacy was consistently superior in subjects adjusted to q8w dosing as compared with those maintained on q12 week dosing: <ul style="list-style-type: none"> A higher proportion of subjects achieved a PASI 75 response at Week 52 (68.8% with q8w dosing versus 33.3% with q12w dosing; p = 0.004); PASI 50, 75, and 90 responses and PGA responses over time after Week 36 were consistently higher in subjects randomized to 90 mg q8w versus 90 mg q12w; PASI and PGA responses were consistently higher in each baseline weight strata (≤ 100 kg or > 100 kg), and response patterns paralleled the response observed in the overall population of partial responders. Among Week 28 partial responders in the 45 mg group, no improvements in PASI or PGA response were observed in subjects adjusted to q8w dosing as compared with those maintained on q12 w dosing. The majority of subjects maintained a high level of response with q12w dosing through Week 52. Approximately 90% of subjects in the 45 mg and 90 mg groups who did not undergo dose adjustment maintained a PASI 75 response at Week 52. The levels of efficacy observed with self-administration and health care professional administration of CNTO 1275 were consistent. Overall, the incidence of subjects positive for antibodies to CNTO 1275 was low. In the 45 mg group, subjects positive for antibodies to CNTO 1275 may trend to lower clinical efficacy; however, antibody positivity does not preclude a clinical response. There was no evidence of lower clinical efficacy with an antibody positive response in the 90 mg group. <p>Safety Results: CNTO 1275 was generally well tolerated. Through Week 52, 1212 subjects received at least 1 dose of CNTO 1275. Subjects randomized to CNTO 1275 treatment at Week 0 and maintained on q12w dosing could have received up to 5 injections of CNTO 1275 through Week 52, providing safety data associated with up to 12 months of exposure.</p> <ul style="list-style-type: none"> Among subjects randomized to CNTO 1275 at Week 0, 155 subjects were partial responders at Week 28 and were randomized to q8w versus q12w dosing. Among subjects randomized at Week 28, rates of specific AEs were generally comparable between the q8w and q12w groups. The pattern of AEs reported during the dosing interval adjustment period were similar to those reported in the overall population. Through Week 52, the AE profile of the 45 mg and 90 mg groups remained comparable. The most commonly reported system-organ class of AEs was infections and infestations, and the most commonly reported AE was nasopharyngitis. 		

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<ul style="list-style-type: none"> • The percentage of subjects who experienced SAEs during the randomized dose interval adjustment period was low and was not higher in the q8w groups (1.3%) compared with the q12w groups (6.3%). • Through Week 52, SAEs were reported in 67 (5.5%) CNTO 1275-treated subjects with an average follow up of 46.5 weeks. Compared to the 2.6% of CNTO 1275-treated subjects reporting SAEs through Week 28, this rate does not suggest a disproportionate increase in the proportion of subjects reporting SAEs over time. • The most frequently reported SAEs were in the cardiac disorders and infections and infestations system-organ classes with generally comparable rates observed in subjects receiving 45 mg dosing (ie, 45 mg and placebo → 45 mg groups) versus 90 mg dosing (ie, 90 mg and placebo → 90 mg groups). • The proportion of subjects reporting at least 1 infection during the randomized dose interval adjustment period was comparable between the combined q8w and the combined q12w groups (22.4% and 26.6%, respectively). The types of infections reported during this period were similar to those reported in the overall population through Week 28. • Infection rates and the profile of infections observed through Week 52 were similar in the 45 mg and 90 mg groups (rates of 45.7% and 47.7%, respectively). • Rates of serious infections were remained low with 10 (0.8%) CNTO 1275-treated subjects reporting at least 1 serious infection through Week 52. • No cases of active TB or serious potential opportunistic infections were reported. • The incidence of injection site reactions remained low and most reactions were mild. • Injection site reactions appeared to be modestly higher with 90 mg administration. • No possible anaphylactic or possible serum sickness-like reactions to study agent were reported. • Through Week 52, 17 malignancies occurred in 13 subjects. Nonmelanona skin carcinomas were reported in 10 CNTO 1275-treated subjects and 1 placebo-treated subject. Two solid tumors were reported; 1 squamous cell carcinoma of the tongue (CNTO 1275-treated subject) and 1 hepatic neoplasm (placebo-treated subject). There were no cases of lymphoma reported. • There was no clear impact of weight on the rates of AEs, SAEs, infections, or AEs leading study agent discontinuation. • The rates of markedly abnormal values in hematology and chemistry laboratory test results remained low, with no observed disproportionate increase in rates with additional follow-up. The rates were comparable between q8w and q12w dosing. • The pattern of markedly abnormal changes in hematology and chemistry values was similar to the events reported through Week 28. Hemoglobin A1c levels remained stable over time through Week 52. There were small increases in fasting lipid parameters (TC, LDL, HDL, total glycerides) in the placebo, 45mg, and 90 mg groups over 12 weeks, with minimal changes in the atherogenic cholesterol ratios (TC/HDL, LDL/ HDL). • The low incidence of antibody-positive subjects precludes definitive conclusions on the impact of antibody status on the development of injection site reactions, however, there was no apparent association between development of antibodies to CNTO 1275 and the development of injection site reactions. 		

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Conclusions: <ul style="list-style-type: none">• In subjects receiving 90 mg CNTO 1275 dosing who were partial responders after 28 weeks of treatment, significant improvements in efficacy were achieved by shortening the dosing interval from q12w to q8w. In subjects receiving 45 mg, no clear benefit was shown after dosing interval adjustment from q12w to q8w.• The majority of subjects (approximately 90%) who were initially randomized to CNTO 1275 at baseline (45 mg or 90 mg) maintained a high level of response with q12w maintenance therapy through Week 52.• CNTO 1275 therapy was generally well-tolerated with up to 52 weeks of treatment at both 45 mg and 90 mg.• CNTO 1275 therapy was generally well-tolerated in partial responders in whom the dosing interval was adjusted to q8w intervals. AEs, SAEs, AEs leading to study agent discontinuation, and infections were generally comparable between partial responders who adjusted to q8w dosing and those who remained on q12w dosing.• The pattern of AEs, SAEs, AEs leading to study agent discontinuation, and infections through Week 52 were similar to patterns observed in early study periods. The rates of these events did not disproportionately increase with additional follow up.• Comparable efficacy and safety were observed in subjects in whom CNTO 1275 was self-administered versus administered by a health care professional.• The proportion of subjects who developed antibodies to CNTO 1275 remained low through Week 52. Among the small number of subjects who tested positive for antibodies to CNTO 1275, response rates trended lower with 45 mg. No apparent impact on safety was observed.		
Date of Report: 20 Jun 2008		