Synopsis (C0743T08 PHOENIX 1)		
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: C0743T08	**EudraCT No.: 2005-003529-15**	
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(s): Craig Leonardi, MD, Central Dermatology, [redacted]		
Study Center(s): 48 investigative sites: 29 sites in the US, 16 sites in Canada, and 3 sites in Belgium		
Publication (reference): None		
Studied Period: 15 Dec 2005/12 Apr 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. The secondary objectives were to: (1) Evaluate the maintenance of response with CNTO 1275 and (2) Evaluate the impact of CNTO 1275 on quality of life (QOL).		
Methodology: This is a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of 45 mg (Group 1), 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis.		
Number of Subjects (Planned and Analyzed): 750 planned (250 subjects per group); 766 subjects were randomized to treatment and analyzed for efficacy; 765 subjects were treated and analyzed for safety; 751 subjects had samples available for the pharmacokinetics analysis; 743 subjects were analyzed for antibodies of CNTO 1275.		
Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who have a Psoriasis Area and Severity Index (PASI) ≥ 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 at Week 0, were to receive 45 mg or 90 mg CNTO 1275 at Weeks 12 and 16. Subsequent dosing regimens were to be determined by each subject's response status according to the study design. Two lots of CNTO 1275 (D05PE7427 and D05PE7428) were used in the study.		
Duration of Treatment: The first to the last study agent administration was 48 weeks or more; efficacy and safety data were evaluated through the date the last subject completed the Week 52 visit; pharmacokinetic and antibodies to CNTO 1275 data were evaluated through Week 52.		

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Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo was administered by SC injection. Subjects randomized to placebo were to receive 2 placebo injections (0.5 mL and 1.0 mL) at Weeks 0 and 4. Subjects randomized to the CNTO 1275 groups were to receive 2 placebo injections (0.5 mL and 1.0 mL) at Week 12. To maintain the blind associated with CNTO 1275 dose administration, each subject randomized to CNTO 1275 was also given a placebo injection; subjects in the 45 mg group received a 1.0 mL placebo injection, and subjects receiving 90 mg also received a 0.5 mL placebo injection. Two lots of placebo (D05PE7429 and D05PE7430) were used.

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 randomized 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 included subjects who received at least 1 study agent administration; subjects were analyzed according to the actual treatment received.

Pharmacokinetics/Pharmacodynamics: Blood samples were collected from all subjects at selected timepoints through Week 52, for the determination of serum CNTO 1275 concentration overtime. The incidence of antibodies to CNTO 1275 were determined from serum samples collected from all subjects at baseline, Weeks 12, 40, and 52.

Efficacy: The primary endpoint was the proportion of subjects who achieved PASI 75 response at Week 12. Efficacy assessments included PASI and Physician's Global Assessment (PGA), Nail Psoriasis Severity Index (NAPSI), Nail PGA, and Itch VAS. Quality of life evaluations included Dermatology Life Quality Index (DLQI) and SF-36. Health economics assessments included subjects' employment status, number of work days missed, and daily productivity. 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 and SAEs that may have occurred at and between each of the evaluation visits; 3) TB evaluation; 4) changes in routine laboratory analyses (hematology and chemistry); 5) evaluation of fasting glucose, hemoglobin A1c, C-reactive protein (CRP), and D-dimer at selected timepoints.

Statistical Methods: Simple descriptive statistics, such as mean, median, SD, interquartile (IQ) range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. A Cochran-Mantel-Haenszel (CMH) chi-square test was used to compare the proportion of subjects responding to treatment. Survival analysis techniques were used for endpoints defined by time to an event. The stratified log-rank test was used to compare endpoints defined by time to an event (eg, time to loss of PASI 75 response). 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) was used to determine the p-values for comparing the primary endpoint between each of the CNTO 1275 treatment groups and the placebo group. 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 pre-specified order and for each endpoint, the Holm's procedure was used if 2 tests were performed.

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SUMMARY – CONCLUSIONS

Study Population Results: Demographic characteristics were generally well balanced among randomized groups. The majority (69.3%) of subjects were men, most subjects were Caucasian (93.6%), and the median age and body weight of subjects was 45.5 years and 91.6 kg, respectively. The median duration of psoriasis was 18.3 years. The population spanned moderate to severe psoriasis, with a median BSA of 21.0% and a median PASI score of 17.6 and 43.7% had a PGA of marked or severe. Subjects showed an impairment in the QOL with a median DLQI score at baseline of 10.0.

Pharmacokinetic/Pharmacodynamic Results:

- Serum CNTO 1275 concentrations were higher in the 90 mg group than the 45 mg group, with differences between the 2 groups showing dose proportionality.
- Steady state was achieved by Week 28. The median steady-state trough serum concentrations at Week 28 were 0.21 μg/mL (45 mg q12w) and 0.47 μg/mL (90 mg q12w).
- There was no evidence of accumulation in CNTO 1275 concentrations over time when given subcutaneously q12w.
- Subjects of higher weight (> 100 kg) had lower serum CNTO 1275 concentrations compared with subjects of lower weight (≤ 100 kg).
- The overall incidence of antibodies to CNTO 1275 through Week 52 was low with 38 (5.1%) subjects developing an immune response to CNTO 1275.
- The overall incidence of antibodies in the combined 45 mg group was higher than the combined 90 mg group (24 [6.4%] subjects versus 14 [3.8%] subjects).
- Among subjects with weight > 100 kg, a higher rate of antibodies to CNTO 1275 was observed in the combined 45 mg group compared with the combined 90 mg group (19 [14.5%] subjects versus 8 [6.2%] subjects).
- Subjects positive for antibodies to CNTO 1275 exhibited median serum levels of CNTO 1275 that were consistently lower than those in subjects negative or undetectable for antibodies to CNTO 1275.

Efficacy Results: Subjects with moderate to severe psoriasis who received either 45 mg or 90 mg achieved significant improvement in psoriasis as measured by PASI, PGA, NAPSI, and Itch VAS, as well as significant improvements in QOL (DLQI and SF-36) and health economic (productivity VAS) measures.

- The proportion of subjects who achieved the primary efficacy endpoint (PASI 75 response at Week 12) was substantially and significantly greater in the 45 mg 171(67.1%) and 90 mg 170 (66.4%) groups compared with placebo 8 (3.1%) ($p < 0.001$ for each CNTO 1275 group versus placebo). The proportion of subjects who achieved PGA of cleared (0) or minimal (1) at Week 12 (major secondary endpoint) was also substantially and significantly greater in the CNTO 1275 groups than the placebo group which parreled the PASI 75 response.
- Subjects treated with CNTO 1275 demonstrated significant improvements in DLQI score at Week 12 (major secondary endpoint).

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- CNTO 1275 resulted in a rapid, clinically significant and substantial improvement in psoriasis:
  - Significant improvement in psoriasis was observed in each CNTO 1275 group compared with placebo by Week 2, as measured by the percent improvement in PASI and PASI 50 response ($p < 0.001$ for each comparison);
  - At Week 4, the proportion of subjects achieving a PASI 75 response in each CNTO 1275 group was significantly higher compared with placebo ($p < 0.001$);
  - The proportions of PASI 90 responders at Week 12 were substantially and significantly higher in the 45 mg 106 (41.6%) and 90 mg 94 (36.7%) groups compared with placebo 5 (2.0%) ($p < 0.001$).
  - The great majority of subjects (over 80%) in the CNTO 1275 groups experienced improvement in their psoriasis, as measured by PASI 50 response at Week 12.
- Maximum or near maximum response rates were achieved around Week 24 and were generally maintained through Week 40.
- In subjects who were long-term PASI 75 responders, the major secondary endpoint of maintenance of response was significantly superior in subjects receiving q12w maintenance therapy than in subjects withdrawn from CNTO 1275 ($p \leq 0.001$ in the combined and in each CNTO 1275 maintenance therapy group versus the withdrawal group).
- A dose-response as measured by the proportions of subjects achieving PASI 75 response was observed beginning at Week 16 and after.
  - Dose-response was most apparent in subjects > 100 kg and was less apparent in subjects ≤ 100 kg.
- Substantial proportions of subjects who inadequately responded to q12w dosing (partial responders at Week 28 and PASI 75 nonresponders at Week 40), achieved a PASI 75 response after dosing interval adjustment to q8w.
- PASI 75 responses and PGA scores of cleared or minimal at Week 12 were generally consistent across subgroups defined by demographic features, clinical disease characteristics, and psoriasis medication history.
- Significant improvements in nail manifestations of psoriasis were observed as measured by NAPSI .
- Significant improvements in itch manifestations of psoriasis were observed as measured by Itch VAS.
- Subjects treated with CNTO 1275 demonstrated significant and clinically meaningful improvements in QOL.
- Significant improvements in DLQI scores were observed as early as Week 2. By Week 12, significant improvements in DLQI and DLQI component scores were observed, and approximately one third of subjects treated with CNTO 1275 indicated psoriasis had no detectable impairment on quality of life (DLQI = 0).

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- Significant improvements in SF-36 physical and mental component summary scores were observed, supporting the efficacy of CNTO 1275 in improving QOL.
- In subjects withdrawn from therapy at Week 40, impairment in QOL was observed at Week 52, ie, after 1 missed dose.
- Clinical response was generally associated with serum CNTO 1275 levels. Subjects with higher clinical responses as measured by PASI response had higher median serum concentrations of CNTO 1275 than those with lower clinical responses.
- The low incidence of antibody positive subjects precludes definitive conclusions on the impact of antibody status on clinical response. Subjects positive for antibodies to CNTO 1275 tended to have lower clinical efficacy, however antibody positivity does not preclude a clinical response. In general, subjects classified as undetectable for antibodies were associated with better clinical response.
- Consistent levels of efficacy and maintenance of response were observed with self-administration versus health care professional administration of CNTO 1275.

Safety Results: CNTO 1275 was generally well tolerated. Through the end of the reporting period, 753 subjects received at least 1 dose of CNTO 1275. All subjects could have received at least 6 months of exposure, and subjects randomized to CNTO 1275 at baseline could have received 12 months or more of exposure.

- Through Week 12, AE rates, AE profiles, and rates of AEs leading to study agent discontinuation in each of the CNTO 1275 treatment groups were generally comparable to those observed in the placebo group. Through the end of the reporting period, AE rates, AE profiles, and rates of AEs leading to study agent discontinuation were generally comparable in the 45 mg and 90 mg groups. During the randomized withdrawal portion of the study, AE rates, AE profiles, and rates of AEs leading to study agent discontinuation were generally comparable between the maintenance group and the withdrawal group.
- No deaths were reported through the end of the reporting period. Through Week 12, 0.8% of placebo-treated and 1.2% of CNTO 1275-treated subjects reported at least 1 SAE. Through the end of the reporting period, the proportion of subjects reporting at least 1 SAE was comparable between the 45 mg and 90 mg groups (4.7% and 3.9%, respectively). The rates of SAEs in the overall population and in CNTO 1275-treated subjects through the end of the reporting period were generally consistent with the rates of hospitalizations reported by participating subjects in the year prior to their entry into the study.
  - Rates of serious infections, malignancies, and cardiovascular events occurred at generally low rates in all groups.
  - No dose-response in SAE rates or profile was apparent.
- Infection rates and the profile of infections observed through Week 12 were similar in placebo- and CNTO 1275-treated subjects (rates of 26.7% and 28.6%, respectively). Infection rates and the profile of infections observed through the end of the reporting period were similar in the 45 mg and 90 mg groups (rates of 59.2% and 64.3%, respectively). Rates of serious infections were generally low. The rates of serious infections in the overall population and in CNTO 1275-treated subjects through the end of the

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reporting period were generally consistent with the rates of infections requiring hospitalization reported by participating subjects in the year prior to their entry into the study.

  - No cases of TB were reported.
  - One serious potential opportunistic infection of cutaneous disseminated herpes zoster was reported in the 90 mg group.

- The incidence of injection site reactions was low and generally mild in nature. Injection site reactions appeared to be modestly higher with 90 mg administration. The majority of injection site reactions were not related to allergic or hypersensitivity reactions. No possible anaphylactic or possible serum sickness-like reactions to study agent were reported.
- No malignancies were reported through Week 12. Through the end of the reporting period, malignancies occurred in 9 subjects. Four noncutaneous solid tumor malignancies were reported in 4 subjects in the 45 mg group (one case each breast, prostate, and thyroid cancers and a malignant kidney neoplasm). Basal cell skin carcinomas were reported in 5 subjects (2 subjects in placebo → 45 mg group, 1 subject in the 45 mg group, and 2 subjects in the 90 mg group).
- Rates and profiles of nonserious and serious cardiovascular events were comparable in placebo and CNTO 1275-treated subjects through Week 12 and comparable in the 45 mg and 90 mg groups through the end of the reporting period.
- There was no clear impact of weight on the rates of AEs, SAEs, or AEs leading to study agent discontinuation in either CNTO 1275 group. In subjects > 90 kg, slightly more subjects overall experienced infections in the 90 mg groups as compared to the 45 mg groups, though a consistent pattern of specific infections was not observed.
- The proportions of subjects experiencing markedly abnormal values in hematology and chemistry laboratory test results were low and generally comparable between the placebo and CNTO 1275 groups. Shifts in fasting glucose, D-dimer, and hemoglobin A1c levels were generally similar among the placebo and CNTO 1275 groups. Among subjects with abnormal baseline CRP, more CNTO 1275-treated had normal CRP by Week 12 than placebo-treated subjects. Among subjects with normal baseline CRP, the proportion of subjects shifted to abnormal at Week 12 was comparable among the placebo and CNTO 1275 groups.
- Safety, including rates of subjects with AEs, SAEs, infections, and study agent discontinuations due to an AE, were comparable between subjects in whom CNTO 1275 was self-administered versus health care professional administered.
- 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:

- Treatment with CNTO 1275, administered as 45 mg or 90 mg SC injections, led to substantial, significant, clinically meaningful improvements in psoriasis and was generally well-tolerated. The improvements in psoriasis were generally consistent across all subgroups.
- A dose response in efficacy was observed with generally higher response rates observed in the 90 mg group versus the 45 mg group. The dose response began to emerge at Week 16, reached a maximum around Week 24, and was generally maintained through Week 40.
- Maintenance of response and response over time were significantly superior in subjects who continued q12w maintenance dosing at Week 40 than in subjects withdrawn from CNTO 1275.
- Comparable efficacy and safety were observed in subjects in whom CNTO 1275 was self-administered versus administered by a health care professional.
- Treatment with CNTO 1275 resulted in significantly improved QOL, as measured by the DLQI and SF-36. Impairment in QOL was observed after 1 missed dose in subjects withdrawn from treatment at Week 40.
- Steady-state trough serum CNTO 1275 concentrations were achieved at Week 28. There was no evidence of accumulation in CNTO 1275 concentrations over time when given subcutaneously q12w.
- Clinical response was associated with serum CNTO 1275 concentration. Subjects who were PASI 75 responders at Week 28 exhibited higher median serum concentrations of CNTO 1275 than partial responders and nonresponders.
- Antibodies to CNTO 1275 developed at a low incidence rate through Week 52, precluding any definitive conclusions about the relationship of serum concentrations, efficacy, and safety to antibody status.
- Clinical response appeared to be impacted by subject weight. In subjects ≤ 100 kg, efficacy was similar with 45 mg or 90 mg dosing, whereas in subjects > 100 kg, higher levels of efficacy were observed with 90 mg than with 45 mg dosing.
- Serum CNTO 1275 concentrations appeared to be affected by subject weight. Median trough serum concentrations of CNTO 1275 in subjects with higher weight (> 100 kg) in the 90 mg group were comparable to those in subjects with lower weight (≤ 100 kg) in the 45 mg group.
- CNTO 1275 was generally well-tolerated with a safety profile generally comparable to placebo through Week 12. The safety profile of CNTO 1275 did not appear to be impacted by subject weight.

Date of Revised Report: 30 Jul 2008

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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: C0743T08	**EudraCT No.:** 2005-003529-15

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: Craig Leonardi, MD, Central Dermatology, [redacted].

Study Centers: 48 investigative sites: 29 sites in the United States, 16 sites in Canada, and 3 sites in Belgium

Publication (reference): Leonardi, CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). *Lancet* 2008;371:1665-74.

Studied Period: 15 Dec 2005/27 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. The secondary objectives were to: (1) Evaluate the maintenance of response with CNTO 1275 and (2) Evaluate the impact of CNTO 1275 on quality of life.

Methodology: This is a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of SC injections of 45 mg (Group 1), 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis.

Number of Subjects (Planned and Analyzed): 750 planned (250 subjects per group); 766 subjects were randomized to treatment and analyzed for efficacy; 765 subjects were treated and analyzed for safety; 751 subjects had samples available for the pharmacokinetics analysis; 746 subjects were analyzed for antibodies of CNTO 1275.

Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who have a Psoriasis Area and Severity Index (PASI) ≥ 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 at Week 0, were to receive 45 mg or 90 mg CNTO 1275 at Weeks 12 and 16. Subsequent dosing regimens were to be determined by each subject's response status according to the study design. Six lots of CNTO 1275 were used in the study.

Duration of Treatment: The first to the last study agent administration was up to 72 weeks; efficacy and safety data evaluated through Week 76; pharmacokinetic data evaluated through Week 72 and antibodies to CNTO 1275 data evaluated through Week 76.

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Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo was administered by SC injection. Subjects randomize to placebo were to receive placebo injections (0.5 mL and 1.0 mL) at Weeks 0 and 4. Subjects randomized to the CNTO 1275 groups were to receive placebo injections (0.5 mL and 1.0 mL) at Week 12. To maintain the blind associated with CNTO 1275 dose administration, each subject randomized to CNTO 1275 was also given a placebo injection; subjects in the 45 mg group received a 1.0 mL placebo injection, and subjects receiving 90 mg also received a 0.5 mL placebo injection. Seven lots of placebo were used in the study.

Criteria for Evaluation:

Pharmacokinetics/Pharmacodynamics:
Serum samples were used to evaluate serum CNTO 1275 concentrations, as well as antibodies to CNTO 1275. Methods used for the determination of serum CNTO 1275 concentration as well as the determination of antibodies to CNTO 1275 were described in the 52-Week CSR (refer to C0743T08 52-Week CSR, Sections 5.4.2.1 and 5.4.2.2, respectively).

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). All positive samples, from baseline through Week 52 from the EIA-positive subjects were tested using a functional cell-based neutralization bioassay. Clinical samples were determined to be positive for presence of NAbs to CNTO 1275 if there is ≥ 36% recovery of IFN-γ response (bioassay cut-off value) reflective of neutralization of the CNTO 1275 inhibition of IFN-γ. The results from these analyses are presented in this 76-Week CSR.

Efficacy:
Efficacy evaluations in this CSR included the Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (of disease severity) (PGA). Quality of life (QOL) evaluations included the Dermatology Life Quality Index (DLQI). A description of the PASI score and PGA score are provided in Appendix A and Appendix B of the protocol (see Appendix 1).

Safety:
Safety evaluations in this 76-Week CSR included the following: 1) AEs and SAEs assessment, and injection site reaction evaluation; 2) TB evaluation; 3) changes in routine laboratory analyses (ie, complete blood count, blood chemistry); and 4) evaluation of hemoglobin A1c at selected timepoints.

Details of the methods used and the definitions applying to the safety assessments, as well as the safety monitoring procedures are described in the 52-Week CSR (refer to C0743T08 52-Week CSR, Sections 5.4.4.1 through 5.4.4.4, respectively).

Statistical Methods: A Cochran-Mantel-Haenszel (CMH) chi-square test was used to compare the proportion of subjects responding to treatment. Survival analysis techniques were used for endpoints defined by time to an event. The stratified log-rank test was used to compare endpoints defined by time to an event (eg, time to loss of PASI response). Continuous response parameters were compared using an analysis of variance (ANOVA) on the van der Waerden normal scores with weight as a binary covariate. In addition to statistical analyses, graphical data displays and subject listings were also used to summarize the data. For data displays (tables and figures), the number of subjects evaluated at each timepoint are provided.

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Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
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SUMMARY – CONCLUSIONS

Study Population Results:

The demographic characteristics of the overall study population were discussed in the 52-Week CSR. Demographic characteristics were generally well balanced across treatment groups for subjects who were randomized at Week 0. The population of subjects enrolled in this study was consistent with other studies of biologic drugs in subjects with psoriasis (Leonardi et al, 2005; Gordon et al, 2006):

- approximately twice as many men (69.3%) as women (30.7%)
- majority of subjects were Caucasian (93.6%)
- median age was 45.5 years
- median weight was 91.6 kg

The safety population during the randomized withdrawal portion of the study included:

- 73 subjects in the 45 mg → placebo (withdrawal) group
  - Prior to Week 76, 45 of the 73 subjects were retreated with 45 mg
- 77 subjects in the 45 mg q12w (maintenance therapy) group
- 87 subjects in the 90 mg → placebo (withdrawal) group
  - Prior to Week 76, 53 of the 87 subjects were retreated with 90 mg
- 84 subjects in the 90 mg q12w (maintenance therapy) group

Of the 160 subjects randomized to the withdrawal group at Week 40, similar proportions of subjects from the 45 mg and 90 mg groups were retreated (45/73 [61.6%] and 53/87 [60.9%], respectively).

Pharmacokinetic/Pharmacodynamic Results:

- For subjects retreated with CNTO 1275 after withdrawal of therapy at Week 40, 97.2% of subjects exhibited undetectable concentrations at the time of retreatment.
- The incidence of antibodies to CNTO 1275 was low (5.1%) with no increase in incidence between Week 52 and Week 76. Subjects who were retreated after a drug free interval were comparable to the overall population.

Efficacy Results:

- The majority of subjects (70.3%) receiving q12w maintenance therapy maintained a ≥ 75% improvement in PASI score from baseline (PASI 75 response) at each visit through 1.5 years.
- PASI 75 response in subjects withdrawn from CNTO 1275 began to separate from the maintenance therapy group by Week 44 and the disparity progressively grew over time through Week 76 when 16.8% of subjects withdrawn from therapy maintained a PASI 75 response versus 70.3% of subjects in the maintenance therapy group.
- PGA response of cleared (0) or minimal (1) was generally sustained over time in subjects receiving maintenance therapy (74.7% and 65.8% of subjects at Weeks 40 and 76, respectively), while PGA response rates declined from 78.8% at Week 40 to 11.5% at Week 76 in subjects withdrawn from CNTO 1275.
- A significantly higher proportion of subjects maintained PASI 75 response through Week 76 in the maintenance therapy groups versus subjects in the withdrawal groups, regardless of baseline weight (≤ 100 kg or > 100 kg) and dose (45 mg or 90 mg).
- Psoriasis recurrence occurred at a similar rate in subjects who were withdrawn from CNTO 1275 after 16 or 28 weeks of dosing.
  - 95.6% had a recurrence within 28 weeks of withdrawal from CNTO 1275.

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- The median duration of PASI 75 response after withdrawal of CNTO 1275 was 15.5 weeks and was comparable between subjects who had received 45 mg or 90 mg dosing.
- Among 195 subjects withdrawn from therapy who experienced loss of therapeutic effect, 84.9% achieved PASI 75 response within 12 weeks of reinitiation of therapy.
- Substantial proportions of subjects who inadequately responded to q12w dosing (subjects with ≥ 50% and < 75% improvement in PASI score from baseline [partial responders] at Week 28 and PASI 75 subjects with <50% improvement in PASI score from baseline [nonresponders] at Week 40), achieved a PASI 75 response after dosing interval adjustment to q8w.
- During the randomized withdrawal period, DLQI score improvements observed at Week 40 were generally sustained at Week 76 in subjects randomized to maintenance therapy (both in the 45 mg and 90 mg groups). In contrast, the improvement in DLQI score was substantially lower at Week 76 (compared with Week 40) in subjects withdrawn from CNTO 1275.
- No clear impact of antibodies to CNTO 1275 on clinical efficacy was apparent. Subjects with undetectable drug levels trended toward lower clinical efficacy, however, antibody positivity did not preclude clinical response.

Safety Results:

- CNTO 1275 was generally well tolerated. Through Week 76, 753 subjects received at least 1 dose of CNTO 1275. Subjects randomized to CNTO 1275 at baseline could have received 18 months or more of exposure.
- During the randomized withdrawal portion of the study, AE rates, AE profiles, and rates of AEs leading to study agent discontinuation were generally comparable between the maintenance group and the withdrawal group.
- Through Week 76, AE rates, AE profiles, and rates of AEs leading to study agent discontinuation remained generally comparable in the 45 mg and 90 mg groups. The most commonly reported system-organ class was Infections and Infestations with nasopharyngitis and upper respiratory infection the most commonly reported AEs.
- During the randomized withdrawal portion of the study, SAEs were not higher in subjects randomized to continuous maintenance therapy (0.6%) than in subjects withdrawn from therapy (3.1% while receiving placebo and 2.0% after retreatment).
- Through Week 76, SAEs were reported in 38 (5.0%) CNTO 1275-treated subjects with an average follow-up of 67.8 weeks, and comparable rates were observed in the 45 mg and 90 mg groups (5.9% versus 5.1%, respectively). No deaths were reported through Week 76.
- During the randomized withdrawal period, rates of infections were not higher in the maintenance therapy group than the withdrawal group despite longer follow-up, and rates of infections and infections requiring treatment were not increased with maintenance therapy.
- Through Week 76, the proportions of subjects reporting at least 1 infection were comparable between the 45 mg and the 90 mg groups (63.1% and 67.1%, respectively), as well as between the placebo → 45 mg and the placebo → 90 mg groups. The pattern and types of infections reported through Week 76 were generally similar to those reported through Week 52.
- Through Week 76, 1 potential opportunistic infection and no cases of TB were reported.
- During the randomized withdrawal portion of the study, no injection site reactions associated with CNTO 1275 treatment were reported.

Synopsis (C0743T08 PHOENIX 1)

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		

- Through Week 76, CNTO 1275 administrations were generally well-tolerated and the proportion of subjects experiencing 1 or more injection site reactions to CNTO 1275 was low and were all considered mild in intensity. Overall, 0.2% of placebo administrations were associated with injection site reactions compared with 0.5% and 0.9% of the 45 mg and 90 mg administrations, respectively.
- No possible anaphylactic or possible serum sickness-like reactions to study agent were reported.
- Through Week 76, 11 subjects were diagnosed with malignancies, including 5 subjects with basal cell cancers and 6 subjects with solid tumor malignancies (1 subject each with breast, colon, lentigo maligna, prostate, thyroid, and transitional cell cancer). A dose-response in malignancy rates was not apparent.
- Rates and profiles of nonserious and serious cardiovascular events were comparable in the 45 mg and 90 mg groups and did not reveal a consistent pattern of events with common pathophysiology or association with CNTO 1275.
- There was no clear impact of weight on the rates of AEs, SAEs, or infections.
- The pattern of AEs with retreatment was consistent with the pattern in other study periods. Rates of SAEs after retreatment were low and no anaphylactic or serum-sickness like reactions were reported.
- During the placebo-controlled period, small increases in TC, LDL, HDL and TG levels were observed in all treatment groups (including the placebo group) without evidence of a dose response. As a result of these changes, a small reduction in the TC/HDL ratio was observed.
- Through Week 76, the proportions of subjects experiencing markedly abnormal values in hematology and chemistry laboratory test results were low, and no dose-response in laboratory abnormalities was apparent. More subjects in the 90 mg group had at least 1 markedly decreased lymphocyte count (4.7% versus 8.2% for the 45 mg and 90 mg groups, respectively), but the abnormalities were generally isolated, one-time abnormalities, and the proportions with more than 1 abnormality were similar (1.2% versus 2.0% for these respective groups).

Conclusions:

- Maintenance of response and response over time through Week 76 were significantly superior in subjects who continued q12w maintenance dosing with CNTO 1275 at Week 40 compared with subjects withdrawn from CNTO 1275 at Week 40.
- Loss of response and impairment in QOL was observed after 1 missed dose in subjects withdrawn from treatment at Week 40.
- Treatment interruption did not appear to impact responsiveness to CNTO 1275. The proportion of subjects who achieved PASI 75 response after retreatment was comparable to the proportion who were PASI 75 responders among subjects who continued maintenance CNTO 1275.
- Efficacy in partial responders after dosing interval adjustment suggested that shortening the dosing interval from q12w to q8w improves response in these subjects.
- Maintenance therapy was generally well tolerated and adverse event rates did not appear to be higher in subjects receiving maintenance therapy compared with subjects withdrawn from CNTO 1275.

Synopsis (C0743T08 PHOENIX 1)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 1275		
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- The pattern of AEs observed in subjects withdrawn from CNTO 1275 and retreated after loss of therapeutic effect did not suggest a pattern of immune-mediated adverse events, and no cases of CNTO 1275-related anaphylaxis or serum sickness-like reactions were reported.
- 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 76, precluding definitive conclusions about the relationship of serum concentrations, efficacy, and safety to antibody status.

Date of Report: 11 Jun 2008