Janssen Research & Development

Clinical Study Report Synopsis (24-Week)
[Protocol C0524T09; Phase 3]

CNTO 148 (golimumab)

Redaction and Removal of Information in This Document

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

Synopsis (C0524T09 GO-RAISE)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 148 (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

Protocol: C0524T09	**EudraCT No.:** 2004-003299-12
Title of the study: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Ankylosing Spondylitis: 24-Week Report	
Principal/Coordinating Investigator(s): [redacted] MD, [redacted] Germany.	
Study Center(s): 46 study centers: 20 in North America (11 in US and 9 in Canada), 17 in Europe (4 in Belgium, 2 in The Netherlands, 8 in Germany, 2 in Finland, and 1 in France), and 9 in Asia (6 in South Korea and 3 in Taiwan).	
Publication (reference): None	
Studied Period: 13 Dec 2005/15 May 2007	**Phase of Development:** 3
Objectives: The primary objective of this trial was to assess the efficacy of SC injections of golimumab in subjects with active ankylosing spondylitis (AS) as measured by reduction in signs and symptoms of active AS at Week 14. The secondary objectives were to assess: (1) The overall safety of golimumab, (2) the effects of golimumab on physical function, range of motion, structural damage, and quality of life in subjects with AS, and (3) the population pharmacokinetic (PK) and pharmacodynamic (PD) effects of golimumab in subjects with AS.	
Methodology: This was a multicenter, randomized, double-blind, placebo-controlled (through Week 24) study designed to assess the efficacy, safety, and clinical pharmacology of golimumab 50 mg or 100 mg administered as subcutaneous (SC) injections every 4 weeks in adult subjects with active AS. Subjects are to be treated through Week 100 and followed for routine efficacy and safety assessments through Week 104. The long-term extension of the study starts with the Week 104 study agent injection and ends when the last subject enrolled completes the Week 268 visit. This 24-Week report describes the placebo-controlled portion of the study (Weeks 0 to 24).	
Number of Subjects (Planned and Analyzed): Subjects were randomly assigned in a 1:1.8:1.8 ratio to 1 of 3 treatment groups: placebo (n = 75 planned; 78 actual), golimumab 50 mg (n = 135 planned; 138 actual), golimumab 100 mg (n = 135 planned; 140 actual). All 356 subjects were analyzed for safety, efficacy, and health economics, and 142 (of 150 planned) were analyzed for biomarkers.	
Diagnosis and Main Criteria for Inclusion: Subjects eligible for this study were men and women with a diagnosis of AS for at least 3 months prior to first study agent administration who had active AS despite current or previous disease-modifying antirheumatic drug (DMARD) or non-steroidal anti-inflammatory drug (NSAID) therapy, and who had not previously been treated with anti-tumor necrosis factor alpha (anti-TNFα) therapy.	
Test Product, Dose and Mode of Administration, Batch Number: Golimumab was supplied as a sterile liquid for SC injection at a volume of 0.5 mL or 1.0 mL in 2 mL single-use glass vials (lot numbers: D05PJ7456, 6ES39, 6ES3C, D05PJ7455, and 6HS3R). Each vial contained 50 or 100 mg golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5.	
Duration of Treatment: The study agent was administered through Week 20	

Synopsis (C0524T09 GO-RAISE)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 148 (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo, consisting of an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5, was also supplied as a sterile liquid for SC injection at a volume of 0.5 mL or 1.0 mL in single-use 2 mL glass vials (lot numbers: 6ES14, 6HS2J, 6ES15, D05PJ7457, and D05PJ7458).

Criteria for Evaluation: All efficacy analyses were based on randomized subjects; ie, the intent-to-treat population. Clinical pharmacology and safety analyses were based on subjects who received at least 1 study agent administration.

Pharmacokinetics/Pharmacodynamics: Serum golimumab concentrations, antibody to golimumab status, the relationships between antibody to golimumab status and serum concentration and between antibody to golimumab status and selected safety and efficacy measures, levels of serum markers of inflammation and bone and cartilage metabolism and their correlation with change from baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 14 were assessed.

Efficacy: Primary endpoint was Assessment in Ankylosing Spondylitis (ASAS) 20 response at Week 14. Major secondary analyses included Assessment of ASAS 20 response at Week 24, improvement from baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Metrology Index (BASMI) at Week 14. In addition, other secondary endpoints related to the signs and symptoms of AS, physical function, and health-related quality of life was evaluated.

Safety: Safety was assessed by evaluating the incidence and type of adverse events (AEs), including serious adverse events (SAEs), reasonably related, severe, or clinically significant AEs, and discontinuations due to AEs; routine clinical laboratory values; the incidences of antibodies to golimumab; and the development of antinuclear antibodies or anti-double-stranded deoxyribonucleic acid (DNA) antibodies.
Health Economics: Resource utilization was evaluated through Week 24.

Statistical Methods: Pearson's chi-square test was used to compare binary categorical data, and the Cochran-Mantel-Haenszel (CMH) chi square test to compare binary categorical data with stratification (stratified by screening c-reactive protein [CRP] levels). Analysis of variance (ANOVA) on van der Waerden normal scores (Conover, 1980) with treatment and screening CRP as factors in the model was used to compare continuous data, unless otherwise specified. In the analyses of efficacy endpoints, the first test compared combined golimumab dose groups versus placebo. If the results were significant, then pairwise comparisons of golimumab 50 mg versus placebo and golimumab 100 mg versus placebo were made. All statistical testing was 2-tailed, at a significance level of 0.05.

SUMMARY – CONCLUSIONS
Study Population Results: Baseline characteristics were generally well balanced across treatment groups. The majority of subjects were men (71.6%), most were Caucasian (73.6%), most were positive for Human Leukocyte Antigen (HLA)-B27 allele, with a median age of 38.5 years. Baseline clinical characteristics were similar across the treatment groups and indicative of subjects with AS of moderate to severe activity regardless of NSAIDs use at maximal doses or DMARDs.

Synopsis (C0524T09 GO-RAISE)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 148 (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

Pharmacokinetic/Pharmacodynamic Results:

- Serum golimumab concentrations achieved steady state by Week 12. Serum golimumab concentration was approximately proportional to dose following SC administrations of golimumab 50 mg and 100 mg. At Week 12, the median trough concentrations were 0.6 µg/mL (50 mg only group) and 1.1 µg/mL (100 mg group).
- The overall incidence of antibodies to golimumab was 4.1%. Serum golimumab concentrations were generally higher in those subjects in whom antibodies to golimumab were undetectable than in subjects who were antibody positive or negative.
- Treatment with golimumab resulted in early reductions in select markers of inflammation and IL-6 and vascular endotheial growth factor (VEGF) levels correlated with improvement in BASDAI. Further, golimumab treatment resulted in early increases in osteocalcin and N-terminal propeptide of Type 1 procollagen (PINP) levels and both markers correlated with improvement in BASDAI.

Efficacy Results:

Primary Endpoint:

- The proportion of subjects achieving ASAS 20 response at Week 14 in the golimumab 50 mg group (59.4%) and the golimumab 100 mg group (60.0%) was significantly greater ($p < 0.001$) than in the placebo group (21.8%). Sensitivity analyses confirmed the robustness of the results.

Major Secondary and Other Endpoints:

Reductions in Signs and Symptoms

- ASAS 20 response was achieved in a significantly greater ($p < 0.001$) proportion of subjects in both golimumab 50 mg (55.8%) and 100 mg (65.7%) groups than in the placebo group (23.1%) at Week 24.
- Low Disease Activity (ie, ASAS partial response) was achieved in a significantly greater ($p < 0.001$) proportion of subjects in both golimumab 50 mg (23.2%) and 100 mg (20.7%) groups than in the placebo group (5.1%) at Week 14.
- As early as Week 4, the proportion of subjects achieving ASAS 20 response in golimumab 50 mg (47.8%) and 100 mg (45.3%) groups was greater than that in the placebo (12.8%) group; through Week 24, the proportions of subjects achieving ASAS 20 response in the combined golimumab group was consistently greater than that in the placebo group at every visit.
- A treatment benefit versus placebo for subjects in the combined golimumab group was observed in nearly all of the subgroups defined by baseline disease and clinical characteristics, baseline medications and prior therapies, and HLA-B27 antigen status.
- The proportion of subjects achieving ASAS 40 response in golimumab 50 mg (Week 14: 44.9%; Week 24: 43.5%) and golimumab 100 mg (Week 14: 49.3%; Week 24: 54.3%) groups was significantly greater ($p < 0.001$) than in the placebo group (Week 14: 15.4%; Week 24: 15.4%).
- The proportion of subjects achieving ASAS 5/6 response in golimumab 50 mg (Week 14: 50.0%; Week 24: 49.3%) and golimumab 100 mg (Week 14: 48.6%; Week 24: 50.7%) was also significantly greater ($p < 0.001$) than in the placebo group (Week 14: 7.7%; Week 24: 12.8%).
- At Weeks 14 and 24, the proportions of subjects achieving 20%, 50%, 70%, and 90% improvement from baseline in BASDAI response in the golimumab 50 mg and 100 mg groups were significantly greater than that in the placebo group.

Synopsis (C0524T09 GO-RAISE)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 148 (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

- At Weeks 14 and 24, the change from baseline in total back pain assessment was significantly greater ($p < 0.001$) in the golimumab 50 mg and 100 mg groups than in the placebo group. The median improvement from baseline in both the golimumab 50 mg (-3.50) and golimumab 100 mg (-3.90) groups was greater than that in the placebo group (0.40) at Week 24.
- At Week 4 the change from baseline (median value) in CRP levels in the golimumab 50 mg group was -0.700 and in the golimumab 100 mg group was -0.500, and these suppressed levels were sustained through Week 24 ($p < 0.001$).
- Patient global assessment of disease activity improved significantly from baseline in the golimumab 50 mg and 100 mg groups compared to the placebo group at Weeks 14 and 24.
- The change from baseline in night back pain was significantly greater ($p < 0.001$) at Weeks 14 and 24 in the golimumab 50 mg (Week 24: -3.10) and 100 mg (Week 24: -3.45) groups than in the placebo group (Week 24: -0.40).
- In the enthesitis evaluation using University of California San Francisco (UCSF) index criteria, significant improvement was noted in the golimumab 100 mg group over the placebo group at both Weeks 14 ($p = 0.004$) and 24 ($p < 0.001$). A significant improvement ($p = 0.013$) in the golimumab 50 mg group was noted at Week 24.

Improvement in Range of Motion

- There was significant improvement ($p = 0.013$) in chest expansion in the golimumab 50 mg group at Week 24.
- Numeric improvements in BASMI at Weeks 14 and 24 did not reach statistical significance, when comparing the combined or individual golimumab treatment groups to placebo. However, actual measurements of 3 out of the 5 BASMI components lumbar flexion (modified Schober's), lumbar side flexion, and intermalleolar distance) improved significantly at Week 24 for subjects in the golimumab 50 mg group.

Improvement in Physical Function

- A median change of –1.42 from baseline in BASFI was observed for the combined golimumab group and 0.095 for the placebo group at Week 14. Both golimumab groups showed significant improvement ($p < 0.001$) over the placebo group.

Improvement in Health-related Quality of Life

- SF-36 physical component summary score improvement was significantly greater ($p < 0.001$) in each golimumab dose group than in the placebo group at Week 14, and this difference was sustained through Week 24. Significant improvements compared to placebo in the mental component summary score were observed in the golimumab 100 mg group at Weeks 14 and 24, while the improvement observed in the golimumab 50 mg group was of lesser magnitude, but significant, compared to placebo only at Week 14 only.

Improvement in Sleep

- The change from baseline in Jenkins sleep evaluation was significantly greater ($p < 0.001$) in the combined golimumab group as well as in each of the individual golimumab groups than in the placebo group at Weeks 14 and 24.

Anemia

- Among the 53 subjects who were anemic at baseline, significant, median increases from baseline in hemoglobin levels were observed at Week 14 in both the golimumab 50 mg (1.300 g/dL) and golimumab 100 mg (1.550 g/dL) groups compared to placebo (-0.250), with the effect maintained to Week 24.

Synopsis (C0524T09 GO-RAISE)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 148 (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

PK/PD/IR

- No apparent PK/efficacy correlation was observed between steady state trough serum concentration and the proportion of subjects who achieved an ASAS 20 response.
- There was no apparent impact of the presence of antibodies to golimumab on ASAS 20 responses.
- In the combined golimumab group, IL-6 and VEGF levels were correlated with improvement in BASDAI; osteocalcin and PINP levels were also correlated with improvement in BASDAI.

Safety Results:

- Proportions of subjects experiencing at least 1 AE were similar in the combined golimumab and placebo groups (77.3% and 74.0% respectively) through Week 16, and proportions were also similar between treatment groups for reasonably related AEs and through Week 24.
- The system-organ class with the highest incidence of AEs was the Infections and Infestations system-organ class, with nasopharyngitis and upper respiratory infection (URI) as the most frequently reported AEs, regardless of treatment group and through both Week 16 and Week 24.
- AEs occurred more frequently in subjects not receiving DMARDs at baseline than in subjects receiving concomitant DMARDs at baseline in both the golimumab groups as well as the placebo group through Week 24. Additionally, concomitant DMARD use or not did not appear to affect the incidence or types of SAE.
- No deaths occurred during the 24-Week study period.
- SAEs were infrequent and were reported in a lower proportion of subjects in the combined golimumab group than in the placebo group (4.3% vs 5.2% through Week 16 and 5.4% vs 6.5% through Week 24).
- AEs resulted in study agent discontinuation in the golimumab groups were similar to the placebo group. However, the number of subjects discontinuing study agent was low.
- One subject in the placebo group and 2 subjects in the golimumab 100 mg group had serious infections.
- No events of active tuberculosis (TB) were reported through week 24. Forty eight (48) subjects received concomitant prophylactic treatment for latent TB detected during the screening process, and one additional subject received prophylactic treatment for latent TB detected postbaseline.
- Two malignancies were noted through Week 24. One subject each in the golimumab 100 mg group and the placebo group was diagnosed with basal cell carcinoma.
- No subjects experienced anaphylactic reactions or serum sickness reactions through Week 24.
- Injection-site reactions, primarily consisting of injection-site erythema, occurred with low frequency through Week 24, and in a greater proportion of subjects in the all golimumab group (7.2%) relative to the placebo group (2.6%). Most injection site reactions were graded mild in intensity. One subject in the golimumab 50 $\rightarrow$ 100 mg group had a severe but not serious injection-site reaction. No subjects discontinued study agent administration due to injection-site reaction.
- No apparent impact of the development of antibodies to golimumab upon safety (injection-site reaction) was noted.
- Laboratory safety assessments did not identify any unanticipated safety issues. Abnormal transaminase tests (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) were noted more frequently in subjects who received golimumab than in subjects who received placebo, as has been reported with other anti-TNF agents. There was no correlation between elevated ALT values and trough serum golimumab concentrations.
- Markedly abnormal ALT or AST values were noted with a greater incidence in subjects who received DMARDs at baseline than in those that did not, and in greater proportion of subjects in the combined

Synopsis (C0524T09 GO-RAISE)

Name of Sponsor/Company: Centocor, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: CNTO 148 (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

golimumab group (ALT: 4.6%; AST: 1.1%) than in the placebo group (ALT: 0.0%; AST: 0.0%). Markedly abnormal bilirubin values occurred in 4 subjects in the combined golimumab group (2.1%) compared to none in the placebo group (0.0%), with none of the 4 subjects receiving DMARDs at baseline. The proportion of subjects whose ALT or AST values were ≤ ULN at baseline with abnormal ALT or AST values (> ULN) was greater in those subjects who received TB prophylaxis than in those subjects who did not, across all treatment groups. The majority of these subjects had ALT or AST values ≤ 3X ULN.

Conclusions: Golimumab 50 mg or 100 mg administered subcutaneously every 4 weeks:

- Provides substantial benefit to subjects with AS by reducing clinical signs and symptoms.
- Demonstrated significant efficacy that was comparable between golimumab dose groups.
- Is generally well tolerated with similar proportions of subjects with AEs in placebo and golimumab groups with a safety profile similar to other anti-TNF agents. The incidence of SAEs and other significant AEs was comparable between the subjects treated with golimumab and those treated with placebo.
- Resulted in predictable golimumab concentrations in serum and a low incidence of subjects who were positive for antibodies to golimumab, with no apparent effects on safety or efficacy.

Date of Report: 02 Nov 2007