Janssen Research & Development

Clinical Study Report Synopsis: 52-Week
Protocol C0524T05

CNTO148 (golimumab)

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Synopsis (C0524T05 GO-BEFORE)

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: SIMPONI™ (golimumab)		

Protocol: C0524T05	**EudraCT No.:** 2004-003295-10

Title of the study: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, a Fully Human Anti-TNFα Monoclonal Antibody, Administered Subcutaneously, in Methotrexate-naïve Subjects with Active Rheumatoid Arthritis

Principal/Coordinating Investigator(s): [redacted] MD, [redacted] UK

Study Center(s): Eighty-six centers enrolled subjects. The number of enrolling sites by geographic location was as follows: Asia: 25 sites (3 in India, 3 in Malaysia, 5 in the Philippines, 1 in Singapore, 5 in the Republic of Korea, 4 in Taiwan, and 4 in Thailand); Europe/Australia/New Zealand: 31 sites (2 in Australia, 1 in Austria, 2 in Belgium, 3 in Hungary, 3 in New Zealand, 7 in Poland, 4 in Russia, 3 in Spain, 4 in the Ukraine, and 2 in the United Kingdom); Latin America: 10 sites (7 in Argentina and 3 in Chile); North America: 20 sites (3 in Canada and 17 in the United States of America)

Publication (reference): Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum.* 2009;60(8):2272-2283.

Studied Period: 12 Dec 2005/14 Apr 2008 (for this report)	**Phase of Development:** 3

Objectives: The primary objectives of this study are to assess the efficacy of golimumab in subjects with active rheumatoid arthritis (RA) who have not been previously treated with methotrexate (MTX) as measured by the following:

- Reduction of the signs and symptoms at Week 24
- Inhibition of progression of structural damage at Week 52

The secondary objectives are to assess the safety of golimumab, the effect of golimumab on physical function and health-related quality of life, the pharmacodynamics (PD), and population pharmacokinetics (PK) of golimumab in subjects with active RA who have not been previously treated with MTX.

Methodology: This multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group study was designed to assess the efficacy, safety, and clinical pharmacology of golimumab alone or in combination with MTX in MTX-naïve subjects who had RA for at least 3 months prior to randomization. As of the Week 52 database lock, the study is ongoing. Data up to Week 52 are reported herein. Subjects will continue to be treated through Week 252 and followed for routine efficacy and safety through Week 256 with an additional visit at Week 268 to follow safety and to measure antibodies to golimumab and serum golimumab concentrations. The blind was maintained until the last subject completed the Week 52 evaluations and the 52-week database was locked. In general, visits are scheduled every 4 weeks through Week 64 and every 12 weeks thereafter for a total length of follow-up of approximately 5 years from the first administration of study agent. The end of study is defined as the time the last subject completes the Week 268 visit.

Number of Subjects (Planned and Analyzed): 600 planned (150 per treatment arm); 637 randomized and 634 treated. Randomized/treated subjects in each groups were as follows: Placebo + MTX: 160/160; Golimumab 100 mg + placebo: 159/157; Golimumab 50 mg + MTX: 159/158; Golimumab 100 mg + MTX: 159/159.

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Diagnosis and Main Criteria for Inclusion: Men and women 18 years of age or older were eligible to participate in this study if they had a diagnosis of RA (according to the revised 1987 criteria of the American Rheumatism Association [ARA]; Arnett et al, 1988) for at least 3 months before the first administration of study agent, were MTX-naïve and biologic anti-TNFα therapy-naïve, and had active RA. Subjects must not have received disease modifying anti rheumatic drugs (DMARDs)/systemic immunosuppressives; intra-articular, IM, or IV corticosteroids; or anakinra within 4 weeks prior to the first study dose.

Test Product, Dose and Mode of Administration, Batch Number: Golimumab 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 contained 50 or 100 mg golimumab.. No preservatives were present. Lot numbers were as follows: 6ES39, 6ES3C, 6HS3R, 6HS3U, 6KS1K, 6KS1P, 7DSIM, 7DSIN, D05PJ7455, and D05PJ7456. Active MTX capsules were filled with microcrystalline cellulose (Avicel PH 102) and a 2.5 mg MTX tablet. Lot numbers for active MTX were as follows: 13894.14, 18825.1, 18825.15, 18825.17, 18825.26, 18825.27, 18825.29, 18825.31, 18825.45, 18825.5, F20955, F20965, and F24516.
Golimumab was to be administered by SC injection every 4 weeks beginning at Week 0.

Duration of Treatment: Study agent to be administered through the end of Week 252. Duration of treatment for this report is through Week 52.

Reference Therapy, Dose and Mode of Administration, Batch Number: Placebo for golimumab, 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 were as follows: 6ES14, 6ES15, 6HS1W, 6HS2J, D05PJ7457, and D05PJ7458. Placebo MTX capsules were filled with microcrystalline cellulose (Avicel PH 102). Lot numbers for placebo MTX were as follows: 18825.16, 18825.18, 18825.25, 18825.28, 18825.3, 18825.30, 18825.44, 18825.7, 4507.9, F20938, F24373, F20944.
MTX was to be administered orally at a dose of 10 mg/week starting at Week 0, with dose escalation to 20 mg/week by Week 8.

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

Pharmacokinetics/Pharmacodynamics: Golimumab pharmacokinetics were evaluated by summarizing serum golimumab concentrations over time and the proportion of subjects with undetectable golimumab concentrations over time. Antibody to golimumab status was reported according to treatment group, including induced antibody titers, the relationship to trough golimumab concentrations, and comparisons with selected efficacy and safety parameters. The effects of golimumab treatment on serum biomarkers relating to inflammation and bone and cartilage metabolism were assessed including correlation with change from baseline in Disease Activity Score (DAS) 28 (using C-reactive protein [CRP]) at Week 52.

Efficacy: One of 2 primary endpoints of this study (the proportion of subjects who achieved an ACR 50 response at Week 24) and major secondary endpoints (ACR 20 response at Week 24 and ACR 50 response in subjects with abnormal C-reactive protein at baseline) were reported in the C0524T05 24-Week CSR. Data from the coprimary endpoint (change from baseline in van der Heijde modified sharp score at Week 52) and major secondary endpoints (improvement from baseline in HAQ Score at Week 52 and change from baseline in total vdH-S score in subjects with abnormal CRP at baseline at Week 52) are presented in this study report.

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Safety: Safety was assessed by evaluating the incidence and type of AEs, including SAEs, reasonably related, severe, or clinically significant AEs, and discontinuations due to AEs; routine clinical laboratory values; and the development of antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies.
Health Economics: Resource utilization was evaluated through Week 52.

Statistical Methods: Descriptive summary statistics, such as n, mean, SD, median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize data. The Cochran-Mantel-Haenszel (CMH) test or chi-square test was to be used as appropriate to compare the proportion of subjects responding to treatment. Continuous response parameters were to be compared using an analysis of variance on the van der Waerden normal scores (Conover, 1980). All statistical testing was 2-tailed, at a significance level of 0.05. In the analyses of efficacy endpoints, the first test compared the combined golimumab + MTX group versus placebo + MTX. If the results were significant, then pairwise comparisons were performed between each golimumab treatment group (50 mg + MTX, 100 mg + MTX, and 100 mg + placebo) and placebo + MTX.
In addition to statistical analyses, graphical data displays (eg, line plots) and subject listings were also used to summarize or present the data.

SUMMARY – CONCLUSIONS

Study Population Results: Treatment groups were generally well balanced with respect to baseline demographics. Median age was 50 years and the majority of subjects were women (82.9%). The study population was predominantly Caucasian (72.4%) followed by Asian (18.4%). The majority of subjects had early disease (median of 1.0 to 1.8 years), although there were some subjects with long disease duration. Subjects generally had moderate to severe disease activity and the median number of swollen and tender joints were 13 and 26, respectively. Randomization was stratified by investigational site and screening CRP levels, and treatment groups were generally well-balanced for baseline demographics and clinical characteristics. Based upon information obtained during screening, treatment for latent tuberculosis (as prescribed by local guidelines) was initiated for approximately 16.6% of subjects before first administration of subcutaneous study agent.

Pharmacokinetic/Pharmacodynamic Results:
Pharmacokinetics: Consistent with the data reported in the 24-Week CSR, serum trough golimumab concentrations through Week 52 were approximately proportional to dose when SC golimumab 50 mg or 100 mg was administered every 4 weeks in combination with MTX in MTX-naïve subjects with active RA. Serum golimumab concentrations generally achieved steady state by Week 12 and drug exposure was maintained through Week 52. It is noted that there was a trend towards higher median serum trough golimumab concentrations at Weeks 28 and 52 compared with those between Weeks 12 and 24 in the golimumab 100 mg + placebo, golimumab 50 mg + MTX, and golimumab 100 mg + MTX treatment groups. The relatively large variability inherent to the bioassay especially at low concentrations might contribute to this observation. The median serum trough golimumab concentrations after the addition of the remaining 30% of subjects were generally consistent with those presented in the 24-Week CSR, which only included approximately 70% of randomized subjects. Thus, the PK results reported through Week 52 are supportive of the findings reported in the 24-Week CSR.

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Pharmacodynamics: Treatment with golimumab + MTX reduced serum levels of select markers of inflammation at Week 24 and this trend continued at Week 52. Overall treatment with golimumab + MTX resulted in increases in select markers of bone formation and decreases in select markers of bone degradation at Week 52.

Antibodies to Study Agent: The overall incidence of antibodies through Week 52 was 6.5% which is consistent with the incidence at Week 24 (6.3%).

Efficacy Results:

Overall, the benefit of treatment with golimumab + MTX in reducing signs and symptoms of active RA achieved at Week 24 is maintained through Week 52. Both golimumab 50 mg + MTX and golimumab 100 mg + MTX treatment regimens inhibited progression of structural damage. As was observed through Week 24, improvement in signs and symptoms of RA was generally similar between the golimumab 100 mg + placebo and the placebo + MTX groups. Combination treatment with golimumab 100 mg + MTX generally appeared to provide a better response than treatment with golimumab 100 mg + placebo.

Radiographic analyses

- Changes from baseline in total vdH-S score at Week 52 (coprimary endpoint) in both the golimumab 50 mg + MTX and golimumab 100 mg + MTX treatment groups were statistically significantly lower compared with those in the placebo + MTX group.
- At Week 52, the change from baseline in the total vdH-S score in subjects with abnormal (> 1.0 mg/dL) CRP in both the golimumab 50 mg + MTX and the golimumab 100 mg + MTX treatment groups individually was statistically significantly less ($p = 0.010$ and $p = 0.014$, respectively) than in the placebo + MTX group.
- At Week 28, the mean change from baseline in total vdH-S score were as follows: golimumab 50 mg + MTX (0.71, $p = 0.065$) group; golimumab 100 mg + MTX (0.01, $p = 0.003$) group; and placebo + MTX group (1.11).
- At Week 52, the proportion of subjects with no newly eroded joints was statistically significantly greater in the golimumab 50 mg + MTX group ($p = 0.003$) than in the placebo + MTX group. Additionally, the proportion of subjects with no new JSN was statistically significantly greater in the golimumab 100 mg + MTX group ($p = 0.022$) than in the placebo + MTX group.
- The proportion of subjects with change from baseline in total vdH-S score above the SDC (3.82) were as follows: golimumab 50 mg + MTX (6.4%, $p = 0.12$) group; golimumab 100 mg + MTX (2.2%, $p = 0.001$) group; and placebo + MTX group (12.1%).
- The proportion of subjects with change from baseline in total vdH-S score ≤ 0 at Week 52 were as follows: golimumab 50 mg + MTX (71.4%, $p = 0.003$) group; golimumab 100 mg + MTX (61.2%, $p = 0.236$) group; and placebo + MTX group (53.9%).

Analyses Related to Signs and Symptoms

- The proportion of golimumab + MTX treated subjects who achieved an efficacy response (ACR 20, ACR 50, and ACR 70) were maintained from Week 28 through Week 52.
- The proportion of subjects who achieved a major clinical response was statistically significant in the golimumab 50 mg + MTX (15.2%, $p = 0.018$) compared with the placebo + MTX group (6.9%).
- At Week 52, the proportion of DAS28 (CRP or ESR) responders, was significantly greater for both golimumab + MTX groups when compared with the placebo + MTX group.
- Subjects who met criteria for EE consistently had less improvement in efficacy measures than those subjects who did not meet criteria for EE.

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Physical Function Analysis

- At Week 52, the improvement from baseline HAQ score is as follows: golimumab 50 mg + MTX (median: 0.5, p = 0.287) group; golimumab 100 mg + MTX (median: 0.625, p = 0.023) group; and placebo + MTX group (median: 0.625).

Other Analyses

- At Week 52, a significant improvement from baseline in the SF-36 MCS and the SF-36 norm-based role-emotional subscale was noted with golimumab 100 mg + MTX treatment compared with placebo + MTX. The number of subjects who achieved US population norms on the SF-36 MCS was significantly greater for the golimumab 100 mg + MTX group compared with placebo + MTX group, whereas the comparison between the golimumab 50 mg + MTX group and placebo + MTX group yielded a p-value of 0.051.
- All treatment groups showed a reduction in the number of subjects who were unemployable due to RA at Week 52. Subjects in all treatment groups showed an improvement in productivity.
- The number of subjects with anemia and various subsets of anemia were relatively small, which made robust evaluation of treatment effects on anemia not possible. However, for subjects with anemia at baseline there were significant improvements from baseline in hemoglobin level, a greater proportion of subjects with ≥ 1 gm/dL increase, and a greater proportion of subjects with ≥ 2 gm/dL increase at Week 52 in the golimumab 50 mg + MTX group compared with MTX alone.
- Review of cardiovascular markers showed notable improvements (reductions) from baseline in nearly all inflammatory markers following treatment with golimumab + MTX. None of the changes in lipids with golimumab + MTX treatment were significantly different when compared with those with placebo + MTX. Total cholesterol and LDL increased but increases in the atherogenic ratios Total cholesterol/HDL and LDL/HDL were slight, and the Apolipoprotein B/A1 ratio was unchanged. The concentration of large LDL subparticles was significantly increased from baseline in both placebo + MTX and golimumab + MTX treatment groups, which was reflected in a statistically significant increase from baseline in mean LDL size. HbA1c decreased significantly with golimumab + MTX compared with placebo + MTX, and a statistically significant increase from baseline in the Glucose/Insulin ratio was observed, more so with golimumab + MTX treatment than placebo + MTX. However, HOMA-IR, HOMA-%βcell, and QUICKI were not consistently changed by any treatment.
- In the catotid ultrasound substudy (Attachment 5), the relatively small sample size, short period of observation, and the variability of the CCA-IMT measurements precluded meaningful conclusions.
- No apparent correlation was observed between golimumab steady-state trough serum concentration and the proportion of subjects who achieved an ACR 20 or ACR 50 response at Week 52, with or without concomitant use of MTX.
- The small numbers of subjects positive for antibodies for golimumab, precludes any meaningful conclusions regarding the impact of antibody status on efficacy.
- In the golimumab + MTX group, higher baseline levels of RF and reductions in VEGF (at Weeks 4 and 24), RF and anti-CCP Abs (at Week 24) and IL-6 (at Week 52), were significantly associated with reductions in DAS28 scores at Week 52. In the golimumab + MTX group, an increase in P1NP levels (at Week 4), a decrease in COL 2-3/4C levels (at Week 4) and a decrease in PYD levels (at Week 24) was significantly associated with a decrease of DAS28 scores at Week 52).

Safety Results: Golimumab administered SC every 4 weeks, with or without MTX, was generally well tolerated in MTX-naïve subjects with active RA. The safety results observed in this study are consistent with

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the well-known safety profiles of MTX and anti-TNFα agents; no unanticipated safety issues were observed on review of safety data:

Adverse Events: The proportion of subjects with one or more AEs was generally comparable across treatment groups (from 80.9% to 91.9%). Among those who received MTX with or without golimumab, AEs were most frequently associated with Infections and Infestations and GI disorders. In the all golimumab + MTX group, the most frequent AEs were nausea (19.6%), URTI (14.1%) and increased ALT (13.9%). In the golimumab 100 mg + placebo group, the most frequent AEs were injection site erythema (9.6%), nausea (7.6%), and URTI (11.5%). In the placebo + MTX group, the most frequent AEs were nausea (17.6%), ALT increased (10.7%), and URTI (13.2%).

Serious Adverse Events: Through Week 52, SAEs were reported across all randomized treatment groups. SAEs occurred in the following treatment groups: Placebo + MTX (13.8%); golimumab 50 mg + MTX (11.4%); golimumab 100 mg + MTX (13.1%); all golimumab + MTX (12.0%).

Deaths: From Week 0 through Week 52 three deaths were reported. From Week 24 through Week 52, one death was reported in the golimumab 100 mg + MTX group. The subject died of an overdose of [redacted] on the 328th day of the study. The last administration of SC study agent prior to death was study day 311.

Study Agent Discontinuations Due to AEs: The proportion of subjects who discontinued SC study agent was greater in the golimumab + MTX groups (golimumab 50 mg + MTX: 5.7% and golimumab 100 mg + MTX: 10.0%) than in the placebo + MTX group (3.8%) and the golimumab 100 mg + placebo group (4.5%).

Infections: Investigator-identified infections occurred in similar proportions of subjects across treatment groups (from 56.9% [golimumab 100 mg + MTX] to 47.8% [golimumab 100 mg + placebo]); URTI was the most frequent type of infection (from 11.5% [golimumab 100 mg + placebo] to 16.3% [golimumab 100 mg + MTX] across treatment groups).

Serious Infections: Serious infections occurred somewhat more frequently in subjects who received golimumab 100 mg + MTX (6.9%) than in the other treatment groups (from 1.3% to 4.1%).

TB: From Week 0 through Week 52 TB was reported for 3 subjects. From Week 24 through Week 52, TB was reported for 2 subjects. One subject in the golimumab 50 mg + MTX group was diagnosed with pulmonary TB and 1 subject in the golimumab 100 mg + MTX group was diagnosed with TB pleurisy. Both subjects reside in the Philippines.

Malignancies: From Week 0 through Week 52, malignancies were reported for 7 subjects. Malignancies were reported for 2 subjects from Week 24 through Week 52 as follows: 1 subject each with basal cell carcinoma and papillary thyroid cancer.

Injection-site Reactions: The proportion of subjects with an injection-site reaction to golimumab through Week 52 was greater among those who received golimumab (golimumab 100 mg + placebo: 15.9%; golimumab 50 mg + MTX: 5.7%; golimumab 100 mg + MTX: 10.6%; and all golimumab + MTX: 8.2%) than the proportion of subjects who had an injection-site reaction to placebo in the placebo + MTX group (1.3%). The proportion of subjects with an injection-site reaction to golimumab in the golimumab 100 mg + placebo (15.9%) group was greater than in all other golimumab + MTX treatment groups. Injections were generally well tolerated. The most commonly reported reaction to either placebo or golimumab injections were injection site erythema. None of the injection-site reactions were severe, serious, or led to permanent

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discontinuation of study agent administration.

Laboratory Assessments: Laboratory safety assessments did not identify any safety issues not reported with other anti-TNFα agents. A greater proportion of subjects who received MTX with or without golimumab had one or more elevated ALT or AST value than subjects who received golimumab 100 mg + placebo. Some trends were noted for an increased incidence of ALT and/or AST abnormalities among those who received treatment for latent TB than in those who did not receive treatment for latent TB; however, this was not consistently observed across all treatment groups. There was no suggestion that treatment with both golimumab and isoniazid increased the risk of serious ALT or AST abnormalities.

Conclusions:
The following conclusions are based on data collected through Week 52:

- Golimumab 50 mg + MTX and golimumab 100 mg + MTX dose regimens achieved significantly greater inhibition of radiographic progression than MTX alone.
- A greater proportion of subjects in the golimumab 50 mg + MTX group achieved major clinical response (an indication of sustained response) compared with subjects in the placebo + MTX regimen.
- Treatment with golimumab 50 mg or 100 mg every 4 weeks in combination with MTX in MTX-naïve subjects with active RA indicated evidence of improvements in signs and symptoms of RA as assessed by ACR criteria and DAS28 which were maintained to Week 52.
- Improvements in physical function were observed in all treatment groups.
- Golimumab is generally well tolerated, and with or without MTX use, demonstrated a safety profile similar to that observed with other anti-TNF agents.
- Serum trough golimumab concentrations are approximately proportional to dose.
- The overall incidence of antibodies to golimumab was low (6.5%).
- The benefit risk balance supports the use of golimumab + MTX in MTX-naive patient population.

Date of Report: 15 Oct 2009