Janssen Research & Development

Clinical Study Report: Week 24
Protocol C0524T11; Phase 3

CNTO148 (Golimumab)

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- 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 (C0524T11 GO-AFTER)

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: C0524T11	**EudraCT No.:** 2005-001742-16

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 Rheumatoid Arthritis and Previously Treated with Biologic Anti-TNFα Agent(s)

Principal/Coordinating Investigator: [redacted] MD – [redacted] Austria

Study Center(s): Of the 101 investigative sites that received study agent, 86 enrolled subjects (obtained informed consent) in this study. Of the investigative sites that received study agent, 60 were in North America and 41 were in Europe/Australia/New Zealand.

Publication (reference): None

Studied Period: 21 Feb 2006/26 Sep 2007	**Phase of Development:** 3

Objectives: The primary objective of this study was to evaluate the efficacy of golimumab in subjects with active RA who had been previously treated with biologic anti-TNFα agent(s) by assessing the reduction in signs and symptoms of RA at Week 14.
The secondary objectives of this study were to assess the safety, physical function, pharmacodynamics, and population pharmacokinetics of golimumab in subjects with active RA who had been previously treated with biologic anti-TNFα agent(s).

Methodology: Multicenter, randomized, double-blind, placebo-controlled, 3-arm, parallel study of multiple subcutaneous (SC) doses of golimumab

Number of Subjects (Planned and Analyzed): 420 planned (140 each in placebo, golimumab 50 mg and golimumab 100 mg); 461 analyzed (155 placebo, 153 golimumab 50 mg, 153 golimumab 100 mg)

Diagnosis and Main Criteria for Inclusion: Men or women 18 years of age or older with a diagnosis of RA for at least 3 months prior to screening. Subjects must have had active RA, defined as persistent disease activity with at least 4 swollen and 4 tender joints, and must have been previously treated with at least 1 dose of a biologic anti-TNFα agent (ie, etanercept, adalimumab, or infliximab) at least 12 weeks (infliximab) or 8 weeks (adalimumab or etanercept) prior to the first administration of study agent. Discontinuation of these medications could have been for reasons including, but not limited to, lack of efficacy, intolerance, and/or inconvenience.

Test Product, Dose and Mode of Administration, Batch Number: golimumab
- 50 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20
- 100 mg SC injections at Weeks 0, 4, 8, 12, 16, and 20
  lot numbers: 6ES39, 6ES3C, 6HS3R, 6HS3U, 6KS1K, 6KS1P, D05PJ7455, D05PJ7456

Duration of Treatment: 24 weeks

Reference Therapy, Dose and Mode of Administration, Batch Number: placebo
- SC injections at Weeks 0, 4, 8, 12, 16, and 20
  lot numbers: 6ES14, 6ES15, 6HS1W, 6HS2J, D05PJ7457, D05PJ7458

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Criteria for Evaluation: All randomized subjects were included in the primary efficacy and selected secondary analyses. 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 dose of study medication; subjects were analyzed according to the actual treatment received.

Pharmacokinetics/Pharmacodynamics: Pharmacokinetic (PK) evaluations were based on golimumab serum concentrations from subjects who received at least 1 dose of study agent. Pharmacodynamic (PD) evaluations were conducted on blood samples for serum-based biomarkers from subjects who had blood samples drawn for PD biomarker analyses. Analyses for antibodies to golimumab were conducted on serum samples through Week 24.

Efficacy: The primary endpoint was the proportion of subjects with an ACR 20 response at Week 14. Other efficacy endpoints included: ACR 50 response at Week 14, DAS28 (using CRP) response at Week 14, ACR 20 response at Week 24, improvement from baseline in HAQ score at Week 24. Health economic and anemia endpoints were also summarized.

Safety: Safety was assessed by summarizing the incidence and type of AEs by treatment group (actual treatment received). The number and percentage of subjects with serious AEs (SAEs), reasonably related AEs, severe AEs, discontinuations due to AEs, and other significant AEs were summarized by treatment group. The number and percentage of subjects with markedly abnormal laboratory values were summarized by treatment group.

Statistical Methods: The proportion of subjects with an ACR 20 response at Week 14 following treatment with golimumab (golimumab 50 mg and golimumab 100 mg combined) was compared with the proportion of subjects with an ACR 20 response at Week 14 following treatment with placebo using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by baseline MTX use (yes/no) at a 0.05 level of significance. Other ACR and DAS comparisons were made between the combined golimumab group and the placebo group using a 2 sided ($\alpha = 0.05$) CMH test stratified by baseline MTX use (yes/no). If this test was significant, then pairwise comparisons between the individual golimumab groups and the placebo group were to be performed using the same statistical procedure at a significance level of 0.05 each. For the improvement from baseline in HAQ, the comparison between the combined golimumab group and the placebo group used a 2-sided analysis of variance on the van der Waerden normal scores with treatment group and baseline MTX use (yes/no) as factors in the model at a 0.05 level of significance. If the treatment effect was significant, then pairwise comparisons between the individual golimumab groups and the placebo group were to be performed using the same statistical procedure at a significance level of 0.05 each.

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SUMMARY – CONCLUSIONS

Study Population Results:

- At Week 0, 461 subjects were randomly assigned to treatment with either placebo, golimumab 50 mg, or golimumab 100 mg. Of the 461 randomized subjects, 331 (71.8%) were in North America and 130 (28.2%) in Europe/Australia/New Zealand.
- Approximately 80% of randomized subjects were women, 87.4% were Caucasian, 5.4% were black, and 1.7% were Asian. The median age was 54.0 years and the median weight was approximately 75 kg.
- Baseline disease characteristics were generally similar across the treatment groups, and indicated the presence of long-standing disease of substantial impact. Median disease duration ranged from 8.65 years (golimumab 100 mg) to 9.80 years (placebo group). Majority of subjects were in functional Class II or III; the most frequent extra-articular manifestations of RA included rheumatoid nodules (approximately 22%), sicca syndrome (approximately 10%), and peripheral neuropathy (approximately 4%). Median duration of morning stiffness was 90 minutes.
- Treatment for latent TB (as prescribed by local guidelines) was initiated for approximately 6% of subjects before first administration of subcutaneous study agent.
- At baseline, the majority of subjects were taking MTX (approximately 66% of all subjects) and few were taking sulfasalazine or hydroxychloroquine (approximately 5% to 8%). The percentages of subjects receiving oral corticosteroids at baseline ranged from 44.7% (golimumab 100 mg group) to 60.5% (golimumab 50 mg group). Approximately 60% of all randomized subjects were receiving NSAIDs.
- Prior exposure to commercially available anti-TNFα agents was consistent among treatment groups. The most common reason for discontinuing prior anti-TNFα therapy was lack of efficacy (58.4%).

Pharmacokinetic/Pharmacodynamic Results: The pharmacology data from this study showed that:

- Serum trough golimumab concentration was approximately proportional to dose when SC golimumab was administered at 50 mg or 100 mg every 4 weeks in subjects with active RA and previously treated with biologic anti-TNFα agent(s).
- Serum trough golimumab concentration generally achieved steady state by Week 12. Median steady-state trough concentrations at Week 12 were 0.32 μg/mL and 0.77 μg/mL following SC administrations of golimumab 50 mg or 100 mg every 4 weeks, respectively.
- Following SC administrations, subjects receiving MTX had generally higher steady-state trough golimumab concentrations than subjects not receiving MTX in the same golimumab dose group.
- Antibodies to golimumab were detected in 3.7% of subjects receiving golimumab. Antibodies to golimumab were observed in a similar proportion of subjects receiving and not receiving MTX.
- Serum golimumab concentrations were generally low in those subjects who were classified as positive for antibodies to golimumab. Due to the small number (8) of subjects classified as antibody positive, a relationship between antibodies to golimumab and serum golimumab concentrations can not be clearly defined.
- Significant decreases in levels of inflammatory markers (ICAM-1, TNFα, and VEGF) were observed at Week 4 following treatment with golimumab compared with treatment with placebo.
- Treatment with golimumab resulted in significant reductions of ICAM-1, MMP-3, IL-8, TNFα, and RF concentrations at Week 14 compared with placebo.

Efficacy Results: Treatment of subjects with active RA who had previously been treated with at least 1 anti-TNFα agent with SC golimumab showed that:

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- A significantly greater proportion of subjects in the combined golimumab group than in the placebo group achieved the primary endpoint of ACR 20 at Week 14 (36.6% vs 18.1%, respectively; $p < 0.001$). In addition, the proportions of subjects achieving an ACR 20 response at Week 14 in the individual golimumab groups were similar to each other and both were superior to the placebo group ($p < 0.001$ for both comparisons). Efficacy was consistently demonstrated in subgroup analyses for almost all baseline demographic, disease characteristics and baseline medication subgroups as well as for subjects who discontinued 1 or more prior anti-TNFα therapies due to lack of efficacy.
- Numerically greater ACR responses and reductions in DAS28 scores relative to placebo were observed as early as Week 4 (the earliest assessment period) and were sustained through Week 24.
- A significantly greater proportion of subjects in the combined golimumab, as well as the individual treatment groups, than in the placebo group achieved ACR 20 response at Week 24, ACR 50 response at Week 14, DAS28 (using CRP) response at Week 14, and had a significantly greater change from baseline in HAQ score at Week 24.
- DAS28 (using ESR) response, DAS28 remission (using CRP and using ESR), and ACR 50 were achieved in a significantly greater proportion of subjects in the combined golimumab group (and in the golimumab 50 mg and 100 mg groups) than in the placebo group at both Weeks 14 and 24 ($p < 0.001$ for all comparisons of combined golimumab vs placebo).
- The improvements in FACIT-F fatigue scores at Weeks 14 and 24 were significantly greater in the combined golimumab group than in the placebo group ($p < 0.001$ for both analyses). The improvements from baseline in FACIT-F scores in the individual golimumab groups were similar to each other and were superior to the placebo group ($p \leq 0.021$ for all analyses).
- The change from baseline in self-reported productivity was significantly improved in the combined golimumab group compared with the placebo group at Weeks 16 and 24 ($p < 0.001$ for both comparisons). In addition, the changes in self-reported productivity from baseline to Week 16 and from baseline to Week 24 in the individual golimumab groups were similar to each other and each was superior to the placebo group ($p < 0.001$ for all comparisons). The changes in productivity from baseline to Week 24 in the individual golimumab groups were greater than the change from baseline observed at Week 16.
- The proportion of subjects who met criteria for early escape at Week 16 was greater for subjects in the placebo group than for the golimumab groups. Subjects in the placebo group who qualified for early escape had ACR responses at Week 24 similar to those in the golimumab 50 mg group at Week 8. But subjects in the golimumab 50 mg group who qualified for early escape had lower ACR responses after receiving golimumab 100 mg than subjects in the golimumab 100 mg group.
- A trend was observed toward greater ACR and DAS28 responses with golimumab 100 mg than with golimumab 50 mg. In most ACR response endpoints and in all DAS28 (using CRP or ESR) response and remission endpoints, the proportion of subjects achieving these endpoints was greater in the golimumab 100 mg group than the golimumab 50 mg group.
- Although the number of subjects with anemia at baseline was small (15.4%), median increases in hemoglobin levels were numerically greater in the golimumab groups than in the placebo group at both Weeks 14 and 24.
- Although sample sizes were small, no subject classified as positive for antibodies to golimumab achieved an ACR 20 or ACR 50 response.
- In subjects treated with golimumab, decreases in RF at Week 14 were significantly correlated with decreases in DAS28 (using CRP) scores at Week 14.

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Safety Results: Golimumab was generally well tolerated in subjects with active RA who have been previously treated with biologic anti-TNFα agent(s).

- Through Week 16, the proportions of subjects with at least 1 AE were generally similar in the placebo and combined golimumab groups (69.7% vs 67.1%, respectively), and a greater proportion of subjects in the golimumab 100 mg group had AEs than the golimumab 50 mg group (73.0% vs 61.2%, respectively).
- The system-organ class with the greatest proportion of subjects with AEs through Week 16 was Infections and infestations (28.4% in the placebo group vs 27.0% in the combined golimumab group).
- The only preferred term reported for greater than 5% of subjects in the combined golimumab group through Week 16 was URTI (5.8% placebo group vs 8.2% combined golimumab group).
- More than twice as many subjects in the placebo group reported worsening of their RA than in the combined golimumab group through Week 16 (9.7% vs 3.9%, respectively).
- Through Week 16, a similar proportion of subjects who were receiving MTX at baseline had an AE compared with subjects who were not receiving MTX at baseline (65.0% vs 71.3%, respectively, for subjects in the combined golimumab group).
- The proportion of subjects with an SAE through Week 16 was greater in the placebo group than in the combined golimumab group (7.1% vs 3.9%, respectively); a greater proportion of subjects in the golimumab 50 mg group had an SAE compared with the golimumab 100 mg group (5.3% vs 2.6%, respectively). The system-organ class with the greatest proportion of subjects with an SAE was Infections and infestations, reported by a greater proportion of subjects in the placebo group than in the combined golimumab group (2.6% vs 1.3%, respectively).
- Through Week 16, infections were reported in a comparable proportion of subjects in all treatment groups, ranging from 25.0% in the golimumab 100 mg group to 27.7% in the placebo group.
- Through Week 24, serious infections were reported in comparable proportions of subjects in the placebo and combined golimumab groups (3.2% vs 2.0%, respectively).
- Study agent injection-site reactions through Week 16 were reported in a greater proportion of subjects in the combined golimumab group than in the placebo group (7.2% vs 2.6%, respectively) and in a greater proportion of subjects in the golimumab 100 mg group than in the golimumab 50 mg group (10.5% vs 3.9%, respectively). No subject classified as antibody-to-golimumab positive had an injection site reaction.
- Through Week 24, no instances of active or latent TB were reported. At baseline, 10 subjects in the placebo group and 17 subjects in the combined golimumab group received treatment for latent TB, none of whom developed active TB.
- A total of 3 malignancies were reported: a metastatic pancreatic cancer (placebo group), a squamous cell carcinoma (golimumab 50 mg group), and a lymphoma (golimumab 100 mg group).
- One subject (placebo group) died during the study, the subject with metastatic pancreatic cancer.
- Among subjects with normal ALT/AST values at baseline, maximum postbaseline ALT/AST values > ULN were observed in a greater proportion of subjects in the combined golimumab group than in the placebo group regardless of whether subjects were receiving treatment for latent TB.
- No anaphylactic or serum-sickness reactions were reported and markedly abnormal laboratory results were uncommon.

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Conclusions: In subjects with active RA who had previously received at least 1 dose of an anti-TNFα agent(s):

- A significantly greater proportion of subjects receiving golimumab (50 mg or 100 mg) achieved the primary endpoint (ie, the proportion of subjects who achieved an ACR 20 response at Week 14) compared with placebo.
- Among subjects who had discontinued 1 or more previous anti-TNFα agents for lack of efficacy, a significantly greater proportion in the combined golimumab group than in the placebo group achieved an ACR 20 response at Week 14.
- Golimumab was superior to placebo in all major secondary endpoints.
- Treatment with golimumab 50 mg and golimumab 100 mg significantly reduced fatigue associated with RA and increased self-reported productivity.
- Golimumab 50 mg or golimumab 100 mg administered SC every 4 weeks resulted in adequate golimumab exposure for clinical efficacy. Treatment with SC golimumab (50 mg or 100 mg) in subjects receiving MTX resulted in higher trough serum concentrations than the same golimumab dose in subjects not receiving MTX.
- Golimumab was generally well tolerated. In the placebo-controlled portion of the study, approximately equal proportions of subjects in the placebo and golimumab groups had at least 1 AE. Within the golimumab groups, a slightly greater proportion of subjects with AEs was observed in the golimumab 100 mg group than in the golimumab 50 mg group.
- The system-organ class with the greatest proportion of subjects with AEs was Infections and infestations with approximately equal proportions of subjects in the placebo and golimumab groups having at least 1 infection. The only preferred term reported for greater than 5% of subjects in the combined golimumab group was URTIs, which occurred in slightly more subjects in the golimumab than in the placebo groups. No cases of TB were reported through Week 24, and the proportion of subjects classified as antibody-to-golimumab positive was low.

Date of Report: 17 Jan 2008