Janssen Research & Development

Clinical Study Report Synopsis: 52-Week
Protocol C0524T06; Phase 3

CNTO148 (Golimumab)

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- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

Synopsis (C0524T06)

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

Protocol: C0524T06	**EudraCT No.:** 2004-003296-36

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 Despite Methotrexate Therapy

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

Study Center(s): Of the 66 investigative sites, 66 sites enrolled (obtained informed consent from) subjects in this study. The study population included 444 randomized subjects from 12 countries, including Argentina (10 sites), Australia (3 sites), Canada (6 sites), Chile (5 sites [4 of which had randomized subjects]), Germany (6 sites), Hungary (2 sites[1 of which had randomized subjects]), Mexico (3 sites [1 of which had randomized subjects]), New Zealand (3 sites), Poland (8 sites [6 of which had randomized subjects]), South Korea (6 sites), Taiwan (1 site), and the US (13 sites [12 of which had randomized subjects]).

Publication (reference): Keystone EC, Genovese MC, Klareskog L, et al. Golimumab, a human antibody to TNF-{alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate: The GO-FORWARD Study. *Ann Rheum Dis.* 2008.

Studied Period: 19 Dec 2005 to 30 Apr 2008 (for this report)	**Phase of Development:** 3

Objectives: The primary objective of this study was to assess the efficacy of golimumab in subjects with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy as measured by American College of Rheumatology (ACR) 20 response at Week 14, and improvement from baseline in health assessment questionnaire (HAQ) at Week 24. The secondary objectives were to assess the safety of golimumab, the effects of golimumab on structural damage and health-related quality of life, and to describe the population pharmacokinetics of golimumab in subjects with active RA despite MTX therapy.

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of golimumab 50 mg + MTX or 100 mg + MTX compared with placebo + MTX, and golimumab 100 mg + placebo compared with placebo + MTX in subjects with active RA despite MTX therapy. Subjects received subcutaneous injections at Week 0 and every 4 weeks (q4wk) thereafter through Week 48. Treatment regimens were escalated in all treatment groups (except the 100 mg + MTX treatment group) in a double-blind fashion at Week 16 for subjects meeting early escape criteria. At Week 24, all subjects receiving subcutaneous placebo + MTX began receiving subcutaneous golimumab + MTX. Subjects were to be followed for routine efficacy and safety assessments through Week 52. The long-term extension of the study starts with the Week 52 study agent injection and ends when the last subject enrolled completes the Week 268 visit. This report describes data through Week 52, including efficacy for signs and symptoms and physical function after Week 24 through Week 52, radiographic data from Week 0 through Week 52, and safety from Week 0 through Week 52.

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Number of Subjects (Planned and Analyzed): Subjects (400 planned) were randomly assigned in a 3:3:2:2 ratio to 1 of the following 4 treatment groups: placebo + MTX (n = 120 planned; 133 actual), golimumab 100 mg + placebo (n = 120 planned; 133 actual), golimumab 50 mg + MTX (n = 80 planned; 89 actual), and golimumab 100 mg + MTX (n = 80 planned; 89 actual). All 444 subjects were analyzed for safety, selected efficacy and health economics parameters.

Diagnosis and Main Criteria for Inclusion: The subjects participating in the study were adults (≥ 18 years of age) who had a diagnosis of RA by ACR criteria (according to the revised 1987 criteria of the American Rheumatism Association [ARA]; Arnett et al, 1988) and had active RA despite a stable dose of MTX of at least 15 mg/week for at least 4 weeks prior to screening. The subjects enrolled must have tolerated MTX (at least 15 mg/wk) for at least 3 months and have had persistent disease activity (defined as having at least 4 swollen and 4 tender joints, plus additional criteria as noted in the protocol). Subjects were excluded from the study if they had received any anti-TNFα biologic therapy.

Test Product, Dose and Mode of Administration, Batch Number: Golimumab was supplied as a sterile liquid for SC injection (lot numbers: 6ES39, 6ES3C, 6HS3R, 6HS3U, 6KS1K, 6KS1P, 7DS1M, 7DS1N, D05PJ7455, and D05PJ7456). Oral MTX was supplied as a capsule for oral administration filled with microcrystalline cellulose (Avicel PH 102) and a 2.5 mg MTX tablet (lot numbers: 18825.11, 18825.13, 18825.19, 18825.2, 18825.21, 18825.23, 18825.33, 18825.35, 18825.36, 18825.41, 18825.43, 18825.47, 18825.49, 18825.6, 4507.1, 4507.8, F20957, F20959, F20961, F20963, F20967, F20969, F20971, F20973, F24518, F24520, F24524, and F24526).

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, 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 (lot numbers: 6ES14, 6ES15, 6HS1W, 6HS2J, D05PJ7457, and D05PJ7458). Oral placebo (sham MTX) was supplied as capsules filled with microcrystalline cellulose (Avicel PH 102) (lot numbers: 18825.12, 18825.14, 18825.20, 18825.22, 18825.24, 18825.34, 18825.37, 18825.4, 18825.42, 18825.46, 18825.8, F18196, F20936, F20940, F20942, F24371, F24375).

Criteria for Evaluation: All primary and major secondary efficacy analyses were based on randomized subjects; ie, the intent-to-treat (ITT) population. Other efficacy analyses presented in this report were generally based upon observed data. 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, trough golimumab levels in the presence or absence of MTX, 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.

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Efficacy: The 2 coprimary endpoints of this study (the proportion of subjects who achieved an ACR 20 response at Week 14, and the improvement from baseline in HAQ score at Week 24) and 3 of the 4 major secondary endpoints (DAS28 response at Week 14, ACR 20 response at Week 24, and improvement from baseline in HAQ at Week 14) were reported in the Week 24 CSR.
Data on the change from baseline in vdH-S score at Week 24 are presented in this 52-Week Report.
Results for improvements in signs and symptoms and physical function after Week 24 through Week 52 are described in this report.

Safety: Safety was assessed by evaluating the incidence and type of adverse events (AEs), including serious AEs (SAEs), reasonably related, severe, or clinically significant AEs, and discontinuations due to AEs; routine clinical laboratory values; the relationship between formation of antibodies to golimumab to injection site reactions; and the development of antinuclear antibodies (ANA) or anti-double-stranded DNA antibodies.

Health Economics: Resource utilization was evaluated through Week 52

Statistical Methods: In this report, statistical hypothesis was tested on the major secondary endpoint, ie, the change from baseline in van der Heijde Modified Sharp (vdH-S) score at Week 24 using a 2-sided analysis of variance on the van der Waerden normal scores at 0.05 level of significance. For all other analyses, descriptive statistics, such as the mean, median, standard deviation (SD), range, and the interquartile range for continuous variables, and counts and percentages for categorical variables were used to summarize data.

SUMMARY – CONCLUSIONS

Study Population Results: The study population included 444 randomized subjects. Most subjects were females (81%) and most were Caucasian (77%). Asian subjects comprised 15% of the study population, the median age was 51 years and median weight was 70 kg. Randomization was stratified by investigational site, and treatment groups were generally well-balanced for baseline demographics and clinical characteristics, which generally indicated the presence of long-standing moderate to severe disease.

Pharmacokinetic/Pharmacodynamic Results:
Pharmacokinetics:

- Consistent with the 24-Week CSR, serum trough golimumab concentration through Week 52 was approximately proportional to dose when SC golimumab was administered at 50 mg or 100 mg every 4 weeks in combination with MTX in subjects with active RA despite MTX therapy.
- Serum golimumab concentrations generally achieved steady state by Week 12 and drug exposure was maintained over time. Compared to steady-state trough serum golimumab concentrations from Week 12 to 24, similar median trough serum golimumab concentration was observed at Week 52 in golimumab 100 mg + placebo, golimumab 50 mg + MTX and golimumab 100 mg + MTX groups.
- The median serum trough golimumab concentrations after the addition of the remaining 20% of subjects were generally consistent with those presented in the 24 Week CSR, which only included approximately 80% randomized subjects. Thus, the PK results reported through Week 52 are supportive of the findings reported in the 24-Week CSR.

Antibodies to Golimumab:

- The overall cumulative incidence of antibodies through Week 52 (3.97%) was low and consistent with that observed through Week 24 (2.1%). The majority of these antibodies (16 of 17) were neutralizing to study agent.
- The proportion of subjects who developed antibodies to golimumab was lower in subjects who had received concomitant MTX (2.4%) compared with subjects who did not receive MTX (9.7%).

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Efficacy Results:

Coprimary Endpoints: The 2 coprimary endpoints of this study were the proportion of subjects who achieved an ACR 20 response at Week 14, and the improvement from baseline in HAQ score at Week 24. Both coprimary endpoints were reported in the Week 24 CSR. Improvement in signs and symptoms and physical function was significantly better with golimumab + MTX treatment as compared with MTX alone.

Major Secondary Endpoints: Three of the 4 major secondary endpoints (DAS28 response at Week 14, ACR 20 response at Week 24, and improvement from baseline in HAQ at Week 14) were reported in the Week 24 CSR and showed statistically significant differences between golimumab + MTX and placebo + MTX.

The fourth major secondary endpoint, change from baseline in vdH-S score at Week 24 did not show a statistically significant difference between golimumab treatment groups and placebo + MTX group. Radiographic progression as measured by change from baseline in total vdH-S score was minimal in all treatment groups.

Radiographic Data

There was minimal change in all treatment groups and no significant differences were observed between golimumab treatment groups and placebo + MTX in the following vdH-S based measures at Week 24:

- Change in total vdH-S score by type of damage
- Change in total vdH-S score by region
- Number of subjects with no newly eroded joints
- Number of subjects with no new JSN
- Number of joints with new erosions that were uninvolved at baseline
- Number of joints with new JSN that were uninvolved at baseline
- Number of subjects with radiographic progression based on SDC
- Number of subjects with maintenance of joint damage-free state
- Number of subjects with change in vdH-S score ≤ 0
- Radiographic progression as measured by the various endpoints was minimal in all treatment groups.

At Week 52 by ITT analysis change from baseline in total vdH-S score continued to be minimal in all treatment groups.

Subjects who entered EE appeared to have greater change from baseline in total vdH-S score at Week 52 compared with subjects who did not early escape.

Other Efficacy Assessment

Signs and Symptoms of Arthritis

After Week 24 the proportion of golimumab treated subjects achieving ACR 20, ACR 50, and ACR 70 responses was sustained through Week 52 for all golimumab treatment groups. Improvement from baseline in swollen and tender joint counts and CRP was maintained after Week 24 through Week 52 in all treatment groups. The ACR-N index of improvement observed at Week 24 was maintained in each treatment group at Week 52.

DAS28 (using CRP) response was achieved in greater than 80% to 85% of subjects in all treatment groups with the exception of the placebo + MTX $\rightarrow$ golimumab 50 mg + MTX EE and golimumab 100 mg + placebo $\rightarrow$ golimumab 100 mg + MTX (EE) groups. The improvement in DAS28 with golimumab + MTX observed at Week 24 was maintained at Week 52. Subjects who met EE criteria generally experienced less improvement.

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Physical Function
The improvement in HAQ observed at Week 24 with golimumab + MTX treatment was maintained at Week 52. At Week 52, the proportion of subjects achieving an improvement in HAQ of ≥ 0.25 in golimumab 50 mg + MTX only, golimumab 50 mg + MTX → golimumab 100 mg + MTX, and combined golimumab 100 mg +MTX was 76.8%, 73.3%, and 78.5%, respectively. Subjects who met EE criteria generally experienced less improvement.

Health-Related Quality of Life:
Improvements in SF-36 PCS observed at Week 24 with golimumab + MTX treatment were maintained at Week 52. At Week 52, subjects in the golimumab 50 mg + MTX only and golimumab 100 mg + MTX only groups had a median change from baseline in SF-36 PCS of 8.85 and 9.90, respectively, and in SF-36 MCS of 2.55 and 3.70, respectively. At Week 52, the proportion of subjects in the golimumab 50 mg + MTX only and golimumab 100 mg + MTX only groups achieving US population norms in SF 36 PCS were 39.2% and 36.0%, respectively, and in SF-36 MCS were 56.8% and 60.0%, respectively. Subjects who met EE criteria generally experienced less improvement.

Cardiovascular Disease
Through Week 52, 4 subjects in the placebo + MTX group and 1 subject in the golimumab 100 mg + placebo group had at least 1 cardiovascular event (myocardial infarction, congestive heart failure, and ischemic heart disease), while there were no events reported in subjects in the golimumab + MTX groups.
Significant improvements in inflammatory markers associated with cardiovascular disease were observed at Week 52 with golimumab + MTX treatment. As was observed at Week 24, there appeared to be a suggestion of a shift in size distribution to larger LDL particles with golimumab + MTX treatment at Week 52.
Improvements in markers of glucose homeostasis were seen in some selected measures.

Pharmacokinetics:
There was no apparent correlation between steady state trough serum golimumab concentration and ACR 20 and ACR 50 responses at Week 52 regardless of MTX usage.

Antibodies to golimumab:
ACR 20 was achieved by 59%, 49% and 70% of subjects who were positive, negative and undetectable for antibodies to golimumab, respectively. ACR 50 was achieved by 47%, 31% and 46% of subjects who were positive, negative and undetectable for antibodies to golimumab, respectively. Overall, it appears that the presence of antibodies to golimumab does not preclude clinically meaningful ACR response rates.

Safety Results:

Adverse Events:
The proportion of subjects experiencing at least 1 AE was similar across all treatment groups with no notable differences between subjects receiving MTX compared with those not receiving MTX, and no notable differences between golimumab + MTX dose groups. As in other studies of anti-TNFα agents, the AEs most frequently reported were in the Infections and infestations system-organ class.

Serious Adverse Events:
Through Week 52, 43 of 337 (12.8%) subjects in the All golimumab + MTX group experienced SAEs. A greater proportion of subjects with SAEs were observed in the golimumab 100 mg + MTX group (18.0%) as compared with the golimumab 50 mg + MTX only (10.1%) and golimumab 100 mg + placebo groups (12.0%). Across all treatment groups, from 3.7% to 20.0% of subjects experienced a SAE.

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Infections
Through Week 52, the most commonly reported infections in subjects receiving golimumab were upper respiratory tract infection, nasopharyngitis, bronchitis, pharyngitis, UTI, and oral herpes. The proportion of subjects who experienced one or more infections was 49.4% in the golimumab 50 mg + MTX only group, 58.4% in the golimumab 100 mg + MTX group, 50.4% in the golimumab 100 mg + placebo group, and 50.7% in the All golimumab + MTX group.

Serious Infections
Through Week 52, 14 (4.2%) of 337 subjects in the All golimumab + MTX group experienced serious infections. A greater proportion of subjects with serious infections were observed in the golimumab 100 mg + MTX group (7.9%) as compared with the golimumab 50 mg + MTX only (2.2%) and golimumab 100 mg + placebo groups (3.8%).

Tuberculosis:
Ninety-two subjects (20.7%) required treatment (usually INH) for latent TB at baseline. The proportion of subjects that required treatment for latent TB at baseline was similar across all treatment groups. No subject required initiation of treatment for latent TB postbaseline. From Week 0 through Week 52, there was 1 subject who developed active TB. The event was TB pleurisy and occurred after Week 24.

Deaths:
From Week 0 through Week 52 two deaths were reported. One death was reported in the study through Week 24 in the golimumab 100 mg + placebo group. The subject was hospitalized with diarrhea and dehydration, and developed aspiration pneumonia and sepsis. After Week 24 through Week 52, one death was reported in the golimumab 100 mg + placebo group. The subject died due to fulminant hepatic failure on the 323rd day of the study. The last administration of SC study agent prior to death was study Day 286.

Malignancies:
From Week 0 through Week 52, malignancies were reported for 8 golimumab treated subjects as follows: basal cell carcinoma (3 subjects), squamous cell carcinoma (2 subjects), and breast cancer (3 subjects).

Laboratory Safety Assessments:
Laboratory safety assessments did not identify any safety issues not reported with other anti-TNF therapies. Through Week 52, markedly abnormal changes were observed in ALT/SGPT in 7 (2.1%) of subjects and in AST/SGOT in 3 (0.9%) of subjects in the All golimumab + MTX group. Markedly abnormal chemistry test results that occurred in any subject more than one time were observed only for glucose, alkaline phosphatase and total bilirubin, with each occurring in only 1 subject. The incidence of subjects with ALT or AST values < ULN at baseline who had maximum postbaseline ALT or AST values > ULN was greater in those subjects who received treatment for latent TB than in those subjects who did not; however these LFTs were low level and predominantly < 3 x ULN. There was no suggestion that treatment with both golimumab and INH increased the risk of serious ALT or AST abnormalities.

Injection Site Reactions:
Injection site reactions to golimumab injections occurred with low frequency (5.3% of subjects in the All golimumab + MTX group) through Week 52. Injection site erythema, bruising and irritation were the most commonly reported injection site reactions. No serious injection site reactions were reported. From Week 0 through Week 52, 1 subject discontinued after Week 24 due to repeated injection site reactions of erythema that were nonserious and mild to moderate in intensity.

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Conclusions:

- Golimumab 50 mg + MTX or 100 mg + MTX provides substantial benefit to subjects with active RA despite MTX therapy by reducing clinical signs and symptoms of arthritis and improving physical function, which was maintained through Week 52.
- The two golimumab + MTX dose groups appeared generally comparable in efficacy.
- Radiographic progression was minimal for all treatment groups, including the placebo + MTX group, with no significant differences between groups.
- Golimumab is generally well tolerated, and with or without MTX use, demonstrated a safety profile similar to that of other anti-TNFα agents. The proportion of subjects experiencing SAEs, in particular serious infections, was somewhat greater in subjects treated with golimumab 100 mg + MTX than golimumab 50 mg + MTX.
- Golimumab 100mg + MTX generally resulted in higher trough concentrations than golimumab 100 mg + placebo.
- The overall incidence of antibodies to golimumab was low (3.97%).

Date of Report: 15 Oct 2009