Synopsis (C0524T12 GO LIVE)

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: C0524T12	**EudraCT No.:** 2005-003232-21

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

Principal/Coordinating Investigator(s): Joel Kremer, MD, Albany Medical College, The Center for Rheumatology ([redacted], US)

Study Center(s): The long-term extension (LTE) of this study was conducted at 76 of the original 86 sites were enrolled in the study extension.

Publication (reference): None

Studied Period: 24 Aug 2006/26 Sep 2009	**Phase of Development:** 3

Objectives:
The primary objective of this study was to:

- Assess the clinical efficacy and safety of golimumab IV infusions every 12 weeks with and without methotrexate (MTX), compared with MTX alone, in subjects with active rheumatoid arthritis (RA) despite concurrent MTX treatment.

The secondary objectives of this study were to:

- Evaluate the effects on physical function and quality of life (QOL), the population PK of IV golimumab, and the pharmacodynamics of IV golimumab in subjects with active RA.
- Evaluate the safety of SC golimumab after transition from IV golimumab.

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter, 5-arm study of the efficacy and safety of IV administration of 2 mg or 4 mg golimumab (given with or without MTX over a period of 30 minutes every 12 weeks) for at least 48 weeks in subjects with active RA despite concurrent MTX therapy. At Week 16 and Week 24, joint assessment results were used to allow subjects to enter early escape (EE) and dose regimen adjustment (DRA), respectively, in a blinded fashion. All subjects remained on the same assigned and blinded treatment that they received at Weeks 24, 36, and 48 and were followed for routine efficacy and safety assessments until database lock. No changes in concomitant medications for RA were allowed. Treatment assignments were unblinded after the 48-week database lock. Within 3 months of the 48-week database lock, subjects were given the option to enter the long-term extension and receive SC golimumab 50 mg every 4 weeks for 24 weeks of treatment designated by Week E-0 through Week E-24.

Number of Subjects (Planned and Analyzed): A total of 625 subjects were planned, 643 subjects were randomized in the main study, 508 enrolled in the study extension.

Diagnosis and Main Criteria for Inclusion: The subjects participating in the study were adults (≥ 18 years of age) who had a diagnosis of RA for at least 3 months before screening. The subjects enrolled had active RA and must have tolerated MTX (at least 15 mg/wk and ≤ 25 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).

Test Product, Dose and Mode of Administration, Batch Number: Golimumab was supplied as a sterile liquid for SC injection at a fill volume of 0.5 mL in single-use prefilled syringes (PFS). Each PFS contained

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50 mg golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5 that was free of preservatives (lot number 07H021). For the IV phase of the study, golimumab was supplied as a sterile liquid for IV infusion at a volume of 1 mL in 2 mL single-use glass vials, active MTX capsules were filled with microcrystalline cellulose. IV placebo solution, consisting of an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5, was supplied as a sterile liquid for IV infusion at a volume of 1 mL in 2 mL single-use glass vials. Placebo capsules were filled with microcrystalline cellulose. For lot numbers of the study drugs used during the IV phase of the study refer to the synopsis of the C0524T12 48-Week CSR.

Duration of Treatment: Minimum 48 weeks IV and a minimum 24 weeks SC.

Reference Therapy, Dose and Mode of Administration, Batch Number: MTX was not supplied by the sponsor after the 48-week database lock, unblinding, and SC study agent administration. Beginning at Week E-14, subjects may have had MTX added, discontinued, or its dose adjusted to their treatment at the investigator's discretion.

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

Pharmacokinetics/Pharmacodynamics: For PK and immunogenicity analyses, subjects were evaluated by treatment groups. Data of serum golimumab concentration and antibodies to golimumab through Week E-0 are summarized based on the IV treatment groups, while the corresponding data collected between Week E-0 and Week E-40 are shown mainly based on the SC treatment groups with the original IV treatment group being indicated for the summary of PK data. No PD analysis was done in the LTE.

Efficacy: Summaries were performed over time for efficacy data at Week 48, through Week E-0, and Week E-0 through Week E-40. Assessments included ACR 20, 50, 70, and 90 responses, DAS28 (using CRP and ESR), improvement in HAQ score, and change in SF-36 scales.

Safety: Safety was assessed by summarizing the occurrences and type of AEs and examining the changes in the laboratory parameters. Subjects who received at least 1 IV study agent administration were included in the analysis.

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. Cochran-Mantel-Haenszel (CMH) tests (stratified analyses) were used to compare the proportion of subjects achieving a specified endpoint (eg, proportion of subjects with an ACR 50 response) between treatment groups. All statistical tests were 2-sided and performed at $\alpha = 0.05$. In addition to statistical analyses, subject listings were also used to summarize/present the data.

SUMMARY – CONCLUSIONS

Study Population Results: A total of 508 were enrolled in the study extension. Baseline demographics were generally comparable across treatment groups. Approximately 81.0% of randomized subjects were women and 69.5% were Caucasian in all golimumab treatment groups combined. The median age was 51.0 and the median weight was approximately 69.1 kg. There were no overall differences in background medical histories in treatment groups. During the LTE (Week E-0 though Week E-40), 13.5% subjects from all golimumab treatment groups combined required treatment for latent TB at baseline and no subjects required treatment for latent TB postbaseline. However, one subject started 'rifampicin' drug on day 617 and 624.

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Pharmacokinetic/Pharmacodynamic Results:

- Compared with median trough serum golimumab levels following administration of IV golimumab 2 mg/kg or 4 mg/kg every 12 weeks, median trough serum golimumab concentrations from administrations of SC golimumab 50 mg every 4 weeks were higher. These results support the finding that ACR responses induced by IV treatment were well-maintained by SC golimumab during the long-term extension.
- Compared with the cumulative incidence (7.4%) of antibodies to golimumab following IV administrations through Week E-0, the cumulative incidence of antibodies to golimumab (10.4%) through Week E-40 seemed to be slightly increased.

Efficacy Results:

- Overall efficacy (ACR 20, 50, 70 and DAS 28 using CRP) and improvements in ACR components while receiving IV golimumab 2 or 4 mg/kg + MTX were sustained or increased through the IV treatment period.
- In the long-term extension following the week 48 database lock, in subjects who received SC golimumab 50 mg q4wks or SC golimumab 50 mg + MTX q4wks, overall efficacy (ACR 20, 50, 70) and improvements in ACR components were sustained in the majority of subjects regardless of whether subjects had received IV golimumab 2 or 4 mg/kg with or without MTX.
- The proportion of ACR 50 responders at Week E-14 and Week E-24, who were also ACR 50 responders during the IV golimumab phase was highest in subjects originally assigned to the IV golimumab 4 mg/kg + MTX treatment group.
- There was a gradual increase in DAS28 (using CRP) remission over time through Week E-0 while on golimumab IV 2 or 4 mg/kg + MTX.
- Improvement in DAS 28 and CRP measurements continued to increase while subjects were on SC golimumab 50 mg compared to the improvement seen with IV golimumab 2 or 4 mg/kg. However, DAS28 (using CRP) remission rates appeared to reach a plateau during treatment with SC golimumab 50 mg compared with rates while on IV golimumab 2 or 4 mg/kg. This was true regardless if the subject was given MTX.
- At Week E-14 and Week E-24 the proportion of DAS28 (using CRP) responders with good or moderate response, while receiving SC golimumab 50 mg through the SC treatment period, was highest in subjects originally assigned to the golimumab 4 mg monotherapy treatment group.
- The proportion of subjects with DAS28 (using CRP) remission through the SC treatment period was maintained.
- HAQ score improved or remained the same through the SC treatment period regardless of the original IV treatment group.
- The number of HAQ responders achieving ≥ 0.25 and ≥ 0.3 improvement from baseline was maintained when subjects changed from IV golimumab 2 or 4 mg/kg to SC golimumab 50 mg.
- The number of subjects positive for antibodies to golimumab ([n = 46] through Week E-0) is too small to support any conclusions regarding the impact of antibody status on efficacy.

Safety Results:

IV administration through Week E-0

- Overall, there were more AEs and SAEs reported for subjects who received golimumab with and without MTX than in subjects who received IV placebo + MTX. However, follow-up times were longer for subjects who received golimumab. Therefore, no pattern can be ascertained.

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- For the IV portion of the study, frequency and types of AEs and SAEs were generally similar to those identified in the Week-48 clinical study report.
- The most frequent system organ class category of AEs in all treatment groups was infections and infestations in the IV portions of the study.
- For most organ system classes there were no apparent differences in AE rates between the golimumab and IV placebo + MTX treated subjects.
- In the IV portion of the study, there was no apparent difference in the number of neoplasms identified in golimumab treated subjects than in IV placebo treated subjects. No lymphomas were reported in the study.
- There were more cardiovascular events noted in subjects who received IV golimumab than in those who received IV placebo.
- Deaths noted in golimumab treated subjects in the IV portion of study did not appear to be dose related.
- Infusion reaction rates for golimumab treated subjects remained lower than for those subjects receiving placebo infusions.
- At week 72, 2.5% subjects were newly positive for ANA in the IV placebo + MTX treatment group, while the proportion of subjects who were newly positive was 1.1% in the all golimumab treatment groups combined.
- No clinically relevant increase in cardiac events occurred between the Week 48 and the Week E-40 database lock.

Long-term Extension SC Administration

- In the long-term extension the overall types and relative rates of AEs observed from Week E-0 on SC golimumab through Week E-40 were similar to those observed through Week E-0.
- The most frequent system organ class category of AEs in all treatment groups was infections and infestations in the SC portions of the study.
- AE and SAE rates and types in the long-term extension portion of the study are similar to those identified for the golimumab 50 mg dose regimen (with and without MTX) in the SC golimumab Phase III development program.
- There was no apparent difference in cardiovascular events noted in subjects who received SC golimumab monotherapy than in subjects who received SC golimumab + MTX.
- The proportion of subjects with newly positive test results for ANA in the SC golimumab 50 mg monotherapy treatment group was greater through Week E-40 than for those in the SC golimumab 50 mg + MTX treatment group.

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Conclusions:

- Overall efficacy (ACR 20, 50, 70; and DAS 28 using CRP) and improvements in ACR components while receiving IV golimumab 2 or 4 mg/kg + MTX were sustained or increased through the IV treatment period.
- There was a gradual increase in DAS28 (using CRP) remission over time through Week E-0 while on IV golimumab 2 or 4 mg/kg + MTX.
- In the long-term extension following the Week-48 database lock, in subjects who received SC golimumab 50 mg + MTX q4wks, overall efficacy (ACR 20, 50, 70) and improvements in ACR components were sustained through the SC treatment period in the majority of subjects regardless of whether subjects received IV golimumab 2 or 4 mg/kg + MTX. Generally, the highest proportion of ACR responders were from subjects originally in the IV golimumab 4 mg/kg + MTX treatment group.
- Intravenous and subcutaneous golimumab treatment with and without concomitant MTX had a safety profile consistent with other anti-TNFs and was well-tolerated based upon limited differences in AE and SAE rates reported for golimumab and placebo-treated subjects and low rates of infusion and injection-site reactions in all treatment groups.
- In general, this study supports the maintenance of effect with longer term treatment with IV golimumab 2 and 4 mg/kg infusions as well as the continued efficacy benefit of SC golimumab following IV golimumab administration.

Date of Report: 26 Aug 2010

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