Janssen Research & Development

Clinical Study Report Synopsis: 48-Week Protocol C0524T12; Phase 3

CNTO148 (golimumab)

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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)		

Test Product, Dose and Mode of Administration, Batch Number: Golimumab was supplied as a sterile liquid for IV infusion at a volume of 1 mL in 2 mL single-use glass vials (lot numbers: 16487.17, D05PJ7456, D06PJ7526, V07PB9976, V07PE7054, and V07PF7062). Active MTX capsules were filled with microcrystalline cellulose (Avicel PH 102) and a 2.5 mg MTX tablet (lot numbers: 16487.13, 16487.14, 16487.18, 16487.20, 16487.22, 16487.25, 16487.26, 16487.27, 16487.28, 16487.3, 16487.30, 16487.32, 16487.33, 16487.34, 16487.38, 16487.41, 16487.45, 16487.46, 16487.47, 16487.50, 16487.6, 16488.2, 16488.4, F29956, F29980, F29985, and F29987).

Duration of Treatment: 48 weeks.

Reference Therapy, Dose and Mode of Administration, Batch Number: 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 (lot numbers: 16487.16, D05PJ7458, D06PJ7528, D07PH7601). Placebo capsules were filled with microcrystalline cellulose (Avicel PH 102) (lot numbers: 16487.19, 16487.21, 16487.23, 16487.29, 16487.35, 16487.36, 16487.39, 16487.40, 16487.43, 16487.49, 16488.1, 19299.1, F29989, F29991).

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 IV study agent administration.

Pharmacokinetics/Pharmacodynamics: For PK analyses, subjects were evaluated by treatment groups. Subjects were included in only 1 treatment group (except for the combined golimumab + placebo treatment group and the combined golimumab + MTX treatment group). The PK treatment groups evaluated the PK profiles of subjects who were exposed to different golimumab doses and treatment scenarios, including EE at Week 16 and DRA at Week 24. For PD analyses, subjects were included in the treatment groups similar to those groups for PK analyses. The PD treatment groups were defined with the intent to explore different golimumab doses (as well as changes in treatment) and make comparisons to placebo.

Efficacy: The primary endpoint was the proportion of subjects who achieved an American College of Rheumatology (ACR) 50 response at Week 14. The major secondary endpoints of this study were:

- The proportion of subjects achieving an ACR 50 response at Week 24.
- The proportion of subjects /achieving an ACR 20 response at Week 14.
- The proportion of subjects with good or moderate Disease Activity Index Score 28 (DAS28) (using C-reactive protein [CRP]) at Week 14.
- The change from baseline in physical component summary (PCS) score of the SF-36 at Week 14.

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.

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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. Chi-square tests (unstratified analyses) or 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. Continuous response parameters (eg, ACR-N type analyses) were compared using an analysis of variance (ANOVA) on the van der Waerden normal scores. All statistical tests were 2-sided and performed at $\alpha = 0.05$. In addition to statistical analyses, graphical data displays (eg, line plots) and subject listings were also used to summarize/present the data.

SUMMARY – CONCLUSIONS

Study Population Results: The study population included 643 randomized subjects. Baseline demographics were generally comparable across treatment groups. Approximately 80.4% of randomized subjects were women and 69.5% were Caucasian. The median age was 51.0 and the median weight was approximately 69.9 kg. There were no overall differences in background medical histories in treatment groups. The ACR Core baseline disease characteristics of RA were consistent with a population with moderate to severe RA. Baseline disease characteristics were generally comparable across treatment groups. Based on information obtained during screening, treatment for latent TB was initiated for approximately 13.8% of subjects before dose administration with study agent. There was 1 subject (initially tested negative for TB) treated for TB after baseline.

Pharmacokinetic/Pharmacodynamic Results:
Pharmacokinetics:

- Serum golimumab concentration was approximately proportional to dose following an IV infusion of golimumab 2 mg/kg or 4 mg/kg every 12 weeks with and without concomitant use of MTX in subjects with RA.
- When golimumab was administered every 12 weeks, median trough serum golimumab concentrations were below LLOQ [redacted] for golimumab 2 mg/kg + placebo, golimumab 4 mg/kg + placebo, and golimumab 2 mg/kg + MTX treatment groups. The golimumab 4 mg/kg+ MTX treatment group had steady-state trough levels of approximately 0.2 µg/mL to 0.3 µg/mL.
- Concomitant use of MTX slightly increased median serum golimumab concentrations and lowered the proportion of subjects with serum golimumab concentration below LLOQ at different visits.
- When golimumab was given on a mg/kg (body weight) basis, heavier subjects generally had higher median serum golimumab concentrations than lighter subjects.

Antibodies to Golimumab:

- The incidence of antibodies to golimumab was low (5.1% and 7.0% through Week 24 and Week 48, respectively) following repeated IV administrations of golimumab at 2 mg/kg or 4 mg/kg every 12 weeks.
- Concomitant use of MTX was associated with a lower incidence of antibodies to golimumab (3.3% versus 8.8% through Week 24).
- Serum golimumab concentrations were generally lower in subjects who tested positive for antibodies to golimumab than in subjects who were negative.

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Pharmacodynamics:

- Decreases in MMP-3, intercellular adhesion molecule-1 (ICAM-1), IL-6, vascular endothelial growth factor (VEGF), and IL-8 levels were observed at Week 4 and Week 14 after treatment with golimumab + MTX and also golimumab + placebo. Overall lesser reductions were observed for subjects treated with placebo + MTX. Lesser decreases in these markers were generally observed at Week 24 and Week 48 relative to the changes seen at Week 14.
- Treatment with golimumab + MTX group resulted in reductions in rheumatoid factor (RF) and anti-CCP antibody levels at Week 14. Similar reductions were observed in subjects treated with placebo + MTX.

Efficacy Results:

Efficacy Findings Through Week 24:

ACR Responses

- Subjects who received golimumab 2 mg/kg + MTX or golimumab 4 mg/kg + MTX did not demonstrate a significantly greater proportion of ACR 50 response at Week 14 (primary endpoint) when compared with IV placebo + MTX. P-value for the combined golimumab + MTX treatment group approached statistical significance ($p = 0.051$). Conclusions based on individual p-values for all other endpoints should be interpreted accordingly.
- A statistically greater ACR 50 response was observed at Week 24 for both the combined and individual golimumab + MTX treatment groups (secondary endpoint). For the golimumab 4 mg/kg + MTX treatment group the proportion of subjects with an ACR 50 response increased between Week 14 and Week 24, whereas the other treatment groups decreased.
- Significantly higher rates of ACR 20 response were achieved by all subjects who received golimumab with or without MTX when compared with IV placebo + MTX at Week 14 (secondary endpoint). Subjects in the golimumab + placebo treatment groups did not have significantly higher ACR 20 responses compared with IV placebo + MTX by Week 24, and the proportion of subjects with an ACR 20 response in the golimumab 2 mg/kg + MTX treatment group at Week 24 was diminished compared with Week 14.
- There was no significant difference in the proportion of subjects who achieved an ACR 70 response at either Week 14 or Week 24 between any golimumab-treated subjects and IV placebo + MTX treated subjects.
- Subjects in the both golimumab + MTX dose groups had significantly higher ACR-N scores when compared with the IV placebo + MTX treatment group at Week 14 and Week 24.
- In general, subjects who received golimumab regardless of concomitant MTX demonstrated significantly greater improvement in the ACR core components at Week 14. There was a clinically important reduction in the percent of improvement in some of the ACR core components by Week 24.

SF-36

- Subjects in the combined and individual golimumab + MTX treatment groups had significant physical improvements in SF-36 at Week 14 compared with the IV placebo + MTX treatment groups (secondary endpoint).

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DAS28

- A significantly higher percentage of golimumab-treated subjects, regardless of concomitant MTX, achieved a good or moderate DAS28 (using CRP) responses at Week 14 (secondary endpoint). Additionally, there was a significantly higher percentage of subjects who received golimumab 4 mg/kg + MTX who achieved DAS28 (using CRP) remission at Week 14 and Week 24.

Efficacy Findings Week 24 Through Week 48

- Among all golimumab treatment groups, the golimumab 4 mg/kg + MTX treatment group achieved the highest proportion of responders for ACR 20, ACR 50, and ACR 70 at Week 48.
- The golimumab 4 mg/kg + MTX treatment group demonstrated median percent improvement from baseline in all ACR components at Week 48 compared with Week 36. This was not demonstrated in any other golimumab treatment group. Similar results were also observed in the analyses for HAQ, SF-36, DAS28 response and DAS28 remission.
- At Week 48, 42.9% of subjects who were maintained on golimumab 4 mg/kg + MTX from Week 0 achieved DAS28 (using CRP) remission.

Safety Results:

Safety Findings through Week 24:

- The proportion of AEs reported by subjects through Week 16 was similar between golimumab-treated subjects and IV placebo + MTX treated subjects. The most commonly reported AEs were upper respiratory tract infection, nasopharyngitis, bronchitis, sinusitis, and urinary tract infections.
- There were more SAEs through Week 16 in all golimumab treatment groups combined than in the IV placebo + MTX treatment group. These SAEs were predominantly serious infections.
- There were no cases of TB or serious opportunistic infections through Week 24.
- The percentage of infusions with infusion reactions and subjects with infusion reactions were similar between golimumab-treated subjects and IV placebo + MTX treated subjects through Week 16.
- There were no deaths through Week 24.
- There was no notable difference in ALT abnormalities between golimumab-treated subjects and IV placebo + MTX treated subjects, particularly in the 4 mg/kg treatment groups as well as in subjects receiving concomitant anti-TB prophylactic treatment.
- Antibodies to golimumab were present in a low percentage of subjects (5.1% at Week 24) following repeated IV administrations of golimumab at 2 mg/kg or 4 mg/kg every 12 weeks.

Safety Findings through Week 48:

- The proportion of subjects experiencing 1 or more AEs through Week 48 was 81.6% in the all golimumab treatment groups combined and 72.1% in the IV placebo+ MTX treatment group. The most commonly reported AEs were upper respiratory tract infection, bronchitis, nasopharyngitis, urinary tract infection, and sinusitis.
- There were more infections requiring antimicrobial treatment reported in all golimumab treatment groups combined compared with placebo and rates of infections requiring antimicrobial therapy were highest in the golimumab 4 mg/kg + placebo treatment group and golimumab 4 mg/kg + MTX treatment group. The most commonly reported infections requiring oral or parenteral antimicrobial therapy for all golimumab treatment groups combined (≥ 5.0%) were upper respiratory tract infection, bronchitis, urinary tract infection, and sinusitis. One subject received treatment for TB.
- Through Week 48, SAEs were more commonly reported in all golimumab treatment groups combined (10.1%) compared with the IV placebo + MTX treatment group (5.4%).

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- Through Week 48, there were 3 deaths due to cardiovascular events (1 each from the golimumab 4 mg/kg + MTX, 4 mg/kg + placebo, and 2 mg/kg + placebo treatment groups).
- Through Week 48, the malignancy rates were similar in all golimumab treatment groups combined compared with IV placebo + MTX treatment group. Singular malignancies such as colon cancer, bladder cancer, and lung cancer were observed in the golimumab 4 mg/kg + placebo and golimumab 4 mg/kg + MTX treatment groups.
- Through Week 48, 2710 golimumab infusions were administered. A total of 1.2% infusions in all golimumab treatment groups combined were complicated by an infusion reaction compared with 2.0% of IV placebo + MTX treatment group infusions. The golimumab 4 mg/kg + MTX treatment group had the lowest proportion of infusions complicated by infusion reaction. There were no serious infusion reactions and 1 severe infusion reaction.
- Antibodies to golimumab were present in a low percentage of subjects (7.0% at Week 48) following repeated IV administrations of golimumab at 2 mg/kg or 4 mg/kg every 12 weeks.

Conclusions:

- Golimumab administered intravenously at 2 mg/kg and 4 mg/kg + MTX every 12 weeks closely approached but did not reach statistical significance ($p = 0.051$) of the primary endpoint (ACR 50 at Week 14). Improvements were seen for the major secondary endpoints including ACR 20, DAS28, SF-36 responses at Week 14, and ACR 50 at Week 24.
- Golimumab alone when compared with placebo + MTX resulted in numerically greater improvements across efficacy measures (DAS28 and ACR), which was statistically significant at Week 14 but was not maintained through Week 24.
- Golimumab treatment with and without concomitant MTX was safe and well-tolerated based upon limited differences in AE rates reported for golimumab and placebo-treated subjects and low rates of infusion reactions in both treatment groups.
- Treatment resulted in the presence of antibodies to golimumab in a low proportion of subjects (approximately 7%) after repeated IV infusions of golimumab every 12 weeks for 48 weeks. Subjects treated with concomitant MTX tended to have lower rates of antibody formation.
- Serum golimumab concentrations were dose proportional and decreased to undetectable median serum concentrations in the majority of subjects over the 12 week dosing interval. Alteration of dosing posology is indicated in future trials.
- In total, data support efficacy benefit of IV golimumab (and in particular, golimumab 4 mg/kg + MTX dosing) compared with IV placebo infusions, as defined by ACR 20 and ACR 50 responses at Week 24 and Week 48.

Date of Report: 23 Jul 2009