Synopsis (C0524T14)

Name of Sponsor/Company: Centocor R&D, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: SIMPONI™ (golimumab)		
Name of Active Ingredient: CNTO 148 (golimumab)		

Protocol: C0524T14	**EudraCT No.:** Not applicable

Title of the study: An Open-label Randomized Phase 1 Study to Investigate the Pharmacokinetics and Pharmacodynamics of Subcutaneous and Intravenous Administration of Golimumab to Subjects with Rheumatoid Arthritis

Principal/Coordinating Investigator(s): Charles A. Birbara, MD.

Study Sites: 9 sites in the United States

Publication (reference): There were no publications based on the study.

Studied Period: 27 Dec 2007/25 Feb 2009	**Phase of Development:** 1

Objectives:
Primary Objective:

- To assess the pharmacokinetics (PK) of golimumab following multiple intravenous (IV) or subcutaneous (SC) administrations of golimumab in subjects with rheumatoid arthritis (RA).

Secondary Objectives:

- To assess the early changes in serum pharmacodynamic (PD) markers following SC or IV administrations of golimumab.
- To assess changes in urine/serum hepcidin following SC or IV administrations of golimumab.
- To assess the efficacy, safety, and tolerability of SC or IV administrations of golimumab.

Methodology: Open-label, Phase 1, randomized outpatient study of golimumab administered SC and IV. Subjects were randomly assigned in a 2:1 ratio to receive golimumab SC or IV.

Number of Subjects (Planned and Analyzed): A total of approximately 45 subjects were planned to be randomized; 30 subjects to SC injection and 15 subjects to IV infusion. Fifty-one subjects were randomized into the study. Forty-nine subjects were treated: 33 subjects in Group I (SC) and 16 subjects in Group II (IV).

Diagnosis and Main Criteria for Inclusion: The study population were to be men or women 18 years of age or older who met the 1987 American Rheumatism Association (ARA) revised criteria for the classification of RA for more than 3 months. Refer to Section 5.2 of the report for a full list of inclusion/exclusion criteria.

Test Product, Dose and Mode of Administration, Batch Number:
Group I: SC injection of 100 mg of golimumab, every (q) 4 weeks, through Week 20 (Batch number: 07A212 prefilled syringes).
Group II: IV infusions of 2 mg/kg golimumab on Days 1 and 85 (Batch number: 6KS1P vials).

Duration of Treatment: Up to approximately 34 weeks in the SC golimumab group; up to approximately 28 weeks in the IV golimumab group.

Reference Therapy, Dose and Mode of Administration, Batch Number: Not applicable

Criteria for Evaluation:

- The PK Evaluable Population was defined as all subjects whose PK profiles allowed accurate calculation of some or all of the PK parameters.
- The Efficacy Analysis Population was defined as all subjects who were randomly assigned to a treatment group, whether or not they actually received the assigned treatment.
- The Safety Analysis Population was defined as all subjects who received an administration of

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golimumab during the study.

- The Antibody Analysis Population was defined as all golimumab-treated subjects.

Pharmacokinetics/Immunogenicity/Pharmacodynamics:

Pharmacokinetics:

- PK parameters following multiple SC administrations of golimumab included Cmax, tmax, AUC(0-28d), t1/2, R(AUC(0-28d), R(Cmax), CL/F, and Vz/F.
- PK parameters following IV administration of golimumab included Cmax, AUClast, AUCinf, AUC(0-84d), t1/2, R(AUC[0-84d]), R(Cmax), CL, Vss, and Vz.

Immunogenicity:

- The antibodies to golimumab status (positive or negative) was summarized through each specified timepoint (ie, Day 85, Day 169, and Day 211) by treatment group based on the Antibody Analysis Population. Injection-site reactions (related to SC administration) or infusion reactions (related to IV administration) were summarized by antibodies to golimumab status.

Pharmacodynamics:

- All PD measures were summarized over time by treatment group. Associations between changes from baseline in serum biomarkers including C-reactive protein (CRP), interleukin (IL) 6, serum amyloid A (SAA), tumor necrosis factor alpha (TNFα), matrix metalloproteinase (MMP)-3, hyaluronic acid, and haptoglobin and select efficacy measures were explored. The relationship between changes from baseline in urine/serum hepcidin levels and transferrin receptor, reticulocyte count, serum iron, total iron-binding capacity (TIBC), serum ferritin, and hemoglobin (Hgb) was explored and correlated with efficacy measures.

Efficacy: Efficacy data were presented in individual listings, summary tables and graphs, as appropriate for American College of Rheumatology (ACR) 20, 50, 70, Disease Activity Index Score 28 (DAS28) score responses and remission, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), and Health Assessment Questionnaire (HAQ) scores.

Safety: Safety was monitored throughout the study by the review of listings and summary vital signs, adverse events (AEs), laboratory results, and electrocardiograms (ECGs).

Statistical Methods: Descriptive statistics was used to summarize serum concentration over time data, PK parameters and baseline characteristics. The summary statistics included N, mean, standard deviation (SD), coefficient of variation (CV), median, minimum, maximum, and interquartile (IQ) range for continuous variables, and frequency and proportion for categorical variables. PK parameters were also summarized by antibodies to golimumab status and by methotrexate (MTX) use at baseline. Serum PD markers and urine/serum hepcidin were summarized over time, by treatment group, using descriptive statistics.

SUMMARY – CONCLUSIONS

Study Population Results:

- Four subjects in Group I (SC) were discontinued from the study. Two subjects (6.1%) were discontinued due to AEs; two (6.1%) were discontinued for other reasons. No subject in Group II (IV) withdrew study agent or from the study.
- Subjects ranged in age from 19 to 76 years and were predominantly Caucasian (83.7%, 41/49 subjects) and female (75.5%, 37/49 subjects).
- At baseline, mean duration of RA was 8.9 years in Group I (SC) and 10.3 years in Group II (IV); 63.6% of subjects in Group I (SC) and 68.8% of subjects in Group II (IV) had positive rheumatoid

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factor and anti-CCP tests.

- Anemic subjects at baseline comprised 15.2% (5/33 subjects) in Group I (SC) and 0.0% (0/16 subjects) in Group II (IV).

Pharmacokinetic/Immunogenicity/Pharmacodynamic Results:

Pharmacokinetics

- Following 100 mg SC administration every 4 weeks, golimumab serum concentration achieved steady state by Day 84. The median steady-state trough serum golimumab concentrations ranged from 0.87 to 1.04 µg/mL.
- The mean t1/2 after SC administration was 13.1 days, which was similar to that after IV administrations (13.2 days). The average absolute bioavailability for SC administration was estimated to be 53%.
- Golimumab mean body weight-adjusted CL/F at steady state following SC golimumab treatment was 36.2% lower in subjects receiving concomitant MTX therapy compared to those not receiving concomitant MTX therapy.
- After 2 mg/kg IV administration, golimumab serum concentrations declined in a biphasic manner. The median trough serum concentration before the second dose was 0.16 µg/mL.

Immunogenicity

- The incidence of antibodies to golimumab in this study was low in both Group I (SC) (2/32; 6.3%) and Group II (IV) (0/16; 0.0%). One antibody-positive subject had a much shorter t1/2 (2.9 days) and higher CL/F compared to the antibody-negative subjects.

Pharmacodynamics

- Serum PD markers showed decreased concentrations immediately following treatment, but returned to baseline by Day 60.
- At baseline, no PD markers correlated with the change in Day 169 DAS28 (CRP).
- Increasing concentration of hyaluronic acid at early timepoints following treatment reflected decreasing Day 169 DAS28 (CRP).
- At baseline, CRP concentration correlated with improvement in Day 169 SJC.
- Early reductions in CRP and SAA reflected improvement in Day 169 SJC.
- At baseline, no PD marker correlated with Day 169 TJC.
- Early reductions in CRP and hyaluronic acid correlated with the reduction in Day 169 TJC.
- Serum or urine hepcidin levels were not elevated at baseline. Following either SC or IV administration of study agent, mean serum hepcidin levels decreased rapidly through Day 3 and levels remained below baseline through the end of the study. Mean urine hepcidin levels decreased through Day 15 and remained below baseline values through the end of the study.
- Early decreases in serum hepcidin concentrations tended to reflect decreased IL-6 concentrations in Group II (IV).
- Serum and urine hepcidin were positively correlated at all timepoints.

Efficacy Results:

- The mean percent improvement from baseline to Day 169 in TJC was 57.82% in Group I (SC) and 50.72% in Group II (IV); and in SJC was 72.33% and 75.67%, respectively.
- The mean percent improvement in pain from baseline to Day 169 was 49.49% in Group I (SC) and 28.84% in Group II (IV).
- The mean percent improvement in disease activity from baseline to Day 169 according to subject's

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assessments was 43.36% in Group I (SC) and 36.64% in Group II (IV), and according to the physician's assessments was 47.85% and 58.51%, respectively.

- The mean decrease in HAQ scores from baseline to Day 169 was 0.40 in Group I (SC) and 0.46 in Group II (IV) indicating that both treatment groups appeared to have physical functional improvement as measured by the HAQ.
- The mean increase in FACIT-F scores from baseline to Day 169 was 8.9 in Group I (SC) and 2.6 in Group II (IV) indicating that both treatment groups appeared to have less fatigue.
- At Day 169, the percentage of subjects that achieved an ACR20 response was 62.1% in Group I (SC) and 56.3% in Group II (IV); the percentage of subjects that achieved an ACR50 response was 31.0% and 25.0%, respectively, and the percentage of subjects that achieved an ACR70 response was 20.7% and 18.8%, respectively.
- The mean decreases in DAS28 (CRP and ESR) scores from baseline to Day 169 indicated that both treatment groups appeared to have improvement in disease activity as measured by the DAS28.
- At Day 169, the percentage of subjects with a good DAS28 (CRP) response was 51.7% in Group I (SC) and 50.0% in Group II (IV), and the percentage of subjects with a moderate response was 34.5% and 18.8%, respectively. The percentage of subjects with a good DAS28 (ESR) response was 31.0% in Group I (SC) and 25.0% in Group II (IV), and the percentage of subjects with a moderate response was 48.3% and 37.5%, respectively.
- At Day 169, the percentage of subjects with DAS28 (CRP) remission was 36.4% in Group I (SC) and 31.3% in Group II (IV). The percentage of subjects with DAS28 (ESR) remission was 24.2% and 6.3%, respectively.

Safety Results:

- Golimumab was generally well tolerated in this study.
- Twenty-nine subjects (87.9%) in Group I (SC) and 16 subjects (100.0%) in Group II (IV) completed treatment with the test agent; mean duration of exposure was 129 days and 86 days, respectively.
- Approximately 75% of subjects had at least one TEAE during the study. Overall, TEAEs occurred most frequently within the SOC categories of Infections and Infestations (36.7%); Musculoskeletal and Connective Tissue Disorders (36.7%); and Gastrointestinal Disorders (28.6%). The most frequently reported TEAE was RA (14.3% overall), reported as symptoms secondary to RA, flare of RA, worsening of RA, or RA exacerbation. Overall, commonly reported TEAEs were vomiting (12.2%), upper respiratory tract infection (10.2%), bursitis (10.2%), and headache (10.2%); other TEAEs occurred in less than 10% of subjects. The majority of the TEAEs were mild in intensity.
- In Group I (SC), two subjects (6.1%) had a TEAE considered definitely related to study agent (injection site irritation). Three subjects (9.1%) had TEAEs probably related to study agent (injection site erythema, erythema, herpes zoster, and headache) and five subjects (15.2%) had TEAEs possibly related to study agent (diarrhea, abdominal discomfort, fatigue, edema, sinusitis, nasopharyngitis, headache, dizziness, paresthesia, and pharyngolaryngeal pain, pruritus, hypotension, and systolic hypertension).
- In Group II (IV), one subject (6.3%) had TEAEs probably related to study agent (sinusitis and sinus congestion) and two subjects (12.5%) had TEAEs possibly related to study agent (diarrhea, nausea, tooth impacted, vomiting, fatigue, postnasal drip, and seasonal rhinitis). No subjects in Group II (IV) had TEAEs considered definitely related to study agent.
- There were no deaths during this study.
- Two subjects (6.1%) in Group I (SC) and two subjects (12.5%) in Group II (IV) had at least one

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TESAE. Treatment-emergent SAEs included non-cardiac chest pain, pneumonia, fractured sacrum, pubic rami fracture, acoustic neuroma, and asthma; none of the TESAE was considered related to study agent.

- Two subjects in Group I (SC) permanently discontinued study agent due to TEAEs (papilloma viral infection and pruritus); no subjects in Group II (IV) had a TEAE leading to study agent discontinuation.
- TEAEs due to infection were observed in 12 subjects (36.4%) in Group I (SC) and in 5 subjects (31.3%) in Group II (IV).
- There were no clinically relevant changes in physical examination findings, laboratory test results, ECG, or vital sign parameters.
- All subjects had negative results for TB skin test and QuantiFERON-TB Gold test at all visits.
- In Group I (SC), four subjects had injection-site reactions (one [50%] positive and three [10%] negative) for antibodies to golimumab. No subject had a severe or serious injection-site reaction or an injection-site reaction that led to discontinuation of study agent. There was no subject in Group II (IV) who had injection-site or infusion reactions.

Conclusions:

- Following 100 mg SC administration every 4 weeks, golimumab serum concentration achieved steady state by approximately 84 days. The median steady-state trough serum golimumab concentrations ranged from 0.87 to 1.04 μg/mL.
- The mean t1/2 after SC administration was 13.1 days, which was similar to that after IV administrations (13.2 days). The average F% for SC administration was estimated to be 53%.
- Concomitant use of MTX reduced golimumab mean body weight-adjusted CL/F by 36.2% following SC administration of golimumab 100 mg every 4 weeks.
- The incidence of antibodies to golimumab in this study was low following multiple SC (6.3%; 2/32) or IV (0.0%, 0/16) administrations.
- Serum PD markers showed decreased concentrations immediately following treatment, but returned to baseline by Day 60. Serum or urine hepcidin levels were not elevated at baseline. Following either SC or IV administration of study agent, mean serum hepcidin levels decreased rapidly through Day 3 and levels remained below baseline through the end of the study.
- Mean urine hepcidin levels decreased through Day 15 and remained below baseline through the end of the study.
- Golimumab administered as SC injection or IV infusion appeared to be generally efficacious, safe and well tolerated.

Date of Report: 08 Oct 2009

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