SYNOPSIS

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Name of Sponsor/Company	Janssen Research & Development, Inc.
Name of Finished Product	SIMPONI® (golimumab)
Name of Active Ingredient(s)	golimumab

Protocol No.: CNTO148ART3001

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

Study Name: GO-FURTHER

EudraCT Number: 2008-006064-11

NCT No.: NCT00973479

Clinical Registry No.: CR015784

Principal Investigator(s): Principal Investigator: Michael E. Weinblatt, MD – Brigham and Women's Hospital, [redacted] USA.

Study Center(s): The following sites randomized subjects for this study: Argentina (9 sites), Australia (5 sites), Columbia (4 sites), Hungary (5 sites), Korea (4 sites), Lithuania (7 sites), Malaysia (8 sites), Mexico (5 sites), New Zealand (2 sites), Poland (14 sites), Russia (10 sites), Ukraine (12 sites), USA (7 sites).

Publication (Reference): None

Study Period: 14 Sep 2009 (informed consent) – 18 May 2011 (last study-related procedure). 31 Aug 2011 (database lock).

Phase of Development: 3

Objectives: The primary objective of this study was to assess the clinical efficacy of IV administration of golimumab 2 mg/kg + methotrexate (MTX) compared with MTX alone in subjects with active rheumatoid arthritis (RA) despite MTX therapy.

The secondary objectives of this study were:

- To evaluate safety parameters
- To evaluate physical function and disability
- To characterize population pharmacokinetics (PK) and pharmacodynamics (PD) of IV golimumab
- To evaluate effects of golimumab on structural damage

Methodology: This was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study in subjects with moderate to severely active RA despite MTX therapy. Subjects were administered golimumab IV 2 mg/kg + MTX at Weeks 0, 4, and every 8 weeks (q8w) subsequent or Placebo + MTX in a similar pattern through Week 24. Placebo-treated subjects were eligible to enter early escape at Week 16 if they demonstrated < 10% improvement in both tender and swollen joint count and then received golimumab infusions of 2 mg/kg at Weeks 16 and 20 and every 8 weeks thereafter. Study agent will be administered through Week 100 with a 12 week safety follow-up.

Number of Subjects (planned and analyzed): Approximately 564 subjects were planned, and 592 were randomized.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women 18 years of age or older with a diagnosis of RA for at least 3 months prior to screening and had to have moderate to severely active RA, defined as ≥ 6 tender and ≥ 6 swollen joints, at screening and at baseline, despite concurrent MTX therapy. At screening, subjects had to have C-reactive protein (CRP) ≥ 1.0 mg/dL, and be rheumatoid factor (RF) positive and/or anti-cyclic citrullinated peptide (CCP) positive.

Test Product, Dose and Mode of Administration, Batch No.: Golimumab was supplied as a sterile liquid for IV infusion at a volume of 4 mL (50 mg, 12.5 mg/mL) in single-use vials. Each vial contained golimumab in an aqueous medium of histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives were present. Golimumab Batch Numbers: 8BS54, 9DS18, 8BS54, 9JS1N, AAS6A00, BCS2Z00. Subjects randomized to golimumab received 2 mg/kg of golimumab intravenously over a 30 ± 10 minute infusion time. Additionally, subjects were maintained on their stable dose of commercial MTX (between 15-25 mg/week) throughout the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was a 0.9% saline solution supplied as a sterile liquid for IV infusion in single-use infusion bags (Baxter Viaflex 2B1307 or Viaflo WE1307 bags). No preservatives or excipients were present. Additionally, subjects were maintained on their stable dose of commercial MTX (between 15-25 mg/week) throughout the study and received appropriate placebo infusions of 0.9% saline over a 30 ± 10 minute infusion time to maintain the blind. MTX, oral or injectable, was not supplied by the sponsor but was acquired by the subjects from a commercial pharmacy.

Duration of Treatment: Randomization was stratified based upon a screening CRP of < 1.5 mg/dL or ≥ 1.5 mg/dL. Subjects were randomized 2:1 to golimumab + MTX or placebo + MTX at Weeks 0, 4, and q8w thereafter. Subjects who were randomized to placebo infusions + MTX and who did not qualify for early escape were maintained on placebo infusions + MTX for 24 weeks. Subjects on placebo infusions + MTX who qualified for and underwent early escape received placebo infusions + MTX for 16 weeks and then began receiving golimumab 2 mg/kg infusions + MTX at Weeks 16 and 20 and then q8w subsequent. Subjects randomized to golimumab 2 mg/kg + MTX received golimumab 2 mg/kg infusions administered at Weeks 0 and 4 then q8w regardless of whether they qualified for early escape. Subjects randomized to placebo who did not early escape at Week 16 received golimumab at Weeks 24, 28, and q8w thereafter. The duration of treatment for the entire study will be 100 weeks with a 12 week safety follow-up period.

Criteria for Evaluation:

Pharmacokinetics: The PK of golimumab were evaluated by summarizing serum golimumab concentrations over time 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, relating to trough golimumab concentrations and comparing with selected efficacy and safety parameters.

Immunogenicity: The incidence of antibodies to golimumab during the study was summarized for all subjects who had appropriate serum samples for antibody detection. The relationships of antibodies to golimumab with serum golimumab concentrations and selected efficacy and safety measures were also assessed.

Efficacy: Joint assessment, patient's assessment of pain, Patient's and Physician's Global Assessments of Disease Activity, Disability Index of the Health Assessment Questionnaire (HAQ-DI), CRP levels, 36-item short form health survey (SF-36) version 2 and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) were used to assess efficacy through 24 weeks in this study.

Safety: Safety evaluations for all subjects were monitored through Week 24 and included measurement of vital signs, the assessment of AEs that may have occurred between each of the evaluation visits and infusion reaction evaluations from baseline through the 24-Week safety database lock. Tuberculosis evaluations, including QuantiFERON-TB Gold test and Mantoux tuberculin skin test (in countries where QuantiFERON-TB testing was not licensed), were performed. Samples for routine laboratory analyses were collected. Serum samples for the determination of the presence of antinuclear antibodies (ANA)/anti-dsDNA antibodies were also collected.

Statistical Methods: Binary categorical data (eg, the proportion of subjects with an ACR 20 response) were analyzed using the chi-square test or the Cochran-Mantel-Haenszel (CMH) test when stratification was employed. Continuous data was analyzed using an analysis of variance (ANOVA) test on van der Waerden normal scores. All efficacy analyses were based on the intent-to-treat principle; thus, subjects were analyzed according to the treatment for which they were randomized regardless of the treatment they actually received. All statistical testing was performed 2-sided at an alpha level of 0.05.

RESULTS:

STUDY POPULATION:

In this study, 592 subjects were randomized with 197 assigned to receive placebo + MTX and 395 assigned to receive golimumab 2 mg/kg IV + MTX. In addition, 68 subjects in the placebo + MTX group underwent early escape at Week 16 and began receiving golimumab + MTX at Week 16.

The majority (80.4%) of subjects were Caucasian, and 81.6% of the subjects were female. The median age was 52 years (ranging from 18 to 83 years of age).

In total, 570 (96%) of 592 subjects completed the 24-week study. The remaining 22 (4%) subjects discontinued the study before Week 24. Most discontinuations were due to AEs (9 [2.3%] subjects in the golimumab + MTX group and 2 [1.0%] subjects in the placebo + MTX group).

EFFICACY RESULTS:

The primary endpoint was met.

A significantly greater proportion of subjects in the golimumab + MTX group (58.5%) achieved an ACR 20 response at Week 14 compared with subjects in the placebo + MTX group (24.9%, $p < 0.001$). The treatment effect is consistent in subjects with either a CRP $\geq$ 1.5 mg/dL or < 1.5 mg/dL at screening. For the primary analyses, if a subject discontinued because of treatment failure, that subject was treated as a non-responder in the analysis. If a subject discontinued for other reasons, the data was treated as missing and the last observation carried forward was used in the data analysis.

All secondary endpoints analyzed in this report were met.

A significantly greater proportion of subjects in the golimumab + MTX group had good or moderate DAS28 responses (using CRP) at Week 14 (81.3%) compared with subjects in the placebo + MTX group (40.1%, $p < 0.001$).

There was a significantly greater improvement in median HAQ-DI disability scores at Week 14 in subjects in the golimumab + MTX group (0.5000) compared with subjects in the placebo + MTX group (0.1250, $p < 0.001$).

Subjects who received golimumab + MTX had a statistically significantly greater ACR 50 response at Week 24 (34.9%) compared with subjects who received placebo + MTX (13.2%, $p < 0.001$). The treatment effect is consistent in subjects with either a CRP $\geq$ 1.5 mg/dL or < 1.5 mg/dL at screening.

Other:

Signs and Symptoms of Arthritis

A significantly greater proportion of subjects in the golimumab + MTX group achieved an ACR 20 response at Week 24, ACR 50 response at Week 14 and an ACR 70 response at Week 14 and Week 24 compared with the placebo + MTX group ($p < 0.001$ for all comparisons). The percentage of improvement in the individual ACR components from baseline at Week 14 and Week 24 were significantly greater ($p < 0.001$ for each component) for the golimumab + MTX group than for the placebo + MTX group. A response was observed as early as Week 2.

The median percent improvement from baseline in CRP was statistically significant for the golimumab + MTX group compared to the placebo + MTX group ($p < 0.001$) at Weeks 14 and 24. Swollen and tender joint count median percent improvement from baseline through Week 24 was greater in the golimumab + MTX group compared with the placebo + MTX group at all timepoints.

A significantly greater proportion of subjects in the golimumab + MTX group achieved a good or moderate DAS28 (using CRP) response at Week 24 and DAS28 (using CRP) remission (< 2.6), and DAS28 response at Week 14 and Week 24 compared to the placebo + MTX group ($p < 0.001$ for all comparisons).

Physical Function

There was a significantly ($p < 0.001$) greater improvement in HAQ-DI score at Week 24 in subjects in the golimumab + MTX group (0.5000) compared with subjects in the placebo + MTX group (0.1250). The proportion of subjects achieving a clinically meaningful improvement ($\geq$ 0.25) in HAQ-DI from baseline was greater in the golimumab + MTX group relative to the placebo + MTX group at Week 14 and Week 24 ($p < 0.001$ for both comparisons).

Patient-Reported Outcomes

Statistically significant greater improvement in the mental and physical component summary scores of the SF-36 (version 2) as well as all 8 scales of the SF-36 instrument were observed in golimumab + MTX treatment relative to placebo + MTX treatment at Weeks 12, 16, and 24 ($p < 0.001$ for all comparisons). Clinically meaningful improvements in fatigue (FACIT-Fatigue improvement $\geq$ 4 points) and in general health state as measured by the EQ VAS and EQ-5D index were observed in the golimumab + MTX treatment group relative to the placebo + MTX treatment group.

Subgroup Analysis

A consistent treatment benefit was observed within subgroups of demography, baseline clinical characteristics including screening CRP values of < 1.5 mg/dL and ≥1.5 mg/dL and baseline CRP values of < 1.0 mg/dL and ≥1.0 mg/dL, and prior exposure to medications for RA.

Efficacy and Antibodies to Golimumab

At Week 24, ACR 20 and ACR 50 responses were observed in 6 (46.2%) of 13 and 3 (23.1%) of 13 subjects who were antibody positive, respectively, versus 231 (54.7%) of 422 and 132 (31.3%) of 422 subjects who were antibody negative, respectively. The correlation between antibody positivity and efficacy is difficult to evaluate since the number of subjects who were antibody positive was too small to make a definitive conclusion.

PHARMACOKINETIC RESULTS:

Pharmacokinetics:

- After administration of 2 mg/kg golimumab at Week 0 and Week 4, the median pre-infusion (trough) and post-infusion (peak) golimumab concentrations were 1.23 µg/mL and 41.56 µg/mL, respectively, at Week 4. The median trough serum golimumab concentration in subjects receiving IV administration of golimumab at 2 mg/kg q8w with MTX at Week 12 was 0.28 µg/mL and at Week 20 was 0.22 µg/mL.
- The proportion of subjects who had undetectable trough serum golimumab concentrations (ie, LLOQ) was 14.1% at Week 12 and 17.4% at Week 20.
- At Week 12 and Week 20, subjects with greater body weight (> 81.2 kg) had higher median serum trough golimumab concentrations.
- Median serum trough golimumab concentrations at Week 12 and Week 20 were similar in subjects with a screening CRP < 1.5 mg/dL and CRP ≥ 1.5 mg/dL.

Antibodies to Golimumab:

- Antibodies to golimumab were detected in 13 (3.0%) of 440 golimumab-treated subjects through Week 24. For the subjects who were positive for antibodies to golimumab, 100% were positive for neutralizing antibodies.
- Serum golimumab concentrations were generally lower in subjects who tested positive for antibodies to golimumab than in subjects who were negative.

SAFETY RESULTS:

The proportion of subjects who reported an AE was comparable between the golimumab + MTX and placebo + MTX groups through Week 16 (47.3% compared with 43.7%, respectively) and Week 24 (52.9% compared with 49.2%, respectively). At Week 24, the most commonly reported system organ class (SOC) AEs were infections and infestations (27.2% and 23.9% in the combined golimumab + MTX [which includes subjects who received golimumab initially and subjects from the placebo group who underwent early escape at Week 16 and then received golimumab] and placebo + MTX groups, respectively), and were predominantly upper respiratory tract infection (URTI), urinary tract infection (UTI) and nasopharyngitis.

The SAE occurrences through Week 24 in the combined golimumab + MTX group were higher (4.1%) compared with the placebo + MTX group (2.0%). The SAEs were predominantly musculoskeletal and connective tissue disorders (0.6% in the combined golimumab + MTX group and 0.5% in the placebo + MTX group), infections and infestations (0.6% in the combined golimumab + MTX group and

0% in the placebo + MTX group), renal and urinary disorders (0.6% in the golimumab + MTX group and 0.0% in the placebo + MTX group), and gastrointestinal disorders (0.4% in the combined golimumab + MTX group and 1.0% in the placebo + MTX group)

One subject in the placebo + MTX group died (presumed stroke due to hypertensive crisis; no autopsy performed).

There were 2 malignancies, breast cancer in a golimumab-treated subject and non-treatment-emergent lung adenocarcinoma in a placebo-treated subject, through Week 24.

Serious infections occurred in 0.9% of the subjects in the combined golimumab + MTX group and in none of the subjects in the placebo + MTX group as reported by investigators.

There were no cases of TB, and no serious opportunistic infections were reported; however, there was 1 case of non-serious esophageal candidiasis reported in the combined golimumab + MTX treated group.

The incidence of infusion reactions was 1.1% in the combined golimumab + MTX group and 0.2% in the placebo + MTX group.

The proportion of subjects with infusion reactions were 3.5% in the combined golimumab + MTX group and 0.5% in the placebo + MTX group. No severe or serious infusion reactions were reported. It should be noted that all placebo infusions consisted of 0.9% normal saline alone rather than a true matched placebo.

The differences in proportions of subjects with markedly abnormal changes in clinical chemistry and hematology evaluations between the placebo group and golimumab treatment group were small.

Of the subjects with normal ALT (alanine aminotransferase) at baseline, 31.3% of subjects who received golimumab and concomitant TB prophylaxis and 20.6% of subjects who received placebo and TB prophylaxis had abnormal ALT measurements through Week 24. Of the subjects with normal ALT at baseline, 28.1% of subjects who received golimumab without TB prophylaxis and 21.6% of subjects who received placebo without TB prophylaxis had abnormal ALT measurements through Week 24.

There was 1 subject positive for antibodies to golimumab who had a non-severe, non-serious infusion reaction through Week 24.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

Golimumab 2 mg/kg administered intraveneously and MTX at Weeks 0, 4 and then q8w thereafter:

- Provided substantial benefit to subjects with moderate to severely active RA despite MTX therapy by rapidly (as early as Week 2) reducing clinical signs and symptoms of arthritis and improving physical function through Week 24.
- Is generally well-tolerated. The incidence of AEs and SAEs was slightly greater in subjects treated with golimumab + MTX than placebo + MTX; no serious opportunistic infections, lymphomas, or demyelinations were reported. The overall safety profile of golimumab is consistent with the safety profile of SC golimumab and other TNFα blockers in comparable RA patient populations.

- Results in adequate PK exposure for clinical efficacy and safety as demonstrated by:
  - The median pre-infusion (trough) and post-infusion (peak) golimumab concentrations were 1.23 µg/mL and 41.56 µg/mL, respectively, at Week 4. The median trough serum golimumab concentration in subjects receiving IV administrations of golimumab at 2 mg/kg q8w with MTX was 0.28 µg/mL at Week 12 and 0.22 µg/mL at Week 20.
  - The overall incidence of antibodies to golimumab was low.
  - A single incidence of infusion reaction was reported. There were no severe or serious infusion reactions in subjects positive for antibodies to golimumab.

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