SYNOPSIS

Issue Date: 20 June 2013

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	SIMPONI®
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: Michael E. Weinblatt, MD
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Study Center(s): The following countries 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): Weinblatt ME, Bingham CO, Mendelsohn AM, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. Ann Rheum Dis. 2013; 72:381-389.

Study Period: 14 Sep 2009 (informed consent) to 08 Feb 2013 (last study-related procedure); 08 Mar 2013 (clinical database lock).

Phase of Development: 3

Objectives: The primary objective of this study was to assess the clinical efficacy of intravenous (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 at Weeks 0 and 4 and every 8 weeks (q8w) thereafter plus concomitant weekly MTX, 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 counts and then received golimumab infusions of 2 mg/kg at Weeks 16 and 20 and q8w thereafter. Subjects randomized to golimumab infusions who qualified for early escape continued on golimumab 2 mg/kg infusions on the original schedule without changes in dose schedule or dose escalation but received placebo infusions at Week 16 to maintain the blind. All subjects who received placebo + MTX began receiving golimumab IV 2 mg/kg at Week 24, followed by a second dose at Week 28 and q8w thereafter, plus concomitant weekly MTX. Study agent was administered through Week 100. Radiographs of the hands and feet were to be performed at Week 0, Week 16 or 24, Week 52, and Week 100 for all subjects. Subjects who met early escape criteria underwent radiographic evaluation at Week 16, but not at Week 24; all other subjects underwent radiographic evaluation at Week 24.

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 before 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 (1.0 mg/dL was the upper limit of the normal range [ULN] for the high-sensitivity assay used for this study) and be rheumatoid factor positive and/or anti-cyclic citrullinated peptide 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. The golimumab batch numbers used in this study were 8BS43, 9DS18, 9JS1N, AAS6A00, BCS2Z00, and BCS2Z22. Subjects randomized to golimumab received 2 mg/kg of golimumab IV over a 30 ± 10-minute infusion time. Additionally, subjects were maintained on their stable dose of commercial MTX (between 15 and 25 mg/week) throughout the study. MTX, oral or injectable, was not supplied by the sponsor but was acquired by the subjects from a commercial pharmacy.

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 and 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 in a 2:1 ratio to golimumab + MTX or placebo + MTX at Weeks 0 and 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 who were on placebo infusions + MTX and 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 q8w thereafter. Subjects who were randomized to golimumab 2 mg/kg + MTX received golimumab 2 mg/kg infusions administered at Weeks 0 and 4 and q8w thereafter, regardless of whether or not they qualified for early escape. Subjects who were randomized to placebo and did not early escape at Week 16 received golimumab at Weeks 24 and 28 and q8w thereafter. The overall study duration was 112 weeks, which included 100 weeks of treatment plus an additional 12 weeks of follow-up for safety and some measurements of health-related quality of life.

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.

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 assessments, patient's assessment of pain, Patient's and Physician's Global Assessments of Disease Activity, Disability Index of the Health Assessment Questionnaire (HAQ), radiographs of the hands and feet, CRP levels, 36-item Short Form Health Survey (SF-36), version 2, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue), EQ-5D, and productivity assessments were used to assess efficacy through 112 weeks in this study.

Safety: Safety evaluations for all subjects were monitored through Week 112 and included measurement of vital signs, the assessment of adverse events (AEs) that may have occurred between evaluation visits and infusion reaction evaluations from baseline through the 112-week safety database lock. Tuberculosis (TB) evaluations, including QuantiFERON-TB Gold testing and Mantoux tuberculin skin testing (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 American College of Rheumatology [ACR] 20 response) were analyzed using the chi-square test or the Cochran-Mantel-Haenszel 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 at a 2-sided 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. Of note, 68 subjects in the placebo + MTX group underwent early escape at Week 16 and began receiving golimumab + MTX at Week 16.

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

Through Week 112, 481 (81.3%) of the 592 randomized subjects completed study agent administrations and post-treatment follow-up; 5 (0.8%) subjects completed study agent administrations but not post-treatment follow-up; and 106 (17.9%) discontinued study agent administration before Week 100, predominantly because of AEs. Only 12 (2%) subjects discontinued the trial due to lack of efficacy through Week 112.

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 1.21 and 41.41 µg/mL, respectively, at Week 4. Steady state was achieved at Week 12. At Weeks 12, 20, 52, 76, and 100, the median trough serum golimumab concentration in subjects receiving IV administration of golimumab 2 mg/kg q8w + MTX was 0.27, 0.21, 0.30, 0.35, and 0.31 µg/mL, respectively, suggesting that drug exposure was maintained through Week 100.
- Subjects with greater body weight tended to have higher serum golimumab concentrations, although differences among the 4 quartiles were relatively small and the IQ ranges largely overlapped.
- Median serum trough golimumab concentrations at Weeks 12, 20, 52, 76, and 100 were similar in subjects with screening CRP levels either < 1.5 mg/dL or ≥ 1.5 mg/dL, indicating that serum trough golimumab concentrations were unaffected by screening CRP level.

Antibodies to Golimumab

- Antibodies to golimumab were detected in 6.7% of golimumab-treated subjects through Week 100. Among subjects who were positive for antibodies to golimumab through Week 100, 86.5% were positive for neutralizing antibodies.

EFFICACY RESULTS:

The primary endpoint was met. A significantly greater proportion of subjects in the golimumab + MTX group achieved an ACR 20 response at Week 14 compared with subjects in the placebo + MTX group. This endpoint was reported in the CNTO148ART3001 24-Week CSR.

All 4 of the major secondary endpoints were met. Three of the 4 major secondary endpoints (Disease Activity Index Score [DAS28] response using CRP at Week 14, change from baseline in HAQ at Week 14, and ACR 50 response at Week 24) showed statistically significant improvements in the golimumab + MTX group compared with the placebo + MTX group and were reported in the CNTO148ART3001 24-Week CSR.

The fourth major secondary endpoint, change from baseline in the total modified van der Heijde Sharp (vdH-S) score at Week 24, achieved statistically significant improvements ($p < 0.001$) in the golimumab + MTX group compared with the placebo + MTX group and was reported in the CNTO148ART3001 52-Week CSR.

Other Efficacy Analyses:

Radiographic Endpoints

- Subjects who were randomized to golimumab + MTX demonstrated continued inhibition of radiographic progression at Weeks 52 and 100, as measured by the change from baseline in total vdH-S score compared with subjects randomized to placebo + MTX (all $p < 0.01$).
- Subjects randomized to placebo + MTX who began golimumab treatment at Week 16 or Week 24 demonstrated numerically greater changes from baseline in total modified vdH-S score through Week 100 compared with subjects who were initially randomized to golimumab + MTX. This was likely due to the additional 24 weeks of radiographic progression that occurred in these subjects while they were still on placebo; radiographic inhibition was evident after the subjects began treatment with golimumab.

- Radiographic progression from Week 52 to Week 100 was minimal in both treatment groups, supporting the effect of IV golimumab on the inhibition of structural damage progression.

Signs and Symptoms of RA

- High levels of ACR 20, ACR 50, and DAS28 (CRP) response rates were maintained through Week 100 among subjects treated with golimumab 2 mg/kg +MTX.
  - At Week 100, 69.1% of subjects randomized to golimumab + MTX achieved ACR 20 responses.
  - At Week 100, 45.1% of subjects randomized to golimumab + MTX achieved ACR 50 responses.
  - At Week 100, 84.1% of subjects randomized to golimumab + MTX achieved DAS28 (CRP) moderate or good responses.
- Subjects randomized to placebo + MTX, which included subjects who were eligible for early escape at Week 16 and subjects who crossed over to golimumab at Week 24, also maintained the clinically important response rates they had demonstrated at Week 52 (66.0% with ACR 20 response at Week 100); similar patterns were observed with ACR 50, ACR 70, and ACR 90 response rates.

Physical Function

- Subjects in the golimumab + MTX group demonstrated a median improvement in HAQ scores of 0.50 through Week 100.
  - At Week 100, 67.3% of subjects randomized to golimumab + MTX achieved ≥ 0.25 HAQ improvement.

Patient-Reported Outcomes

- There was evidence supporting sustained clinically important improvements in health-related quality of life measurements (eg, SF-36, EQ-5D, FACIT-Fatigue) at Week 112.

Efficacy and Antibodies to Golimumab

- At Week 100, ACR 20 and ACR 50 responses were slightly lower in antibody-positive subjects. However, the number of antibody-positive subjects was small, and an association between efficacy and antibodies to golimumab cannot be determined.

SAFETY RESULTS:

Because safety results are reported from Week 0 through Week 112, and because there was no pure placebo group from Week 24 through Week 112, the safety discussion emphasized the golimumab combined + MTX group, which includes subjects in the golimumab + MTX group and subjects in the placebo + MTX → golimumab + MTX group.

Adverse Events: Through Week 112, 79.1% of subjects in the golimumab combined group reported an AE. The most commonly reported AEs through Week 112 were in the system organ classes (SOCs) of Infections and infestations (50.5%), Musculoskeletal and connective tissue disorders (22.4%), and Gastrointestinal disorders (17.6%). Individual AEs reported with a frequency ≥ 5% were upper respiratory tract infection (11.5%), bronchitis (8.9%), rheumatoid arthritis (8.7%), nasopharyngitis (6.7%), urinary tract infection (UTI) and alanine aminotransferase increased (6.5% each), and pharyngitis and headache (5.8% each).

Serious Adverse Events: Through Week 112, 18.2% of subjects in the golimumab combined group reported a serious adverse event (SAE). The SOC with the highest incidence of SAEs was Infections and infestations (5.5%).

Deaths: Six deaths were reported through Week 112: 1 through Week 24 in a subject in the placebo + MTX group (cerebrovascular accident); 1 through Week 52 in a subject in the golimumab 2 mg/kg + MTX group (pneumonia and myocardial infarction); and 4 after Week 52 through Week 112 (2 subjects in the placebo + MTX→ 2 mg/kg + MTX at Week 24 group [due to dehydration and to an unknown cause], and 2 subjects in the golimumab 2 mg/kg + MTX group [due to acute abdominal syndrome (with abdominal fluid positive for TB) and to septic shock secondary to pyogenic lung abscess]).

Malignancies: Six malignancies were reported through Week 112 in the golimumab combined group: breast cancer through Week 24; basal cell carcinoma and cervix carcinoma in situ through Week 52; and basal cell carcinoma, Bowen's disease, and chronic lymphocytic leukemia (Rai stage I) after Week 52 through Week 112.

Serious Infections: Serious infections occurred in 6.2% of subjects in the golimumab combined group through Week 112. Serious infections generally occurred in singular subjects, with the exceptions of pneumonia (n=5), UTI (n=4), active TB infection (n=3), and erysipelas (n=2).

Infusion Reactions: The proportion of infusions with infusion reactions was 0.4% in the golimumab combined group through Week 112. No serious or severe infusion reactions were reported. The proportion of subjects with infusion reactions was 3.9% in the golimumab combined group through Week 112.

Markedly Abnormal Changes in Clinical Chemistry and Hematology: Through Week 112, the proportions of subjects in the golimumab combined group with markedly abnormal changes in clinical chemistry and hematology evaluations were small. Markedly abnormal changes were few in number, predominantly self-limited (ie, they resolved spontaneously or after drug discontinuation), and of limited clinical importance.

Abnormal ALT Measurements: Among subjects in the golimumab combined group with a normal (ie, ≤ ULN) alanine aminotransferase (ALT) value at baseline, 44.4% who received concomitant TB prophylaxis and 45.4% who did not receive TB prophylaxis had had at least 1 postbaseline abnormal ALT value through Week 112.

Abnormal AST Measurements: Among subjects in the golimumab combined group with a normal (ie, ≤ ULN) aspartate aminotransferase (AST) value at baseline, 42.0% who received concomitant TB prophylaxis and 34.1% who did not receive TB prophylaxis had had at least 1 postbaseline abnormal AST value through Week 112.

Antibody Response and Infusion Reactions: Through Week 100, 3 (8.1%) of 37 subjects who were positive for antibodies to golimumab had an infusion reaction, only 1 (2.7%) of whom had an infusion reaction that led to discontinuation. Of the 516 subjects who were negative for antibodies to golimumab, 22 (4.3%) had infusion reactions, none of which led to discontinuation. The presence of antibodies to golimumab did not have an apparent impact on the occurrence of infusion reactions.

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

CONCLUSIONS:

Golimumab 2 mg/kg administered intravenously at Weeks 0 and 4 and then q8w with concomitant weekly MTX through Week 100:

- Provided substantial benefit to subjects with moderately to severely active RA despite MTX therapy by reducing clinical signs and symptoms of RA, and improving physical function, through Week 100.
- Achieved significantly greater inhibition of radiographic progression at Week 24 compared with placebo + MTX. This benefit was maintained through Week 52 and Week 100 in subjects receiving golimumab + MTX, although subjects initially randomized to placebo did demonstrate evidence of radiographic inhibition at Weeks 52 and 100.
- Was generally well-tolerated and demonstrated a safety profile that was consistent with the class of anti-TNFα agents with no new safety signals reported.
- Resulted in adequate PK exposure for clinical efficacy and safety as demonstrated by:
  - Serum trough concentrations of 0.2 to 0.3 µg/mL maintained through Week 100.
  - Low (4.6%) overall incidence of antibodies to golimumab after golimumab treatment through Week 100.

Based on 100 weeks of treatment and 112 weeks of safety and health-related quality of life follow-up, the benefit-risk balance continues to support the use of golimumab 2 mg/kg administered intravenously over 30 minutes (±10 minutes) at Week 0 and Week 4 and q8w thereafter, plus concomitant weekly MTX, in subjects with moderately to severely active RA despite prior MTX therapy.

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