SYNOPSIS

Issue Date: 13 Jul 2012

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

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. *Ann Rheum Dis* 2012. doi:10.1136/annrheumdis-2012-201411

Study Period: 14 Sep 2009 (informed consent) – 25 Nov 2011 (last study-related procedure). 01 Mar 2012 (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 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 scheduling or dose escalation. All subjects receiving placebo + MTX began receiving golimumab IV 2 mg/kg + MTX q8w at Week 24, followed by a second dose at Week 28 and then q8w. Study agent was administered through Week 52. Radiographs of the hands and feet were performed at Week 0 for all subjects. Subjects meeting early escape criteria underwent radiographic evaluation at Week 16, but not at Week 24. All other subjects underwent radiographic evaluation at Week 24, and all subjects subsequently had radiographs taken at Week 52.

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 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. 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. 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 15-25 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 overall study duration is 112 weeks which includes 100 weeks of treatment plus an additional 12 weeks of follow-up for safety.

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 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), radiographs of the hands and feet, 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 52 weeks in this study.

Safety: Safety evaluations for all subjects were monitored through Week 52 and included measurement of vital signs, the assessment of adverse events (AEs) that may have occurred between each of the evaluation visits and infusion reaction evaluations from baseline through the 52-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 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 (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 study agent in the 24-week study. The remaining 22 (4%) subjects discontinued study agent 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).

From Week 24 through Week 52, 553 (96.5%) of 573 subjects completed the 52-week study. Most discontinuations were due to AEs (5 [1.3%] 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 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 of the 4 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-DI at Week 14, and ACR 50 Response at Week 24) showed statistically significant improvements between golimumab + MTX and placebo + MTX and were reported in the CNTO148ART3001 24-Week CSR.

The fourth major secondary endpoint, change from baseline in van der Heijde Sharp (vdH-S) score at Week 24, achieved statistical significance ($p < 0.001$) in the golimumab + MTX group (mean change 0.03, median 0.00) compared with the placebo + MTX group (mean change 1.09, median 0.00). Results were consistent regardless of screening CRP level < or ≥ 1.5 mg/dL. A consistent treatment benefit was generally observed for most subgroups defined by demography, baseline disease characteristics, and baseline medications.

Other Efficacy Analyses:

Radiographic Endpoints

At Week 24:

- Subjects in the golimumab + MTX group showed significantly less change from baseline in both erosion score ($p < 0.001$) and joint-space narrowing (JSN) score ($p = 0.002$) compared with the placebo + MTX group.
- Subjects in the golimumab + MTX group showed less change from baseline in total score, erosion scores and JSN scores in both hands and feet than subjects in the placebo + MTX group.
- In the golimumab + MTX group, a significantly smaller proportion of subjects demonstrated radiographic progression, radiographic erosion progression, and radiographic JSN progression based on smallest detectable change (SDC) or change in score ≤ 0 compared with the placebo + MTX group.

At Week 52:

At Week 52, study results are reported by randomized groups, ie, golimumab + MTX treatment group: subjects who were randomized to golimumab treatment at Week 0 and the placebo + MTX → golimumab + MTX treatment group: subjects who were randomized to placebo at Week 0 and crossed over to golimumab + MTX at either Week 16 or Week 24.

- The change from baseline in total vdH-S score was significantly less ($p = 0.001$) in subjects in the golimumab + MTX group compared with subjects in the placebo + MTX → golimumab + MTX group.
- Subjects in the golimumab + MTX group showed significantly less change from baseline in both erosion score ($p = 0.010$) and JSN score ($p = 0.016$) compared with the placebo + MTX → golimumab + MTX group.
- Subjects in the golimumab + MTX group showed less change from baseline in total score, erosion scores and JSN scores in both hands and feet than subjects in the placebo + MTX → golimumab + MTX group.
- In the golimumab + MTX group, a smaller proportion of subjects demonstrated radiographic progression, radiographic erosion progression, and radiographic JSN progression based on SDC or change in score ≤ 0 compared with the placebo + MTX → golimumab + MTX group.

Results seen at Week 24 and week 52 were generally consistent between the 2 readers.

Signs and Symptoms of Arthritis

- The proportion of subjects in the golimumab + MTX group who achieved ACR 20, ACR 50, ACR 70 and ACR 90 responses at Week 24 was generally maintained after Week 24 through Week 52. A greater proportion of subjects in the placebo + MTX → golimumab + MTX group began responding after switching to golimumab at Week 16 or Week 24 and similar proportions of subjects in each treatment group were in response at Week 52.
- The percent improvement from baseline in the individual ACR components after Week 24 through Week 52 was either improved or maintained in the golimumab + MTX group and the placebo + MTX → golimumab + MTX group.
- After Week 24 through Week 52, the proportion of subjects in DAS28 response (using CRP) was maintained in the golimumab + MTX group and the placebo + MTX → golimumab + MTX group.

Physical Function

- From Week 24 through Week 52, the improvement from baseline in the median value for HAQ-DI was maintained and improved in the golimumab + MTX group and the placebo + MTX → golimumab + MTX group.
- The proportion of subjects in the golimumab + MTX group with a clinically meaningful ≥ 0.25 improvement in HAQ-DI from baseline was maintained after Week 24 through Week 52. The placebo + MTX → golimumab + MTX group also started responding after switching to golimumab at Week 24, and by Week 52, 62.4% of the subjects had ≥ 0.25 improvement in HAQ-DI from baseline.

Patient-Reported Outcomes

- In all measures of patient reported outcomes ([PROs]: SF-36 Physical Component Summary and Mental Component Summary scores, FACIT-Fatigue, EQ VAS, and EQ-5D index), subjects in the golimumab + MTX group maintained their mean improvement from Week 24 through Week 52. Subjects in the placebo + MTX → golimumab + MTX group improved in all measures of PROs from Week 24 through Week 52.

Efficacy and Antibodies to Golimumab

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

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 and 52, the median trough serum golimumab concentration in subjects receiving IV administration of golimumab 2 mg/kg + MTX q8w was 0.27, 0.21 and 0.30 µg/mL, respectively, suggesting that drug exposure was maintained through Week 52.
- Subjects with greater body weight tended to have higher serum golimumab concentrations though differences among the 4 quartiles were relatively small.

- Median serum trough golimumab concentrations at Weeks 12, 20 and 52 were similar in subjects with screening CRP levels of either < 1.5 mg/dL or ≥ 1.5 mg/dL indicating that serum trough golimumab concentrations were unaffected by disease activity as measured by CRP levels for subjects treated with golimumab.

Antibodies to Golimumab

- Antibodies to golimumab were detected in 26 (4.6%) of 560 golimumab-treated subjects through Week 52. For those subjects positive for antibodies to golimumab, 100% were positive for neutralizing antibodies. However, there was no apparent correlation between antibody positivity and any safety measurements.
- Serum golimumab concentrations were generally lower in subjects who tested positive for antibodies to golimumab than concentrations in subjects who were negative for antibodies to golimumab.

SAFETY RESULTS:

Since safety results are reported from Week 0 through Week 52, and since there is no pure placebo group through Week 52, safety discussion emphasized the combined golimumab + MTX group, which includes subjects in the golimumab + MTX group and subjects in the placebo + MTX → golimumab + MTX group.

Adverse Events (AEs): Through Week 52, 64.6% of subjects in the combined golimumab + MTX group reported an AE. Through Week 52, the most commonly reported AEs were in the system organ classes (SOCs) of Infections and Infestations (37.7%), Musculoskeletal and Connective Tissue Disorders (14.9%), and Gastrointestinal Disorders (12.3%). The only individual AEs that had a frequency ≥ 5% were URTI (8.4%), bronchitis (5.5%), and nasopharyngitis (5.0%) in the Infections and Infestations SOC and headache (5.1%) in the Nervous System Disorders SOC.

Serious Adverse Events (SAEs): Through Week 52, 8.6% of subjects in the combined golimumab + MTX group reported an SAE. The SOCs with the highest incidence of SAEs were Infections and Infestations (1.9%) and Musculoskeletal and Connective Tissue Disorders (1.7%). The incidence of SAEs in all other SOCs was < 1%.

Deaths: There were 2 deaths through Week 52. One subject in the placebo + MTX group died (presumed stroke due to hypertensive crisis; no autopsy was performed), and 1 subject in the golimumab 2 mg/kg + MTX group died of a presumed myocardial infarction secondary to community acquired pneumonia.

Malignancies: There were 4 malignancies through Week 52: 3 malignancies in the golimumab + MTX group (breast cancer, cervix carcinoma stage 0 and basal cell carcinoma) and 1 malignancy in the placebo + MTX group (non-treatment emergent lung adenocarcinoma).

Serious Infections: Serious infections occurred in 1.9% of subjects in the combined golimumab group through Week 52. There was 1 reported case of TB in a subject who crossed over from placebo + MTX to golimumab 2 mg/kg at Week 24. No serious opportunistic infections were reported. All serious infections were singular and did not demonstrate a pattern or relationship with golimumab.

Infusion Reactions: The proportion of infusions with infusion reactions was 0.7% in the combined golimumab group through Week 52. The proportion of subjects in the combined golimumab group with infusion reactions was 3.6% in the combined golimumab + MTX group. No serious or severe infusion reactions were reported.

Markedly abnormal changes in clinical chemistry and hematology: Through Week 52, the proportion of subjects in the combined golimumab group with markedly abnormal changes in clinical chemistry and hematology evaluations was small (the majority 0 or < 1%, but all < 5%).

Abnormal ALT Measurements: Of the subjects with normal ALT at baseline, 38.3% of subjects in the combined golimumab group who received concomitant TB prophylaxis had abnormal ALT measurements through Week 52. Of the subjects with normal ALT at baseline, 35.4% of subjects in the combined golimumab group who did not receive TB prophylaxis had abnormal ALT measurements through Week 52.

Abnormal AST Measurements: Of the subjects with normal AST at baseline, 32.1% of subjects in the combined golimumab group who received concomitant TB prophylaxis had abnormal ALT measurements through Week 52. Of the subjects with normal AST at baseline, 23.0% of subjects in the combined golimumab group who did not receive TB prophylaxis had abnormal ALT measurements through Week 52.

Antibodies to Golimumab and Infusion Reactions: In the combined golimumab group, 1 (3.8%) of 26 subjects who were positive for antibodies to golimumab had an infusion reaction through Week 52. Among subjects who were negative for antibodies to golimumab, infusion reactions to study agent occurred in 23 (4.3%) of 534 subjects through Week 52.

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

CONCLUSIONS:

Golimumab 2 mg/kg + MTX administered intravenously at Weeks 0 and 4 and then q8w through Week 52:

- 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 52.
- Achieved significantly greater inhibition of radiographic progression at Week 24 compared with placebo + MTX. This benefit was maintained through Week 52 in subjects receiving golimumab + MTX.
- 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 0.2-0.3 μg/mL were maintained through Week 52.
  - Low (4.6%) overall incidence of antibodies to golimumab.

The benefit risk balance supports the use of golimumab 2 mg/kg + MTX administered intravenously over 30 minutes at Week 0 and Week 4 and then q8w thereafter in subjects with moderately to severely active RA despite prior MTX therapy.

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