SYNOPSIS

Issue Date: 07 Nov 2011

Document No.: EDMS-ERI-22836553

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.

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.

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
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. 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.