SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company</th>
<th>Janssen Research &amp; Development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Investigational Product</td>
<td>SIMPONI (IV golimumab)</td>
</tr>
</tbody>
</table>

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologies, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term “Sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved  
Date: 9 May 2017  
Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO148AKS3001

Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNFα Monoclonal Antibody, Administered Intravenously, in Subjects With Active Ankylosing Spondylitis

Study Name: GO-ALIVE

EudraCT Number: 2014-000241-74

NCT No.: NCT02186873

Clinical Registry No.: CR103795

Coordinating Investigator: John Reveille, MD – University of Texas Health Sciences Center, USA.

Study Centers: 46 study sites screened subjects (40 study sites randomized subjects) in 8 countries, including Canada (3 study sites; 2 sites randomized subjects), Germany (7 study sites; 4 sites randomized subjects), Republic of Korea (6 study sites; 5 sites randomized subjects), Mexico (1 study site), Poland (7 study sites), Russia (7 study sites), Ukraine (8 study sites), and the United States (7 study sites; 6 sites randomized subjects).


Study Period: 24 September 2014 (first informed consent) – 11 October 2016 (date of last visit for last subject; recorded as part of the final [Week 60] database). The final database was locked on 08 November 2016.

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate the efficacy of intravenous (IV) administration of golimumab 2 mg/kg in subjects with active ankylosing spondylitis (AS) by assessing reduction in signs and symptoms of AS.
The secondary objectives of this study were to assess the following for IV golimumab:

- Efficacy related to improving physical function, range of motion, health-related quality of life (HRQoL), and other health outcomes.
- Safety.
- Pharmacokinetics (PK), pharmacodynamics, and immunogenicity.

**Methodology:** This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of IV golimumab 2 mg/kg compared with placebo in subjects with active AS with an inadequate response or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs). Subjects were randomized to treatment with either IV golimumab 2 mg/kg or placebo (in a 1:1 ratio) at Week 0. Subjects randomized to golimumab received IV golimumab 2 mg/kg infusions at Weeks 0, 4, and 12. At Week 16, subjects in the golimumab 2 mg/kg group received a placebo infusion to maintain the treatment blind, and then continued to receive IV golimumab 2 mg/kg infusions at Week 20 and every 8 weeks (q8w) thereafter through Week 52. Subjects randomized to placebo received placebo IV infusions at Weeks 0, 4, and 12, then crossed over and received IV golimumab 2 mg/kg infusions at Weeks 16, 20, and q8w thereafter through Week 52 (hereafter referred to as the placebo→golimumab 2 mg/kg group after crossing over). Subjects were followed for adverse events (AEs) and serious AEs (SAEs) for at least 8 weeks following the last study agent administration.

Two database locks were planned for this study. The first database lock occurred after all subjects had either completed the Week 28 visit, terminated study agent prior to Week 28 and entered the safety follow-up period, or terminated study participation. At Week 28, the database was locked and unblinded to selected Sponsor personnel. Data through the Week 28 database lock were presented in the 28-Week clinical study report (CSR). The final database lock occurred after all subjects had either completed the Week 60 visit or terminated study participation. Except for the unblinded pharmacist, individual subjects and site personnel remained blinded to assigned treatment for the duration of the study. All Sponsor personnel were unblinded to subject level data after the final (Week 60) database lock. Efficacy and health economics data after Week 28 through Week 60 (end of study), as well as cumulative PK and immunogenicity data through Week 52 and cumulative safety data through Week 60, are presented in this report.

**Number of Subjects (planned and analyzed):** Approximately 200 subjects were planned to be randomized (100 per treatment group) into this study; 208 subjects were randomized (105 to golimumab 2 mg/kg and 103 to placebo), from a total of 40 study sites in 8 countries. Data from all randomized subjects (n=208; ie, full analysis set [FAS]) were analyzed for efficacy, data from all subjects who received at least 1 dose of study agent (n=208) were analyzed for safety (ie, safety analysis set). Data from 99 placebo subjects who crossed over and received at least 1 infusion of golimumab were included in the analysis of safety for the placebo→golimumab 2 mg/kg group. Data from all subjects treated with at least 1 infusion of golimumab were included in the analysis of safety for the all golimumab 2 mg/kg group (ie, combined golimumab 2 mg/kg and placebo→golimumab 2 mg/kg groups; n=204). Data from all treated subjects (who received at least 1 infusion of golimumab) who had sufficient PK samples for analysis (n=204) were analyzed for PK (ie, PK evaluable analysis set). The immunogenicity analysis set (n=204) was the same as the PK evaluable analysis set, and the health economics evaluable set (n=208) was the same as the FAS.

**Diagnosis and Main Criteria for Inclusion:** Subjects were men or women 18 years of age or older with a diagnosis of AS for at least 3 months defined as “definite” by the modified New York criteria, and symptoms of active disease, as evidenced by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 and a visual analogue scale (VAS) score ≥4 for total back pain, each on a scale of 0 to 10 cm. Subjects were required to have a high-sensitivity C-reactive protein (CRP) level ≥0.3 mg/dL.
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 bulk lot numbers were DJS0M01, DLS0000, and FGS4G. Subjects randomized to golimumab and placebo crossover subjects received IV golimumab 2 mg/kg infusions (100 mL) over a 30±10 minute infusion time.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was normal saline (0.9% sodium chloride) supplied as a sterile liquid for IV infusion in single-use 100 mL infusion bags. No preservatives were present. Subjects randomized to placebo received infusions of normal saline over a 30±10 minute infusion time.

Duration of Treatment: The duration of treatment for subjects randomized to golimumab 2 mg/kg was 52 weeks. Subjects randomized to placebo received placebo for 16 weeks followed by golimumab 2 mg/kg for 36 weeks. After completion of treatment, subjects were to complete an 8-week safety follow-up period.

Criteria for Evaluation:

Pharmacokinetics: The PK of golimumab was evaluated by summarizing serum golimumab concentrations over time (predose and postdose) and summarizing the proportion of subjects with undetectable golimumab concentrations over time.

Immunogenicity: The status of antibodies to golimumab 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: Efficacy was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI), patient’s global assessment of disease activity, patient’s assessment of total back pain, BASDAI, Short Form-36 Health Survey (SF-36), Bath Ankylosing Spondylitis Metrology Index (BASMI), Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, chest expansion, night back pain, University of California San Francisco (UCSF) enthesitis index, Medical Outcomes Study Sleep Scale (MOS-SS), and EuroQol-5D-5L (EQ-5D-5L) questionnaire. Health economics were evaluated using the Work Limitations Questionnaire (WLQ) and the work productivity VAS. Blood samples were collected for measurement of CRP levels.

The primary endpoint of this study was the proportion of subjects who achieved a 20% improvement from baseline in the Assessment of SpondyloArthritis international Society (ASAS) Working Group criteria (ie, ASAS 20 responders) at Week 16. The major secondary endpoints were the proportion of subjects who achieved a 40% improvement in ASAS Working Group criteria (ie, ASAS 40 responders), the proportion of subjects who achieved a 50% improvement in BASDAI, and the change from baseline in BASFI at Week 16. Controlled secondary endpoints were the change from baseline in SF-36 physical component summary (PCS) and mental component summary (MCS) scores, the proportion of subjects who achieved low level of disease activity (ASAS partial remission), the change from baseline in ASQoL, and the change from baseline in BASMI at Week 16. These endpoints were reported in the 28-Week CSR.

Safety: Safety evaluations included measurement of vital signs, assessment of AEs, physical examinations, electrocardiograms (screening only), concomitant medications, infusion reaction evaluations, and assessments of allergic reactions. Samples were collected for routine laboratory analyses. Serum samples were also collected for the determination of the presence of antinuclear antibodies (ANA)/anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies. Tuberculosis (TB) evaluations were performed.

Status: Approved, Date: 9 May 2017
Statistical Methods: Descriptive summary statistics, such as number (n), mean, standard deviation (SD), median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. Efficacy and health economics data were summarized by treatment group from Week 28 through Week 52. Cumulative PK and immunogenicity data were summarized by treatment group through Week 52 and cumulative safety data were summarized by treatment group through Week 60. No treatment comparisons were performed after Week 16. Efficacy analyses and summaries of subject information were performed using the FAS (ie, all randomized subjects). Subjects were summarized according to the randomized treatment groups assigned, regardless of the treatment actually received.

RESULTS:

STUDY POPULATION:

A total of 312 subjects were screened and 208 subjects were randomized to treatment: 105 to golimumab 2 mg/kg and 103 to placebo. All randomized subjects were treated with at least 1 dose of study agent. At the end of the placebo-controlled period, 99 placebo subjects began treatment with golimumab 2 mg/kg (ie, placebo→golimumab 2 mg/kg group).

Overall, 191 subjects (91.8%) completed study treatment and 17 subjects (8.2%) discontinued treatment with study agent. The reasons for discontinuation of study agent were withdrawn consent (9 subjects), AE (4 subjects), lost to follow-up (3 subjects), and lack of efficacy (1 subject). Of the 17 subjects who discontinued study agent through Week 60, 12 discontinued after Week 28 (6 subjects withdrew consent, 3 subjects due to an AE, 2 subjects were lost to follow-up, and 1 subject due to lack of efficacy).

Of the 191 subjects who completed study treatment, 190 completed the safety follow-up period (ie, completed study participation) and 1 subject (golimumab 2 mg/kg group) discontinued the study during the safety follow-up period due to withdrawn consent. Of the 17 subjects who discontinued treatment with study agent, 3 subjects completed the safety follow-up period (ie, completed study participation) and 14 subjects discontinued study participation. The reasons for discontinuation from study participation were withdrawn consent (11 subjects) and lost to follow-up (3 subjects).

Of the 14 subjects who were discontinued from the study through Week 60, 10 subjects discontinued after the Week 28 infusion (6 in the golimumab 2 mg/kg group and 4 in the placebo group). The reasons for discontinuation of these 10 subjects were withdrawn consent (8 subjects) and lost to follow-up (2 subjects).

Baseline demographic characteristics were well balanced between the 2 treatment groups. The majority of subjects were white (86.5%) and men (78.4%). The mean age was 38.8 years (ranging from 19-67 years of age). Baseline clinical characteristics were similar between the 2 treatment groups and indicative of subjects with active AS.

EFFICACY RESULTS:

This clinical study had a positive outcome. The results for the primary endpoint and all prespecified major and controlled secondary endpoints demonstrated statistically significant superiority of IV golimumab 2 mg/kg compared with placebo. Other efficacy analyses through Week 28 also supported the primary, key secondary, and controlled secondary analyses.

Selected efficacy endpoints after Week 28 through Week 52 are summarized below. These efficacy results are reported by randomized treatment group, ie, golimumab 2 mg/kg group or placebo group. However, placebo subjects who remained in the study at Week 16 crossed over to treatment with IV golimumab 2 mg/kg from Week 16 through Week 52.
Consistent with the clinically meaningful and robust improvements in efficacy endpoints through Week 28, reductions in the clinical signs and symptoms of AS and improvements in physical function, range of motion, and HRQoL were maintained through Week 52 in both subjects randomized to golimumab 2 mg/kg and in subjects randomized to placebo who crossed over to treatment with golimumab 2 mg/kg at Week 16.

**Signs and Symptoms of AS**

- **Proportion of ASAS responders over time**: ASAS 20, ASAS 40, ASAS partial remission, and ASAS 5/6 response rates at Week 28 were maintained or became greater through Week 52 in subjects randomized to golimumab 2 mg/kg and in subjects randomized to placebo who began treatment with golimumab 2 mg/kg at Week 16.
  - **ASAS 20 response**: The proportion of subjects in the golimumab 2 mg/kg and placebo groups who achieved an ASAS 20 response at Week 52 was similar (69.5% and 65.0%, respectively).
  - **ASAS 40 response**: The proportion of subjects in the golimumab 2 mg/kg and placebo groups who achieved an ASAS 40 response at Week 52 was similar (56.2% and 51.5%, respectively).
  - **ASAS partial remission**: The proportion of subjects in the golimumab 2 mg/kg and placebo groups who achieved an ASAS partial remission at Week 52 was similar (24.8% and 24.3%, respectively).
  - **ASAS 5/6 response**: More than half the subjects in both the golimumab 2 mg/kg group and the placebo group (65.7% and 54.4%, respectively) achieved an ASAS 5/6 response at Week 52.

- **Proportion of subjects with improvement in BASDAI score at Week 52**: The proportion of subjects with improvement in BASDAI score at Week 28 was maintained through Week 52. At Week 52, similar proportions of subjects in the golimumab 2 mg/kg and placebo groups showed ≥20% improvement (77.1% and 73.8%, respectively), ≥50% improvement (56.2% and 55.3%, respectively), ≥70% improvement (33.3% and 35.0%, respectively), and ≥90% improvement (18.1% and 14.6%, respectively) from baseline in BASDAI score.

- **Change from baseline in CRP over time**: The mean improvement in CRP level at Week 28 was maintained through Week 52. Mean decreases (improvement) were similar in the golimumab 2 mg/kg and placebo groups at Week 52 (−12.41 and −11.87 mg/L, respectively).

- **Change from baseline in night back pain over time**: The mean improvement in the patient’s assessment of night back pain score at Week 28 was maintained through Week 52. Similar mean decreases (improvement) from baseline in the patient’s assessment of night back pain were noted in the golimumab 2 mg/kg and placebo groups at Week 52 (−3.75 and −3.77, respectively).

- **Proportion of subjects with Ankylosing Spondylitis Disease Activity Score (ASDAS) score <1.3 (inactive disease) over time**: The proportion of subjects who achieved inactive disease at Week 28 was maintained through Week 52. The proportions were similar in the golimumab 2 mg/kg and placebo groups at Week 52 (30.5% and 33.0%, respectively).

- **Change from baseline in enthesitis score at Week 52**: The mean improvement from baseline in the UCSF enthesitis index score at Week 28 in subjects with enthesitis at baseline was maintained at Week 52. At Week 52, the mean decrease (improvement) from baseline in the UCSF enthesitis index score was similar in the golimumab 2 mg/kg and placebo groups (−3.8 and −3.6, respectively).

**Physical Function**

- **Change from baseline in BASFI score over time**: The mean decreases (improvement) from baseline in BASFI score at Week 28 were maintained in the golimumab 2 mg/kg and placebo groups at Week 52 (−2.737 and −2.570, respectively).

---

Status: Approved, Date: 9 May 2017
Range of Motion

- **Change from baseline in BASMI score at Week 52:** The mean improvement from baseline in BASMI score at Week 28 was maintained at Week 52, with similar mean decreases (improvement) from baseline in the golimumab 2 mg/kg and placebo groups (−0.37 and −0.36, respectively).

HRQoL

- **Change from baseline in SF-36 PCS scale score at Week 52:** The mean increases (improvement) from baseline in SF-36 PCS score at Week 28 were maintained at Week 52 for the golimumab 2 mg/kg and placebo groups (9.47 and 9.68, respectively).
- **Change from baseline in SF-36 MCS scale scores at Week 52:** The mean increases (improvement) from baseline in SF-36 MCS score at Week 28 were maintained at Week 52 for the golimumab 2 mg/kg and placebo groups (7.25 and 5.14, respectively).
- **Change from baseline in MOS-SS sleep problem index and domain scores at Week 52:** The mean improvement from baseline in all MOS-SS domains and in the sleep index score at Week 28 was maintained at Week 52. At Week 52, the mean increase (improvement) in the sleep index score was 6.85 in the golimumab 2 mg/kg group and 6.76 in the placebo group.
- **Change from baseline in ASQoL score at Week 52:** The mean improvement from baseline in ASQoL score at Week 28 was maintained at Week 52, with similar mean decreases (improvement) from baseline in ASQoL score in the golimumab 2 mg/kg and placebo groups (−5.5 and −5.4, respectively).
- **Change from baseline in EQ VAS and EQ-5D-5L index score at Week 52:** The mean improvements in EQ VAS score and EQ-5D-5L index score at Week 28 were maintained at Week 52. At Week 52, the mean increases (improvement) from baseline in EQ VAS and EQ-5D-5L scores were similar in the golimumab 2 mg/kg and placebo groups (EQ VAS: 21.92 and 24.32, respectively; EQ-5D-5L index score: 0.20 and 0.17, respectively).

Efficacy and Pharmacokinetics

- Median serum golimumab concentrations were similar through Week 52 for ASAS 20 responders and nonresponders.
- ASAS 20 and ASAS 40 response rates were generally high; however, there was no consistent trend across the 4 concentration quartiles.
- There was no apparent relationship between ASAS response and serum golimumab concentrations.

Efficacy and Antibodies to Golimumab

- A slightly lower proportion of subjects in the randomized golimumab 2 mg/kg group who were treated and were positive for antibodies to golimumab achieved ASAS 20 and ASAS 40 responses than subjects who were negative for antibodies to golimumab. Subjects treated with placebo→golimumab 2 mg/kg had similar ASAS 20 and ASAS 40 responses regardless of antibody to golimumab status.
PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

**Pharmacokinetics**

- Median serum golimumab concentrations at Week 52 were similar between the 2 groups (ie, golimumab 2 mg/kg and placebo→golimumab 2 mg/kg groups) for both preinfusion and postinfusion, as well as similar with the respective Week 12 and Week 20 median concentration values.
- Median serum golimumab concentrations through Week 52 were generally similar across the body weight quartiles indicating that body weight-based dosing regimen provided consistent serum golimumab concentrations across the 4 body weight quartiles.
- Median serum golimumab concentrations through Week 52 were generally similar in both treatment groups regardless of prior anti-tumor necrosis factor alpha (TNFα) therapy.
- Median serum trough golimumab concentrations through Week 52 were generally similar in subjects with screening CRP levels of either <1.5 mg/dL or ≥1.5 mg/dL, thus unaffected by baseline inflammatory burden.

**Antibodies to Golimumab:**

- The overall incidence of antibodies to golimumab, detected using a highly sensitive drug-tolerant enzyme immunoassay (EIA) method, was 20.2% (41/203 subjects) and was similar between the 2 treatment groups. Antibody titers were generally low in these subjects.
- Overall, of the 41 subjects positive for antibodies to golimumab, 12 were positive for neutralizing antibodies (NAbs), which was also similar between treatment groups. The overall incidence of NAbs was 5.9% (12/203 subjects).
- Median trough golimumab concentrations were generally lower in subjects who were positive for antibodies to golimumab.

HEALTH ECONOMICS RESULTS:

- The mean improvement (decrease) from baseline in the daily productivity (VAS) score at Week 28 was maintained at Week 52 for both the golimumab 2 mg/kg and placebo groups (−3.04 and −3.60, respectively; FAS).
- The WLQ was completed by subjects who worked or volunteered. The mean improvement (decrease) from baseline in WLQ productivity loss score at Week 28 was maintained for both the golimumab 2 mg/kg and placebo groups (−4.53 and −4.14, respectively).

SAFETY RESULTS:

Golimumab 2 mg/kg administered intravenously through Week 52 to subjects with AS was generally well tolerated. Cumulative safety data through Week 60 are presented in the current report for all subjects treated with golimumab 2 mg/kg (ie, golimumab 2 mg/kg group, placebo→golimumab 2 mg/kg group, and all golimumab 2 mg/kg [combined golimumab 2 mg/kg and placebo→golimumab 2 mg/kg] group).

- The proportion of subjects in the all golimumab 2 mg/kg group experiencing at least 1 AE through Week 60 was 55.4%; 48.5% in the placebo→golimumab 2 mg/kg group and 61.9% in the golimumab 2 mg/kg group.
Adverse event findings through Week 60 for the all golimumab 2 mg/kg group were consistent with those through Week 28 in that the most common system organ class (SOC) was Infections and infestations (30.4%) and the most common AE was nasopharyngitis (11.8%). Other AEs reported for ≥5% of subjects in the all golimumab 2 mg/kg group in any SOC were upper respiratory tract infection (7.4%) and alanine aminotransferase (ALT) increased (5.9%).

- Seven subjects in the all golimumab 2 mg/kg group reported a total of 8 SAEs through Week 60 (pneumonia, pancreatitis, appendicitis, pulmonary TB, sinus tachycardia, nonalcoholic steatohepatitis, Henoch-Schonlein purpura, and wrist fracture). Two of these SAEs (pneumonia and pulmonary TB) were considered to be reasonably related to the study agent.

- Four subjects in the golimumab 2 mg/kg group discontinued study agent due to AEs through Week 60. Adverse events that led to discontinuation of study agent were ALT and aspartate aminotransferase (AST) increased (1 subject), ALT increased (1 subject), pulmonary TB (1 subject), and rash (1 subject). Three of these AEs (ALT increased, rash, and pulmonary TB [1 subject each]) were considered reasonably related to study agent.

- No subject died or had a newly diagnosed malignancy, opportunistic infection, anaphylaxis or serum sickness reaction reported through Week 60 of the study.

- No demyelinating event or other neurological event of interest was reported through Week 60. However, 1 subject with a history of epilepsy reported an AE of epilepsy.

- Infusion reactions were reported for 3 subjects in the all golimumab 2 mg/kg group; all infusion related reactions were reported through Week 16 and in subjects who were classified as antibody negative. No infusion reaction was considered to be severe or serious, and none resulted in discontinuation of study agent. There was no impact of antibodies to golimumab on infusion reactions.

- Maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 or 2 low neutrophil counts were reported in 13.7% and 6.9% of subjects, respectively, through Week 60 of subjects in the all golimumab 2 mg/kg group.

- Maximum CTCAE Grade ≥3 postbaseline clinical chemistry parameters through Week 60 were infrequent. Only 1 subject in the all golimumab 2 mg/kg group had a Grade 3 ALT value reported through Week 60. This same subject also had a Grade 3 AST value. No subject in the all golimumab 2 mg/kg group had an ALT or AST value that was ≥3 times (×) upper limit of normal (ULN) and a concurrent bilirubin value that was ≥2×ULN through Week 60.

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

CONCLUSIONS:

This clinical study had a positive outcome. Statistically significant superiority of IV golimumab 2 mg/kg compared with placebo was demonstrated with respect to the primary endpoint of ASAS 20 response at Week 16. Therefore, the primary hypothesis that IV golimumab 2 mg/kg was better than placebo, as measured by the ASAS 20 response and “treatment failure” at Week 16, was supported. In addition, all prespecified major and controlled secondary efficacy endpoints demonstrated statistically significant superiority of IV golimumab 2 mg/kg compared with placebo. Efficacy was maintained with continued treatment through Week 52.
Golimumab 2 mg/kg administered intravenously through Week 52:

- Provided substantial benefit to subjects with active AS who had an inadequate response or intolerance to NSAIDs by rapidly reducing clinical signs and symptoms of AS (as early as Week 2) and improving physical function, range of motion, HRQoL and other health outcomes. Improvement was maintained with continued treatment. These findings were supported by similar improvements noted after Week 16 for placebo→golimumab 2 mg/kg subjects.

- Was generally well tolerated. The proportion of subjects with AEs was higher in subjects treated with golimumab than with placebo, which is expected with the class of anti-TNFα agents. No subject treated with golimumab died. The proportion of golimumab-treated subjects with SAEs and other significant AEs was low. The proportion of subjects with infusion reactions was low and no infusion reaction was serious or severe. No opportunistic infection, malignancy, anaphylaxis or serum sickness reaction, or demyelinating event was reported. One subject was diagnosed with active TB. The overall safety profile of IV golimumab in AS subjects was consistent with that of other anti-TNFα therapies, including golimumab administered intravenously in patients with rheumatoid arthritis and golimumab administered subcutaneously to patients with AS or other rheumatologic diseases.

- Provided adequate PK exposure for clinical efficacy and safety as demonstrated by:
  - Median trough serum golimumab concentration reached steady state by Week 12 and was maintained through Week 52.
  - There was no apparent relationship between ASAS response rate and serum golimumab concentrations.
  - Using a highly sensitive drug-tolerant immunoassay, antibodies to golimumab were detected in 20.2% of subjects treated with golimumab through Week 52. A majority of the antibodies detected were of low titers while the overall incidence of high titer antibodies, which may have an effect on efficacy, was low. The overall incidence of NAbs was 5.9% (12/203 subjects).
  - Antibodies to golimumab were not associated with infusion reactions.
SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor/Company</th>
<th>Janssen Research &amp; Development*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Investigational Product</td>
<td>SIMPONI (IV golimumab)</td>
</tr>
</tbody>
</table>

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc.; Janssen Infectious Diseases BVBA; Janssen Sciences Ireland UC; or Janssen Research & Development, LLC. The term “Sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 30 November 2016
Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO148AKS3001

Title of Study: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Golimumab, an Anti-TNFα Monoclonal Antibody, Administered Intravenously, in Subjects With Active Ankylosing Spondylitis

Study Name: GO-ALIVE

EudraCT Number: 2014-000241-74

NCT No.: NCT02186873

Clinical Registry No.: CR103795

Coordinating Investigator: John Reveille, MD – University of Texas Health Sciences Center, USA.

Study Centers: 46 study sites screened subjects (40 study sites randomized subjects) in 8 countries, including Canada (3 study sites; 2 sites randomized subjects), Germany (7 study sites; 4 sites randomized subjects), Republic of Korea (6 study sites; 5 sites randomized subjects), Mexico (1 study site), Poland (7 study sites), Russia (7 study sites), Ukraine (8 study sites), and the United States (7 study sites; 6 sites randomized subjects).


Study Period: 24 September 2014 (first informed consent) – 03 March 2016 (last observation for last subject recorded as part of the Week 28 database).

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate the efficacy of intravenous (IV) administration of golimumab 2 mg/kg in subjects with active ankylosing spondylitis (AS) by assessing the reduction in signs and symptoms of AS.

The secondary objectives of this study were to assess the following for IV golimumab:

- Efficacy related to improving physical function, range of motion, health-related quality of life (HRQOL), and other health outcomes.
• Safety.
• Pharmacokinetics (PK), pharmacodynamics, and immunogenicity.

**Methodology:** This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of IV golimumab 2 mg/kg compared with placebo in subjects with active AS with an inadequate response or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs). Subjects were randomized to treatment with either IV golimumab 2 mg/kg or placebo (in a 1:1 ratio) at Week 0. Subjects randomized to golimumab received IV golimumab 2 mg/kg infusions at Weeks 0, 4, and 12. At Week 16, subjects in the golimumab 2 mg/kg group received a placebo infusion to maintain the treatment blind, and then continued to receive IV golimumab 2 mg/kg infusions at Week 20 and every 8 weeks (q8w) thereafter through Week 52. Subjects randomized to placebo received IV placebo infusions at Weeks 0, 4, and 12, then crossed over and received IV golimumab 2 mg/kg infusions at Weeks 16, 20, and q8w thereafter through Week 52 (hereafter referred to as the placebo→golimumab 2 mg/kg group after crossing over). Subjects were followed for adverse events (AEs) and serious adverse events (SAEs) for at least 8 weeks following the last study agent administration.

At Week 28, the database was locked and unblinded to selected Sponsor personnel. Data through the Week 28 database lock are presented in this report. Another database lock is scheduled for Week 60 (ie, final safety visit). Data through Week 60 will be presented in a subsequent report. All site personnel and subjects will remain blinded to the treatment assignments, with the exception of the unblinded pharmacists, until the Week 60 database lock has occurred.

**Number of Subjects (planned and analyzed):** Approximately 200 subjects were planned to be randomized (100 per treatment group) into this study; 208 subjects were randomized (105 to golimumab 2 mg/kg and 103 to placebo), from a total of 40 study sites in 8 countries. Data from all randomized subjects (n=208; ie, Full Analysis Set [FAS]) were analyzed for efficacy, data from all subjects who received at least 1 dose of study agent (n=208) were analyzed for safety (ie, Safety Analysis Set). Data from all subjects treated with at least 1 infusion of golimumab were included in the analysis of safety for the all golimumab 2 mg/kg group (ie, combined placebo→golimumab 2 mg/kg and golimumab 2 mg/kg group; n=204). Data from all treated subjects (who received at least 1 infusion of golimumab) who had sufficient PK samples for analysis (n=204) were analyzed for PK (ie, PK Evaluable analysis set). The Immunogenicity Analysis Set (n=204) was the same as the PK Evaluable Analysis Set, and the health economics evaluable set (n=208) was the same as the FAS.

**Diagnosis and Main Criteria for Inclusion:** Subjects were men or women 18 years of age or older with a diagnosis of AS for at least 3 months defined as “definite” by the modified New York criteria, and symptoms of active disease, as evidenced by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 and a visual analogue scale (VAS) score ≥4 for total back pain, each on a scale of 0 to 10 cm. Subjects were required to have a C-reactive protein (CRP) level ≥0.3 mg/dL.

**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 bulk lot numbers were DJ0S0M01, DLS0000, and FGS4G. Subjects randomized to golimumab and placebo crossover subjects received IV golimumab 2 mg/kg infusions (100 mL) over a 30±10 minute infusion time.

**Reference Therapy, Dose and Mode of Administration:** Placebo was normal saline (0.9% sodium chloride) supplied as a sterile liquid for IV infusion in single-use 100 mL infusion bags. No preservatives were present. Subjects randomized to placebo received infusions of normal saline over a 30±10 minute infusion time.

**Duration of Treatment:** The duration of treatment for subjects randomized to golimumab 2 mg/kg is 52 weeks. Subjects randomized to placebo received placebo for 16 weeks followed by golimumab
2 mg/kg for 36 weeks. After completion of treatment, subjects are to complete an 8-week safety follow-up period.

**Criteria for Evaluation:**

*Pharmacokinetics:* The PK of golimumab was evaluated by summarizing serum golimumab concentrations over time (predose and postdose) and summarizing the proportion of subjects with undetectable golimumab concentrations over time.

*Immunogenicity:* The status of antibodies to golimumab 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:* Efficacy was evaluated using the Bath Ankylosing Spondylitis Functional Index (BASFI), patient’s global assessment of disease activity, patient’s assessment of total back pain, BASDAI, Short Form-36 Health Survey (SF-36), Bath Ankylosing Spondylitis Metrology Index (BASMI), Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire, chest expansion, night back pain, University of California San Francisco (UCSF) enthesitis index, Medical Outcomes Study Sleep Scale (MOS-SS), and EuroQol-5D-5L (EQ-5D-5L) questionnaire. Health economics were evaluated using the Work Limitations Questionnaire (WLQ) and the work productivity VAS. Blood samples were collected for measurement of CRP levels.

The primary endpoint of this study was the proportion of subjects who achieved a 20% improvement from baseline in the Assessment of SpondyloArthritis international Society (ASAS) Working Group criteria (ie, ASAS 20 responders) at Week 16. The major secondary endpoints were the proportion of subjects who achieved a 40% improvement in ASAS Working Group criteria (ie, ASAS 40 responders), the proportion of subjects who achieved a 50% improvement in BASDAI, and the change from baseline in BASFI at Week 16. Controlled secondary endpoints were the change from baseline in SF-36 PCS and MCS scores, the proportion of subjects who achieved low level of disease activity (ASAS partial remission), the change from baseline in ASQoL, and the change from baseline in BASMI at Week 16.

*Safety:* Safety evaluations included measurement of vital signs, assessment of AEs, physical examinations, electrocardiogram (screening only), concomitant medications, infusion reaction evaluations, and assessments of allergic reactions and infections. Samples were collected for routine laboratory analyses. Serum samples were also collected for the determination of the presence of antinuclear antibodies (ANA)/anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies. Tuberculosis (TB) evaluations were performed. An independent Data Monitoring Committee was established to monitor safety data at prespecified intervals through the blinded phase and the Week 28 database lock to ensure the safety of subjects in the study.

**Statistical Methods:** Descriptive summary statistics, such as number (n), mean, standard deviation (SD), median, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. Unless otherwise stated, the Cochran-Mantel-Haenszel test stratified by prior use of anti-tumor necrosis factor alpha (TNFα) therapy was used to test the difference between the golimumab 2 mg/kg group and the placebo group for the proportion of subjects responding to treatment. For continuous secondary endpoints (ie, change from baseline), the analysis was performed using a mixed-effect repeated measures (MMRM) model based on observed data. The terms for this model were treatment group, prior anti-TNFα therapy (Yes, No), baseline score, visit week, and an interaction of treatment and visit week. An unrestricted variance-covariance matrix for repeated measures within a subject was used unless there were issues related to convergence. An analysis of covariance model was used to test the difference between the golimumab 2 mg/kg group and the placebo group as a sensitivity analysis for the secondary endpoints and for all other continuous efficacy endpoints. Efficacy analyses and summaries of subject information were performed using the FAS (ie, all randomized subjects unless otherwise specified). Subjects were analyzed...
according to the randomized treatment groups they were assigned to, regardless of the treatment they actually received. All statistical tests were performed at $\alpha=0.05$ (2-sided).

RESULTS:

STUDY POPULATION:

A total of 312 subjects were screened and 208 subjects were randomized to treatment: 105 to golimumab 2 mg/kg and 103 to placebo. All randomized subjects were treated with at least 1 dose of study agent. At the end of the placebo-controlled period, 99 placebo subjects began treatment with golimumab 2 mg/kg (ie, placebo→golimumab 2 mg/kg group).

As of Week 28, 203 of 208 subjects (97.6%) were continuing treatment in the study. One subject (0.5%; in the golimumab 2 mg/kg group) discontinued study agent after Week 16 due to AEs of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased but was continuing in safety follow-up. Four subjects (1.9%; all in the placebo group) discontinued study participation prior to Week 16; 3 subjects due to withdrawal of consent and 1 subject was lost to follow-up.

Baseline demographic characteristics were well balanced between the 2 treatment groups. The majority of subjects were white (86.5%) and men (78.4%). The mean age was 38.8 years (ranging from 19-67 years of age). Baseline clinical characteristics were similar between the 2 treatment groups and indicative of subjects with AS.

EFFICACY RESULTS:

This study had a positive outcome. The results for the primary endpoint and all prespecified major and controlled secondary endpoints demonstrated statistically significant superiority of IV golimumab 2 mg/kg compared with placebo.

The primary endpoint was met.

A greater proportion of subjects in the golimumab 2 mg/kg group achieved $\geq$20% improvement from baseline in ASAS (ASAS 20 response) at Week 16 (ie, end of placebo-controlled period) compared with subjects in the placebo group (73.3% vs 26.2%, respectively), with a statistically significant treatment difference of 47.1% ($p<0.001$). Sensitivity analyses confirmed the robustness of the results.

A consistent treatment benefit was generally observed for the primary efficacy endpoint (ASAS 20 response at Week 16) within the subgroups of demography, baseline disease characteristics, and prior and baseline medications for AS.

All major secondary endpoints were met.

- A greater proportion of subjects in the golimumab 2 mg/kg group achieved $\geq$40% improvement from baseline in ASAS criteria (ASAS 40 response) at Week 16 compared with subjects in the placebo group (47.6% vs 8.7%, respectively), with a statistically significant treatment difference of 38.9% ($p<0.001$).
- A greater proportion of subjects in the golimumab 2 mg/kg group achieved at least a 50% improvement from baseline in BASDAI at Week 16 compared with subjects in the placebo group (41.0% vs 14.6%, respectively), with a statistically significant treatment difference of 26.4% ($p<0.001$).
- The mean decrease (ie, improvement) from baseline in BASFI score was greater in the golimumab 2 mg/kg group at Week 16 compared with the placebo group ($-2.386$ vs $-0.471$, respectively), with a statistically significant least square mean (LSmean) difference of $-1.869$ ($p<0.001$). Sensitivity analysis confirmed the robustness of the BASFI results.
All controlled secondary endpoints were met.

- The mean increase (ie, improvement) from baseline in SF-36 physical component summary (PCS) score was greater in the golimumab 2 mg/kg group compared with the placebo group at Week 16 (8.52 vs 2.86, respectively), with a statistically significant LSmean difference of 5.78 (p<0.001). Sensitivity analysis confirmed the robustness of the SF-36 PCS results.

- The mean increase (ie, improvement) from baseline in SF-36 mental component summary (MCS) score was greater in the golimumab 2 mg/kg group compared with the placebo group at Week 16 (6.47 vs 0.78, respectively), with a statistically significant LSmean difference of 4.81 (p<0.001). Sensitivity analysis confirmed the robustness of the SF-36 MCS results.

- A greater proportion of subjects in the golimumab 2 mg/kg group achieved a low level of disease activity (ie, ASAS partial remission) at Week 16 compared with subjects in the placebo group (16.2% vs 3.9%, respectively), with a statistically significant treatment difference of 12.3% (p=0.003).

- The mean decrease (ie, improvement) from baseline in ASQoL score was greater in the golimumab 2 mg/kg group compared with the placebo group at Week 16 (−5.4 vs −1.8, respectively), with a statistically significant LSmean difference of −3.4 (p<0.001). Sensitivity analysis confirmed the robustness of the ASQoL results.

- The mean decrease (ie, improvement) from baseline in BASMI score was greater in the golimumab 2 mg/kg group compared with the placebo group at Week 16 (−0.38 vs −0.10, respectively), with a statistically significant LSmean difference of −0.26 (p=0.001). Sensitivity analysis confirmed the robustness of the BASMI results.

Other efficacy endpoints:

Other efficacy analyses supported the primary, key secondary, and controlled secondary analyses. Selected other efficacy endpoints are summarized below. Nominal p-values are provided.

**Signs and Symptoms of AS**

- The proportion of subjects achieving an ASAS 20 response was greater in the golimumab 2 mg/kg group than in the placebo group as early as Week 2 (37.1% vs 19.4%, respectively). The difference between the treatment groups in the proportion of ASAS 20 responders increased over time from Week 2 (17.5%, p=0.005) through Week 16 (47.1%, p<0.001).

- The proportion of subjects achieving an ASAS 40 response was greater in the golimumab 2 mg/kg group than in the placebo group as early as Week 2 (14.3% vs 3.9%, respectively). The difference between the treatment groups in the proportion of ASAS 40 responders increased over time from Week 2 (10.4%, p=0.010) through Week 16 (38.9%, p<0.001).

- The proportion of subjects in the golimumab 2 mg/kg group with low disease activity (ie, ASAS partial remission) increased from Week 2 (4.8%) through Week 16 (16.2%). The difference between the golimumab 2 mg/kg and placebo groups in the proportion of subjects with an ASAS partial remission was 3.8% at Week 2 (p=0.105) and increased over time through Week 16 (12.3%, p=0.003).

- The proportion of subjects achieving an ASAS 5/6 response was greater in the golimumab 2 mg/kg group than in the placebo group by Week 2 (27.6% vs 6.8%). The difference between treatment groups increased over time from Week 2 (20.7%, p<0.001) through Week 16 (53.0%, p<0.001).

- The proportion of subjects in the golimumab 2 mg/kg group achieving ≥20%, ≥50%, ≥70%, or ≥90% improvement from baseline in BASDAI score generally increased over time from Week 2 through Week 16 and was greater than in the placebo group. The differences between the treatment groups in each BASDAI category also generally increased over time from Week 2 through Week 16 (p<0.05
for ≥20%, ≥50%, and ≥70% improvement at Weeks 2, 4, 8, 12, and 16 and for ≥90% improvement at Weeks 8, 12, and 16).

- There was a mean decrease from baseline in CRP levels in the golimumab 2 mg/kg group compared with an increase in the placebo group at Week 2 (−17.44 mg/L vs 0.83 mg/L, respectively). The LSmean difference between the treatment groups in the change from baseline in CRP level was −17.86 mg/L at Week 2, and ranged between −13.72 mg/L and −16.56 mg/L at other time points (p<0.001 at Weeks 2, 4, 8, 12, and 16).

- The mean decrease (improvement) from baseline in night back pain was greater in the golimumab 2 mg/kg group compared with placebo by Week 2 (−2.03 vs −0.83, respectively). The LSmean difference between the treatment groups in the change from baseline in night back pain also became more pronounced over time from Week 2 (−1.18, p<0.001) through Week 16 (−2.58, p<0.001).

- The proportion of subjects who achieved inactive disease (based on an Ankylosing Spondylitis Disease Activity Score [ASDAS] <1.3) was greater in the golimumab 2 mg/kg group than in the placebo group (9.5% vs 0%, respectively) by Week 2. The difference between the treatment groups in the proportion of subjects who achieved inactive disease increased over time from Week 2 (9.6%, p=0.001) through Week 16 (24.8%, p<0.001).

- The mean decrease from baseline in the UCSF enthesitis index score was greater in the golimumab 2 mg/kg group than in the placebo group (−2.3 vs −0.7, respectively) by Week 2. The LSmean difference between the treatment groups in the mean decrease from baseline in the UCSF enthesitis index score became greater over time from Week 2 (−2.0, p<0.001) through Week 16 (−2.6, p<0.001).

**Physical Function**

- The mean decrease (improvement) from baseline in BASFI score was greater in the golimumab 2 mg/kg group than in the placebo group by Week 2 (−1.136 vs −0.597, respectively). The LSmean difference between treatment groups became greater over time from Week 2 (−0.502, p=0.033) through Week 16 (−1.782, p<0.001).

**Range of Motion**

- The mean decrease (ie, improvement) from baseline in the BASMI score was greater in the golimumab 2 mg/kg group compared with the placebo group by Week 2 (−0.19 vs −0.05, respectively). The LSmean difference between the treatment groups in the change from baseline in the BASMI score became greater over time from Week 2 (−0.14, p=0.069) through Week 16 (−0.28, p<0.001).

**HRQOL**

- The 4 subscales of the SF-36 that comprise the PCS score (physical functioning, role-physical, bodily pain, and general health) all showed greater improvements from baseline at Weeks 8 and 16 for the golimumab 2 mg/kg group compared with the placebo group (p<0.001).

- Three of the 4 subscales of the SF-36 that comprise the MCS score (vitality, social functioning, and mental health) showed greater improvements for the golimumab 2 mg/kg group compared with the placebo group (p<0.01) at Week 8, and all 4 subscales (vitality, social functioning, role-emotional, and mental health) showed greater improvements from baseline for the golimumab 2 mg/kg group compared with the placebo group at Week 16 (p<0.001).

- The mean decrease (ie, improvement) from baseline in ASQoL score was greater in the golimumab 2 mg/kg group than in the placebo group by Week 8 (−4.5 vs −1.5, respectively). The LSmean difference between the treatment groups in the change from baseline in the ASQoL score increased over time from Week 8 (−2.7, p<0.001) through Week 16 (−3.4, p<0.001).
• There was a greater mean increase (ie, improvement) from baseline in the golimumab 2 mg/kg group compared with the placebo group in the composite sleep problem index score by Week 8 (5.10 vs 1.72, respectively). The LSmean difference between the treatment groups in the change from baseline in the composite sleep problem index score increased over time from Week 8 (3.65, p<0.001) through Week 16 (4.38, p<0.001).

• The mean increase (ie, improvement) from baseline in EQ VAS score was greater in the golimumab 2 mg/kg group than in the placebo group at Week 8 (17.61 vs 6.63, respectively), as was the change from baseline in the EQ-5D-5L index score (0.16 vs 0.04, respectively). The LSmean difference between the treatment groups increased over time from Week 8 (11.13, p<0.001) through Week 16 (15.78, p<0.001) for the change from baseline in EQ VAS score, and for the change from baseline in the EQ-5D-5L index score was 0.11 at both Weeks 8 and 16 (p<0.001).

Other – Week 16 through Week 28

• In subjects randomized to golimumab 2 mg/kg who continued treatment with golimumab 2 mg/kg, reductions in the clinical signs and symptoms of AS and improvements in physical function, range of motion, and HRQOL were maintained through Week 28.

• Subjects randomized to placebo who began receiving golimumab 2 mg/kg at Week 16 showed substantial reductions in the clinical signs and symptoms of AS and improvements in physical function, range of motion, and HRQOL at Weeks 20 and 28 (ie, 4 and 12 weeks after starting treatment with IV golimumab 2 mg/kg).

Efficacy and Pharmacokinetics

• Median serum golimumab concentrations were similar through Week 20 for ASAS 20 responders and nonresponders.

• Consistently high ASAS 20 response rates were observed across the 4 trough serum golimumab concentration quartiles. At Week 20, both ASAS 20 and ASAS 40 increased with increasing trough concentrations up to the third quartile after which higher concentrations were not associated with further increased response rates.

Efficacy and Antibodies to Golimumab

• Generally, fewer subjects who were positive for antibodies to golimumab achieved an ASAS 20 or ASAS 40 response compared with subjects who were negative for antibodies to golimumab.

• For ASAS 20, peak titers up to <1:1000 did not seem to have an impact on response rates while an impact on ASAS 40 response rates was seen below peak titers of 1:1000. However, the small number of subjects who were positive for antibodies to golimumab limits interpretation.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

Pharmacokinetics

• After administration of IV golimumab 2 mg/kg at Week 0 and Week 4, the median preinfusion and postinfusion (peak) golimumab concentrations at Week 4 were 2.33 µg/mL and 51.49 µg/mL, respectively. Serum golimumab concentrations reached steady-state by Week 12. The median trough serum golimumab concentrations after steady state at Week 12 and at Week 20 were 0.77 µg/mL and 0.65 µg/mL, respectively.

• At Week 12 and Week 20, subjects with higher body weights (>94 kg) had slightly higher median trough serum golimumab concentrations.

• Median serum trough golimumab concentrations were generally similar in subjects with screening CRP levels of either <1.5 mg/dL or ≥1.5 mg/dL, thus unaffected by baseline inflammatory burden.
Antibodies to Golimumab

- Antibodies to golimumab were detected using a validated, highly sensitive drug-tolerant EIA method in 20 (19%) of 105 subjects who received golimumab 2 mg/kg through Week 20, and antibody titers were generally low in these subjects. Six (30%) of these 20 subjects were positive for neutralizing antibodies (NAbs).
- Median trough golimumab concentrations were generally lower in subjects who were positive for antibodies to golimumab.

Health Economics Results:

- The mean decrease (ie, improvement) from baseline in daily productivity (VAS) score was greater in the golimumab 2 mg/kg group compared with the placebo group by Week 8 (−2.21 vs −1.07, respectively). The LSmean difference between treatment groups in the change from baseline in daily productivity score became greater over time from Week 8 (−1.18, p<0.001) through Week 16 (−1.89, p<0.001).
- A greater mean decrease (ie, improvement) from baseline in the WLQ productivity loss score was also noted in the golimumab 2 mg/kg group compared with the placebo group by Week 8 (−2.86 vs −1.72, respectively). The LSmean difference between treatment groups in the WLQ productivity loss score became greater over time from Week 8 (−1.44, p=0.04) through Week 16 (−1.97, p=0.009).
- Subjects randomized to golimumab 2 mg/kg who continued treatment with golimumab 2 mg/kg through Week 28 had further mean decreases (ie, improvements) from baseline in daily productivity score (−3.10) and WLQ productivity loss score (−3.91) at Week 28.
- Subjects randomized to placebo who began receiving golimumab 2 mg/kg at Week 16 showed mean decreases (ie, improvements) from baseline in daily productivity score (−3.11) and WLQ productivity loss score (−4.51) at Week 28 (ie, 12 weeks after starting treatment with IV golimumab 2 mg/kg).

Safety Results:

Golimumab 2 mg/kg administered intravenously at Weeks 0 and 4 and then q8w to subjects with AS was generally well tolerated through Week 28.

- The proportion of subjects experiencing at least 1 AE through Week 16 (ie, end of placebo-controlled period) was 32.4% in the golimumab 2 mg/kg group and 23.3% in the placebo group.
  - The proportion of subjects with AEs within each system organ class (SOC) was similar between the 2 treatment groups through Week 16, with the exception of the Infections and infestations, Nervous system disorders, and Investigations SOCs. The proportions of subjects with an AE in the golimumab 2 mg/kg group were approximately 5% or more and about twice that of the placebo group for the Infections and infestations SOC (11.4% vs 5.8%, respectively), Nervous system disorders SOC (6.7% vs 3.9%, respectively), and Investigations SOC (4.8% vs 1.9%, respectively).
  - The only AE that occurred in ≥5% of subjects in the golimumab 2 mg/kg group through Week 16 was nasopharyngitis (5.7%), which occurred in 1.0% of subjects in the placebo group. All other AEs were reported for <5% of subjects in either treatment group.
- The proportion of subjects in the all golimumab 2 mg/kg group (ie, combined placebo→golimumab 2 mg/kg and golimumab 2 mg/kg group) experiencing at least 1 AE through Week 28 was 34.8%; 24.2% in the placebo→golimumab 2 mg/kg group and 44.8% in the golimumab 2 mg/kg group.
Adverse event findings through Week 28 for the all golimumab 2 mg/kg group were consistent with those through Week 16 for the randomized golimumab 2 mg/kg group in that the most common SOC was Infections and infestations (16.2%) and the most common AE was nasopharyngitis (5.4%). All other AEs were reported for <5% of subjects in the all golimumab 2 mg/kg group.

- No subject died or had a newly diagnosed malignancy, opportunistic infection, active TB, anaphylaxis or serum sickness reaction, or neurological event of interest (including demyelinating events) reported through Week 28 of the study.
- Two subjects in the golimumab 2 mg/kg group and no subject in the placebo group reported an SAE (pneumonia and pancreatitis) through Week 16. One of these SAEs (pneumonia) was considered to be reasonably related to the study agent. No additional SAEs were reported through Week 28.
- No subject discontinued study agent or the study due to AEs through Week 16. One subject (in the golimumab 2 mg/kg group) discontinued study agent between Week 16 and Week 28 due to the AEs of AST and ALT increased.
- Infusion reactions were reported for 3 subjects (2.9%) in the golimumab 2 mg/kg group and no subject (0%) in the placebo group through Week 16. No infusion reaction was considered to be serious or severe. No additional infusion reactions were reported through Week 28.
- No subject classified as antibody positive and 3 subjects (3.5%) classified as antibody negative had an infusion reaction through Week 20. There was no impact of antibodies to golimumab on infusion reactions.
- A higher proportion of subjects treated with golimumab 2 mg/kg had maximum Common Terminology Criteria for AEs (CTCAE) Grade 1 or 2 low neutrophil counts (11.4% and 4.8% in the golimumab 2 mg/kg group, respectively) through Week 16 than subjects treated with placebo (1.0% and 0%, respectively); maximum CTCAE Grade 1 or 2 low neutrophil counts were reported in 10.3% and 3.9%, respectively, of subjects in the all golimumab 2 mg/kg group through Week 28.
- CTCAE Grade ≥3 postbaseline clinical chemistry parameters through Week 28 were infrequent and generally balanced between the treatment groups. However, a greater proportion of subjects treated with golimumab 2 mg/kg had Grade 1 transaminase elevations compared with subjects treated with placebo through Week 16 (ALT 27.6% vs 9.7% and AST 16.2% vs 8.7%, respectively); maximum CTCAE Grade 1 elevations of ALT and AST were reported in 25.5% and 13.2%, respectively, of subjects in the all golimumab 2 mg/kg group through Week 28. No subject in either treatment group had an ALT or AST value that was ≥3x upper limit of normal (ULN) and a concurrent total bilirubin value that was ≥2xULN through Week 28.

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

CONCLUSIONS:

This clinical study had a positive outcome. Statistically significant superiority of IV golimumab 2 mg/kg compared with placebo was demonstrated with respect to the primary endpoint of ASAS 20 response at Week 16. Therefore, the primary hypothesis that IV golimumab 2 mg/kg was better than placebo, as measured by the ASAS 20 response at Week 16, was met. In addition, all prespecified major and controlled secondary efficacy endpoints demonstrated statistically significant superiority of IV golimumab 2 mg/kg compared with placebo.

Golimumab 2 mg/kg administered intravenously at Weeks 0 and 4 and then q8w through Week 28:

- Provided substantial benefit to subjects with active AS who had an inadequate response or intolerance to NSAIDs by rapidly reducing clinical signs and symptoms of AS (as early as Week 2)
and improving physical function, range of motion, HRQOL, and other health outcomes. Improvement was maintained with continued treatment through Week 28.

- Was generally well tolerated through Week 28. The proportion of subjects with AEs was higher in subjects treated with golimumab than with placebo. The proportion of subjects with SAEs and other significant AEs was low. The proportion of subjects with an infusion reaction was low and none of the reactions was serious or severe. No subject died and no opportunistic infection, malignancy, active TB, anaphylaxis or serum sickness reaction, or demyelinating event was reported. The overall safety profile of IV golimumab in AS subjects was consistent with that of other anti-TNFα therapies, including golimumab administered intravenously in patients with RA and golimumab administered subcutaneously to patients with AS or other rheumatologic diseases.

- Resulted in adequate PK exposure for clinical efficacy and safety as demonstrated by:
  - Median trough serum golimumab concentration reached steady state by Week 12 and was maintained at Week 20.
  - Serum golimumab concentrations of 0.65 to <1.08 μg/mL were associated with the highest ASAS 20 or ASAS 40 response rate. Lower concentrations were still effective but did not lead to as high a proportion of responders. Higher concentrations were not associated with further increased response rates.
  - Using a highly sensitive drug-tolerant immunoassay, antibodies to golimumab were detected in 19.5% of subjects treated with golimumab through Week 20. A majority of the antibodies detected were of low titers while the overall incidence of high titer antibodies, which may have an effect on efficacy, was low. The overall incidence of NAbs was 5.7% (6/105 subjects).
  - Antibodies to golimumab were not associated with infusion reactions.