Janssen Research & Development

56-Week Clinical Study Report Synopsis
Protocol C0524T28; Phase 3

CNTO148 (golimumab)

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- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	SIMPONI®
Name of Active Ingredient(s)	Golimumab

Status: Approved

Date: 18 Jan 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: C0524T28

Title of Study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Golimumab in the Treatment of Chinese Subjects With Active Rheumatoid Arthritis Despite Methotrexate Therapy

EudraCT Number: Not applicable

NCT No.: NCT01248780

Clinical Registry No.: CR015913

Coordinating Principal Investigator(s): [redacted] MD, [redacted] China

Study Center(s): 15 sites in China

Publication (Reference): None

Study Period: 20 Aug 2010 (first subject consented) to 23 Jul 2012 (last subject completed Week 56 visit)

Phase of Development: Phase 3

Objectives: The primary objective of this study was to assess the efficacy of golimumab (SIMPONI®) in Chinese subjects with active rheumatoid arthritis (RA) despite methotrexate (MTX) therapy as measured by the reduction in the signs and symptoms of RA.

The secondary objective was to assess the safety and the effects of golimumab on physical function and health-related quality of life in Chinese subjects with active RA despite MTX therapy.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study conducted to evaluate the efficacy and safety of golimumab + MTX compared with placebo + MTX in subjects with active RA despite MTX therapy. Subjects were to be randomly assigned to receive golimumab 50 mg or placebo subcutaneous (SC) injections at Week 0 and every 4 weeks (q4w) thereafter through Week 20. At Week 16, all subjects receiving placebo who met early escape (EE) criteria began receiving golimumab SC injections in a blinded fashion. At Week 24, all subjects still receiving placebo injections began receiving golimumab SC injections. Subjects in the golimumab treatment group continued to receive golimumab SC injections. Subjects were to be treated through Week 48 and follow scheduled efficacy, pharmacokinetic (PK), and immunogenicity assessments through Week 52 and safety assessments through Week 56.

Number of Subjects (planned and analyzed): Approximately 260 subjects were planned to be enrolled in the study; 264 subjects were randomized at 15 investigational sites. One subject in the golimumab 50 mg + MTX group was not treated. All 264 randomized subjects were included in efficacy

analyses. All subjects (263) who received study treatment were included in safety analyses, and all subjects (259) who received at least 1 dose of golimumab were included in the PK analyses.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for the study were men or women 18 years of age or older with a diagnosis of RA (according to the revised 1987 criteria of the American Rheumatism Association [ACR]) for at least 6 months prior to screening. Subjects had active RA despite being treated with and tolerated MTX at a dose of at least 7.5 mg/week for at least 6 months prior to screening, and had a MTX dose of ≥7.5 mg/week and ≤20 mg/week and stable for at least 4 weeks prior to screening.

Subjects had at least 4 swollen and at least 4 tender joints at screening and baseline. In addition, subjects had to have C-reactive protein (CRP) ≥15 mg/L at screening or erythrocyte sedimentation rate (ESR) ≥28 mm in the first hour at screening or baseline, and rheumatoid factor (RF) positivity and/or anti-cyclic citrullinated peptide (CCP) positivity at screening.

Test Product, Dose and Mode of Administration, Batch No.: Golimumab was supplied as a sterile, liquid for SC injection at a volume of 0.5 mL in prefilled single-use syringes (PFS). Each PFS contained 50 mg golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5. No preservatives were present. Batch Nos. 09M011, 10B011, and 10J011.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo consisted of an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5 and was supplied as a sterile liquid for SC injection at a volume of 0.5 mL in PFS. Batch No. 09B021.

Duration of Treatment: Subjects were randomized to study agent within 6 weeks of screening. The duration of treatment (interval between first and last administration of study agent) for the entire study was 48 weeks followed by scheduled efficacy, PK, and immunogenicity assessments through Week 52 and safety assessments through Week 56 (end of study).

Criteria for Evaluation:

Pharmacokinetics:

The PK of golimumab was evaluated by summarizing serum golimumab concentrations over time, including trough serum golimumab concentrations (C_{trough}), for subjects who received at least 1 golimumab administration and had at least 1 valid blood sample collected for PK analysis.

Immunogenicity:

The incidence of antibodies to golimumab through Week 52 was summarized for subjects who received at least 1 golimumab administration and had appropriate serum samples for detection of antibodies to golimumab (ie, at least 1 serum sample collected after drug administration).

Efficacy:

Efficacy evaluations included 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), 36-item short form health survey (SF-36), ESR, CRP, and productivity assessment.

Safety:

The assessments used to evaluate safety included vital sign measurements, assessment of adverse events (AEs) that could have occurred at and between each of the evaluation visits, study agent injection-site evaluations and tuberculosis (TB) evaluations. Samples for routine laboratory analyses, antinuclear antibodies (ANA) and anti-double stranded deoxyribonucleic acid (anti-dsDNA) antibodies were collected. Serum samples for the determination of antibodies to golimumab were also collected.

Statistical methods: After Week 24, simple descriptive summary statistics, such as n, mean, standard deviation (SD), median, interquartile (IQ) range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. No formal statistical hypothesis testing was planned for the data obtained after Week 24.

RESULTS:

STUDY POPULATION:

A total of 462 subjects were enrolled (signed an informed consent form), and 264 subjects were randomized to treatment. As of Week 56, among 263 treated subjects, 23 (8.7%) discontinued study agent prior to Week 56 (9 subjects in the placebo + MTX→golimumab 50 mg + MTX group and 14 subjects in the golimumab 50 mg + MTX group). Of the 9 subjects in the placebo + MTX→golimumab 50 mg + MTX group, 4 received placebo + MTX treatment only prior to discontinuation. Nine subjects discontinued study agent due to AEs (2 in the placebo + MTX→golimumab 50 mg + MTX group and 7 in the golimumab 50 mg + MTX group). One subject died after Week 24 due to an acute myocardial infarction (MI).

- The demographic characteristics of randomized subjects at baseline were well balanced across the 2 treatment groups and are reported in the C0524T28 24-Week clinical study report (CSR). All subjects were Asian with a median age of 49 years; the majority were women (81.1% overall).
- The majority of subjects entered the study per protocol; ie, met all inclusion and exclusion criteria. One subject (randomized to the golimumab 50 mg + MTX group) never received treatment due to withdrawal of consent. The remaining subjects received their assigned treatments; however 1 subject (randomized to the golimumab 50 mg + MTX group) incorrectly received a placebo injection at Week 12. The proportions of subjects who were not treatment compliant were similar in the placebo + MTX→golimumab 50 mg + MTX group and in the golimumab 50 mg + MTX treatment group. Treatment noncompliance consisted primarily of receiving treatment outside the protocol-specified window.

EFFICACY RESULTS:

Primary Efficacy Endpoint:

The primary efficacy endpoint, ACR 20 response at Week 14, was achieved and was reported in the C0524T28 24-Week CSR.

Major Secondary Endpoints:

The major secondary endpoints included the proportion of subjects achieving a disease activity index score (DAS) 28 (using CRP) response at Week 14, ACR 20 response at Week 24, and change from baseline in HAQ at Week 24. All major secondary efficacy endpoints were achieved and were discussed in detail in the C0524T28 24-Week CSR.

Analyses After Week 24 Through Week 52

Overall, the efficacy observed in all parameters at Week 24 was maintained through Week 52. After crossing over from placebo to golimumab 50 mg at Week 24, subjects in the placebo + MTX→golimumab 50 mg group showed rapid improvement in all efficacy parameters as early as the next evaluation time at Week 28. Additionally, the improvements from baseline at Week 52 were numerically greater than those at Week 24, and a general upward trend was observed over time after Week 24 through Week 52 in both treatment groups, indicating sustained (or continued) improvement in efficacy.

- The proportions of subjects achieving ACR 20, ACR 50, ACR 70, and ACR 90 responses were generally increased after Week 24 through Week 52.
- The changes from baseline in CRP levels were maintained through Week 52.
- The improvements in joint assessment scores, patient assessments of DAS, physician global assessment, patient assessment of pain scores, DAS scores (using CRP), and physical function were generally increased after Week 24 through Week 52.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

- Median trough serum golimumab concentration at Week 52 was 0.68 μg/mL following administration of golimumab 50 mg q4w + MTX in subjects with RA and is consistent with that (0.61 μg/mL) observed at Week 24.
- The incidence of antibodies to golimumab through Week 52 was 2.4% (6/251) following administration of golimumab 50 mg q4w + MTX in subjects with RA.

PATIENT-REPORTED OUTCOMES RESULTS:

- The improvement in the health-related quality of life as measured by SF-36 was generally sustained from Week 24 to Week 52.

SAFETY RESULTS:

Through Week 56, the overall incidence of AEs was low and the safety results observed in this study are consistent with the well known safety profiles of golimumab and other anti-tumor necrosis factor alpha (TNFα) agents; no unanticipated safety issues were observed.

- Through Week 56, the proportion of subjects who reported an AE in the golimumab 50 mg group and in the all golimumab group was 58.8% and 50.2%, respectively. The most commonly reported AEs in the system organ class (SOC) were Infections and infestations. Upper respiratory tract infection was the most common infection within this SOC.
- A total of 12 subjects had at least 1 serious adverse event (SAE) through Week 56. Eleven subjects had received at least 1 dose of golimumab 50 mg + MTX before the SAE was reported. Seven subjects had an SAE through Week 24, and the remaining 5 subjects had an SAE after Week 24 through Week 56. Two of the 5 subjects with at least 1 SAE were in the placebo + MTX→golimumab 50 mg + MTX group (decrease in white blood cell count, spontaneous abortion) and the remaining 3 affected subjects were in the golimumab 50 mg + MTX group from the first dose of study agent (femoral neck fracture, cerebral haemorrhage, acute MI).
- No malignancies were reported through Week 56.
- A total of 3 subjects had at least 1 serious infection (eg, lung infection, pneumonia, respiratory tract infection) through Week 56. No cases of active TB were reported through Week 56.

- One subject reported a mild injection-site reaction (pain) through Week 24. This injection-site reaction did not lead to discontinuation of study agent. No additional injection-site reactions were reported after Week 24 through Week 56.
- No demyelination events were reported through Week 56.
- No subject had an anaphylactic or serum sickness reaction related to study agent through Week 56.
- Among subjects with baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≤ upper limit normal (ULN), elevated ALT or AST abnormalities were noted with a greater incidence in subjects who received treatment for latent TB than in subjects who did not receive treatment for latent TB; however, the abnormalities were predominately mild with no associated signs and symptoms**.**
- One death occurred due to an acute MI through Week 56.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

Through Week 56, golimumab 50 mg + MTX administered SC q4w:

- Provided substantial benefit to subjects with RA by reducing clinical signs and symptoms of disease, and by improving physical function and health-related quality of life.
- Was well tolerated, with no unexpected safety findings.
- Resulted in adequate golimumab exposure that was maintained over time and yielded a low (2.4%; 6/251) incidence of subjects who were positive for antibodies to golimumab.