Janssen Research & Development

24-Week Clinical Study Report Synopsis
C0524T29; Phase 3

CNTO148 (Golimumab)

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SYNOPSIS

Issue Date: 07 May 2012

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

Protocol No.: C0524T29

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 Ankylosing Spondylitis

EudraCT Number: Not Applicable

NCT No.: NCT01248793

Clinical Registry No.: CR015916

Coordinating Principal Investigator: [redacted], MD

Study Centers: 12 sites in China

Publication (Reference): None

Study Period: 09 Sep 2010 (first subject consented) – 05 Aug 2011 (last subject completed Week 24 visit)

Phase of Development: Phase 3

Objectives: The primary objective of this study is to assess the efficacy of SC injections of golimumab in Chinese subjects with active ankylosing spondylitis (AS) as measured by reduction in the signs and symptoms of disease.

The secondary objectives are to assess the safety and the effects of golimumab on physical function, range of motion, and health-related quality of life in Chinese subjects with AS.

Methodology: This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of the efficacy and safety of golimumab 50 mg compared with placebo subcutaneous (SC) injections alone in Chinese subjects with active AS. Subjects were randomly assigned to receive golimumab 50 mg or placebo SC injections at Week 0 and every 4 weeks (q4w) thereafter through Week 20. At Week 16, all subjects receiving placebo that met early escape 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 treated through Week 48 and followed scheduled efficacy and PK assessments through Week 52 and safety assessments through Week 56.

Number of Subjects (planned and analyzed): Approximately 200 subjects were planned to be enrolled in the study; 213 subjects were randomized at 12 investigational sites. All 213 subjects were included in the efficacy and safety analyses; 169 subjects who received at least 1 dose of golimumab were included in the pharmacokinetic (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 AS for at least 3 months prior to screening and symptoms of active disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥ 4, and a visual analogue scale

[VAS] for total back pain of ≥ 4, each on a scale of 0 to 10 cm). Subjects with prior exposure to biologic anti- tumor necrosis factor alpha (TNFα) agents and subjects with complete ankylosis of the spine were not permitted to be included in the study.

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 syringe contained 50 mg golimumab in an aqueous medium of histidine, sorbitol, and polysorbate 80 at pH 5.5. No preservatives were present. Batch No. 09M011.

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

Duration of Treatment: Subjects were to be 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 is to be 48 weeks followed by scheduled efficacy and PK 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 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 24 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 study agent administration).

Efficacy:

Assessment in Ankylosing Spondylitis (ASAS) 20, Bath Ankylosing Spondylitis Functional Index (BASFI), Musculoskeletal Assessments (Bath Ankylosing Spondylitis Metrology Index [BASMI], Patient Global Assessment (PGA), BASDAI, Total Back Pain, Night Back Pain, Enthesitis Index and Chest Expansion), 36-item short form health survey (SF-36), Jenkins Sleep Evaluation Questionnaire (JSEQ) and Productivity Assessment were used to assess efficacy in this study.

Safety:

The assessments used to evaluate safety included vital sign measurements, assessment of 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 DNA (anti-dsDNA) antibodies were collected. Serum samples for the determination of antibodies to golimumab were also collected.

Statistical Methods: A Cochran-Mantel-Haenszel (CMH) test stratified by IVRS screening C-reactive protein (CRP) level (< 15 mg/L or ≥ 15 mg/L) at a significance level of 0.05 (2-sided) was used to compare the treatment effect between the placebo and golimumab 50 mg groups on the primary efficacy endpoint. In addition to the primary endpoint, 3 major secondary endpoints were tested in the order of importance at the same significance level since the primary endpoint achieved statistical significance.

For all other efficacy endpoints, p-values (2-sided) were calculated for comparison of treatments in support of the primary endpoint analysis. A CMH test stratified by screening CRP level was used for

categorical endpoints, and an analysis of variance (ANOVA) on the van der Waerden normal scores with screening CRP level as a factor in the model was used for continuous endpoints.

Simple descriptive summary statistics, such as n, mean, SD, median, IQ range, minimum, and maximum for continuous variables, and counts and percentages for discrete variables were used to summarize most data.

RESULTS:

STUDY POPULATION:

A total of 299 subjects were enrolled (signed an informed consent) and 213 subjects were randomized to treatment. As of Week 24, 207 (97.2%) subjects were continuing in the study and 6 (2.8%) discontinued study agent prior to Week 24 (3 each in the placebo and golimumab 50 mg groups. Two subjects discontinued study agent due to AEs (1 subject in the placebo group due to transaminases increased and 1 in the golimumab 50 mg group due to ovarian epithelial cancer).

- The demographic characteristics of randomized subjects at baseline were well balanced across the 2 treatment groups. All subjects were Asian with a median age of 29 years; the majority were men (83.1% overall).
- The majority of subjects entered the study per protocol; ie, met all inclusion and exclusion criteria. All subjects in the study received their assigned treatment. The proportions of subjects who were not treatment compliant were similar in the placebo and golimumab treatment groups. Treatment noncompliance consisted primarily of receiving treatment outside the protocol-specified window.

EFFICACY RESULTS:

All key analyses of the 24-week data from this study indicate that golimumab 50 mg administered SC q4w provides substantial benefits to subjects with AS by reducing clinical signs and symptoms of disease and by improving physical function, range of motion, and health-related quality of life.

Primary Efficacy Endpoint:

- A significantly greater proportion of subjects in the golimumab 50 mg group (49.1%) achieved an ASAS 20 at Week 14 compared with subjects in the placebo group (24.8%; $p< 0.001$).
- The results of the sensitivity analyses were consistent with the primary analysis.

Major Secondary Endpoints:

- A significantly greater proportion of subjects in the golimumab 50 mg group (50.0%) achieved an ASAS 20 at Week 24 compared with subjects in the placebo group (22.9%; $p < 0.001$).
- A significantly greater improvement in BASFI from baseline at Week 14 was achieved in the golimumab 50 mg group (median = -0.805) compared with the placebo group (median = 0.180; $p < 0.001$).
- A significantly greater improvement in BASMI from baseline at Week14 was achieved in the golimumab 50 mg group (median=-0.33) compared with the placebo group (median=-0.17; $p=0.021$).

Other Endpoints:

Compared with subjects in the placebo group, significantly greater proportions of subjects in the golimumab 50 mg group achieved: low disease activity; at least a 20%, 50%, 70%, or 90% change from baseline in BASDAI; a BASDAI score < 3; a $\geq$ 2-unit improvement from baseline in BASFI. In addition, compared with subjects in the placebo group, subjects in the golimumab 50 mg group achieved a

significantly greater median percent improvement from baseline in: patient global assessment of disease activity, patient assessment of total back pain and night back pain, BASFI, and inflammation. Median change from baseline in C-reactive protein level was also significantly greater for subjects in the golimumab 50 mg group compared with subjects in the placebo group.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

- Serum golimumab concentrations generally achieved steady state by Week 12. The median trough serum golimumab concentration at Week 12 was 0.85 µg/mL following administration of golimumab 50 mg q4w in subjects with AS.
- The incidence of antibodies to golimumab was 0% through Week 24 in subjects with AS.

PATIENT-REPORTED OUTCOMES RESULTS:

The changes from baseline in SF-36 physical and mental component summary scores and the median changes from baseline in the JSEQ were statistically significantly greater in the golimumab 50 mg group than those in the placebo group at both Week 14 and Week 24.

SAFETY RESULTS:

Through Week 24, the overall incidence of AEs was low and generally comparable between the golimumab 50 mg and placebo groups:

- The proportion of subjects who reported an AE was comparable between the golimumab 50 mg (38.9%) and placebo groups (34.3%). The most commonly reported SOCs were Infections and infestations (22.2% in the golimumab 50 mg group and 19.0% in the placebo group), and Investigations (15.7% in the golimumab 50 mg group and 10.5% in the placebo group). Among Infections and Infestations, upper respiratory tract infection was the most common AE. Among Investigations, liver transaminase elevation was the most common AE.
- One SAE (ovarian epithelial cancer) was reported in the golimumab 50 mg group (0.9%). No SAEs were reported in the placebo group (0.0%).
- One malignancy (ovarian epithelial cancer) was reported in golimumab 50 mg group and was judged by the investigator as doubtfully related to the study agent.
- No events of active TB were reported and no opportunistic infections were reported.
- One mild injection-site reaction (erythema) was reported in the golimumab 50 mg group (0.9%) compared with none in the placebo group (0.0%). No severe injection-site reactions were reported.
- No demyelination events were reported.
- Greater proportions of subjects had markedly abnormal alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) in the golimumab 50 mg group (2.8%/1.9%) compared with the placebo group (0.0%/0.0%). However, no subjects were reported with ALT/AST elevations ≥ 3 x ULN with concurrent bilirubin elevation ≥ 2 x ULN.
- No subjects died.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

Golimumab 50 mg administered SC q4w through Week 24:

- Provided substantial benefit to subjects with AS by reducing clinical signs and symptoms of disease, and by improving physical function, range of motion, and health-related quality of life.
- Demonstrated significant efficacy across key measures evaluated.
- Was well tolerated, with a low incidence of AEs overall that was comparable to that of placebo.
- Resulted in adequate golimumab exposure maintained over time and a 0% incidence of subjects who were positive for antibodies to golimumab.