Janssen Research & Development

Clinical Study Report Synopsis
Protocol C0524T17; Phase 2/3

CNTO148 (Golimumab)

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SYNOPSIS

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

Protocol No.: C0524T17

Title of Study: A Phase 2/3 Multicenter, Randomized, Placebo-controlled, Double-blind Study to Evaluate the Safety and Efficacy of Golimumab Induction Therapy, Administered Subcutaneously, in Subjects with Moderately to Severely Active Ulcerative Colitis

Study Name: PURSUIT - Subcutaneous

EudraCT Number: 2006-003398-28

Principal Investigator: [redacted] MD - [redacted] USA

Publication (Reference): None

Study Period: 18 Jul 2007 – 29 Nov 2010

Phase of Development: Phase 2/3

Objectives:

Part 1: Dose-ranging

1. To evaluate the dose response of subcutaneous (SC) golimumab induction regimens in subjects with moderately to severely active ulcerative colitis (UC).
2. To select SC induction regimen(s) of golimumab, based on safety and efficacy, for continued development in Part 2.

Part 2: Dose-confirming

Primary Objectives

1. To evaluate the efficacy of SC induction regimens of golimumab in inducing clinical response in subjects with moderately to severely active UC.
2. To evaluate the safety of SC induction regimens of golimumab in subjects with moderately to severely active UC.

Secondary Objectives

1. To evaluate the efficacy of SC induction regimens of golimumab in inducing clinical remission.
2. To evaluate the efficacy of SC induction regimens of golimumab in inducing mucosal healing.
3. To evaluate the efficacy of SC induction regimens of golimumab in improving disease-specific health-related quality of life.
4. To provide the target study population to be evaluated in the 1-year golimumab maintenance study C0524T18.

Methods:

This Phase 2/3 multicenter study was divided into 2 parts: Part 1 was the Phase 2 dose-ranging portion and Part 2 was the Phase 3 dose-confirming portion. Both parts were randomized, double-blind, placebo-controlled, parallel-group designs. Part 1 randomized 169 subjects in a 1:1:1:1 ratio at Week 0 to 1 of the following dose regimens:

- Placebo at Week 0 and placebo at Week 2 (placebo)
- Golimumab 100 mg at Week 0 and 50 mg at Week 2 (100 mg → 50 mg)

- Golimumab 200 mg at Week 0 and 100 mg at Week 2 (200 mg → 100 mg)
- Golimumab 400 mg at Week 0 and 200 mg at Week 2 (400 mg → 200 mg)

Part 2 of the study began when the 170th subject was randomized, and approximately 875 subjects were to be randomized at Week 0 in Part 2. While the data from Part 1 were being evaluated, newly enrolled subjects in Part 2 were equally randomized to the same SC doses of golimumab or placebo as in Part 1. After an interim analysis, the 200 mg → 100 mg and 400 mg → 200 mg golimumab SC doses were selected for continued development in Part 2, and newly enrolled subjects in Part 2 were equally randomized to 200 mg → 100 mg or 400 mg → 200 mg golimumab or placebo. At Week 6, subjects were evaluated for clinical response. At this visit all subjects, regardless of the part of the study into which they were enrolled, were eligible to enroll in the 1-year golimumab maintenance study (C0524T18). Subjects not entering the 1-year golimumab maintenance study were evaluated for safety 16 weeks following their last administration of study agent.

Number of Subjects:
The number of subjects randomized to each part of the study was as follows:
- Part 1: 169 subjects
- Part 2: 896 subjects
  - Before the dose selection: 122 subjects
  - After the dose selection: 774 subjects

Diagnosis and Main Criteria for Inclusion:
Subjects had to be men or women 18 years of age or older with moderately to severely active UC as defined by a Mayo score of 6 to 12 inclusive at baseline (Week 0), including an endoscopic subscore of ≥ 2. Subjects must have had a biopsy result consistent with the diagnosis of UC and must have been ambulatory (ie, not at imminent risk of colectomy). Subjects must have demonstrated an inadequate response to or have failed to tolerate oral 5-aminosalicylates (5-ASAs), or oral corticosteroids, or the immunomodulators azathioprine (AZA) or 6-mercaptopurine (6 MP), or have demonstrated corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of UC).

Subjects were not to be enrolled into the study if they were at imminent risk of colectomy. Subjects with UC limited to the rectum only or < 20 cm of the colon, a stoma, a fistula, an obstruction, or adenomatous colonic polyps that were not removed were ineligible for entry into the study. Subjects with a history of latent or active granulomatous infection (including TB), a predisposition to infections, or a history of or increased potential for malignancy were ineligible for entry into the study. Subjects with a diagnosis or history of congestive heart failure, lymphoproliferative disease, systemic lupus erythematosus, or demyelinating disease were ineligible for entry into the study. Subjects with prior exposure to biologic anti-TNF agents were ineligible for entry into the study.

Test Product, Dose and Mode of Administration:
Golimumab was supplied as a sterile liquid for SC injection in single-use prefilled syringes. Each single-use prefilled syringe contained either 50 mg (0.5 mL fill of liquid) or 100 mg (1 mL fill of liquid) golimumab in an aqueous medium of histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives were present. Liquid study agent in prefilled syringes was supplied ready to use. At the study site, prefilled syringes of study agent were to be stored in a secured refrigerator at 2°C to 8°C.

Reference Therapy, Dose and Mode of Administration:
Placebo was supplied by the sponsor as a sterile liquid for SC injection at a fill volume of 0.5 mL or 1.0 mL in single-use prefilled syringes. Each prefilled syringe contained histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives were present. Liquid study agent in prefilled syringes was supplied ready to use. At the study site, prefilled syringes of study agent were to be stored in a secured refrigerator at 2°C to 8°C.

Duration of Treatment:
Randomized subjects received 2 inductions doses of SC golimumab **(**100 mg → 50 mg, 200 mg → 100 mg, or 400 mg → 200 mg) or placebo at Weeks 0 and 2, respectively.

Criteria for Evaluation:
Pharmacology: Golimumab concentrations and antibodies to golimumab were evaluated and summarized. Subjects who consented to participate in biopsy collection for the substudy were evaluated for histological scoring, serum biomarkers analysis, biopsy-based RNA analysis, and whole blood RNA expression analysis.

Efficacy: Efficacy evaluations included the Mayo score, endoscopy, C-reactive protein (CRP), and fecal lactoferrin and calprotectin. Efficacy criteria evaluated at Week 6 included clinical response (the decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore of ≥ 1 or a rectal bleeding subscore of 0 or 1), clinical remission (a Mayo score ≤ 2 points, with no individual subscore > 1), and mucosal healing (an endoscopy subscore of 0 or 1). Patient reported outcomes included the Inflammatory Bowel Disease Questionnaire (IBDQ), 36-item short form health survey (SF-36), and the Euro QOL-5D (EQ-5D).

Safety: Safety was assessed by summarizing AEs and clinical laboratory data (hematology, blood chemistry, ANA and anti-dsDNA antibodies).

Statistical Methods:
Demographic and baseline disease characteristics were summarized for all randomized subjects. Chi-square tests or Cochran-Mantel-Haenszel [CMH] chi square tests, as appropriate, were used to compare the proportions of subjects achieving selected endpoints (eg, clinical remission). Continuous response parameters were compared using an analysis of variance (ANOVA) or an ANOVA on the van der Waerden normal scores, as appropriate. All statistical testing was performed at the $\alpha = 0.05$ (2-sided) level unless otherwise specified. The primary analysis population was composed of subjects randomized in Part 2 after the dose selection. Based on a Health Authority request, the following prespecified analysis populations (besides the primary analysis population) were also evaluated for selected, prespecified efficacy endpoints:

- Subjects randomized in Part 1
- Subjects randomized in Part 2
- Subjects randomized in Part 2 before the dose selection
- First 450 subjects randomized in Part 2 after the dose selection
- All randomized subjects (Part 1 and Part 2 combined).

In keeping with the analysis populations for efficacy, demographic and baseline disease characteristics were also evaluated in these prespecified populations in addition to the primary analysis population, with the focus being on all randomized subjects.

Safety and pharmacokinetics were evaluated in all treated subjects (ie, Part 1 and Part 2 combined) and treated subjects in Part 2 after the dose selection, with the focus being on all treated subjects. Safety and pharmacokinetics were also evaluated separately for subjects randomized in Part 1.

RESULTS:
SUBJECT AND TREATMENT INFORMATION:
A total of 1065 subjects were randomized to treatment, 734 subjects to golimumab (72, 331, and 331 subjects to 100 mg → 50 mg, 200 mg → 100 mg, and 400 mg → 200 mg, respectively) and 331 subjects to placebo. All randomized subjects received the assigned treatment with the exception of 4 subjects (1 subject was never treated and 3 subjects received the incorrect dose at either Week 0 or 2). Of the 1065 randomized subjects, 1015 (95.3%) completed study participation (969 [91.0%] completed the Week 6 visit and entered the C0524T18 maintenance study and 46 [4.3%] completed the Week 16 visit).

Fifty (4.7%) subjects terminated study participation; of these 50 subjects, 35 (3.3%) terminated prior to Week 6, and 15 (1.4%) terminated between Week 6 and Week 16.

Demographics, baseline clinical disease characteristics, and the percentage of subjects receiving concomitant UC medications (including corticosteroids, immunomodulatory drugs, and aminosalicylates) were generally comparable across treatment groups among all randomized subjects. Results were also evaluated in prespecified populations and were generally consistent with those of all randomized subjects.

PHARMACOKINETIC, PHARMACODYNAMIC, AND IMMUNOGENICITY RESULTS:
Among all treated subjects, serum golimumab concentrations were approximately proportional to dose following SC administration of golimumab 100 mg → 50 mg, 200 mg → 100 mg, and 400 mg → 200 mg at Weeks 0 and 2, respectively. At Week 6, almost all subjects maintained serum golimumab concentrations above the detectable limit (0.03905 µg/mL). Among treated subjects in Part 2 after the dose selection, results were generally consistent with those of all treated subjects.

Of 721 golimumab-treated subjects with appropriate samples for immune response, 3 (0.4%) subjects were positive for antibodies to golimumab through the final safety visit.

EFFICACY RESULTS:
The primary endpoint was clinical response at Week 6. The proportions of subjects in clinical response at Week 6 in the primary analysis population were significantly greater in the 200 mg → 100 mg and 400 mg → 200 mg groups (51.8%, and 55.0%, respectively) compared with the placebo group (29.7%, $p < 0.0001$ for each golimumab group versus placebo), and the study was considered to be a positive study. The major secondary endpoints were clinical remission, mucosal healing, and the change from baseline in the IBDQ score, all at Week 6. Among subjects in the primary analysis population, significantly greater proportions in the 200 mg → 100 mg and 400 mg → 200 mg groups achieved:

- Clinical remission (18.7% and 17.8%, respectively) compared with the placebo group (6.3%; $p < 0.0001$ for each golimumab group versus placebo);
- Mucosal healing (43.2% and 45.3%, respectively) compared with the placebo group (28.5%; $p = 0.0005$ and $p < 0.0001$ for the 200 mg → 100 mg and 400 mg → 200 mg groups, respectively, versus placebo).

The mean change in the IBDQ score was also significantly greater in the 200 mg → 100 mg and the 400 mg → 200 mg groups (27.4 and 27.0, respectively) compared with the placebo group (14.6; $p < 0.0001$ for each golimumab group versus placebo).

Results for other clinical and biomarker endpoints at Week 6 in the primary analysis population were as follows:

- Significantly greater mean decreases in the Mayo score in the 200 mg → 100 mg and 400 mg → 200 mg groups (-3.1 each) versus the placebo group (-1.6; $p < 0.0001$ for each golimumab group versus placebo);
- Greater mean decreases in the partial Mayo scores in the 200 mg → 100 mg and 400 mg → 200 mg groups versus the placebo group;
- Across each of the Mayo subscore categories, greater improvement in the 200 mg → 100 mg and 400 mg → 200 mg groups versus the placebo group in the increase in the proportions of subjects with Mayo subscores indicative of normal or mild disease and the decrease in the proportions of subjects with Mayo subscores indicative of moderate or severe disease;
- Significantly greater proportions of subjects with normal or inactive mucosal disease (ie, an endoscopy score of 0) in the 200 mg → 100 mg and 400 mg → 200 mg groups (8.2% and 12.0%, respectively) versus the placebo group (3.9%; $p = 0.0427$ and $p = 0.0007$ for the 200 mg → 100 mg and 400 mg → 200 mg groups, respectively, versus placebo);
- Significantly greater mean decreases from baseline in CRP concentrations in both golimumab groups (-3.35 in the 200 mg → 100 mg group and -2.76 in the 400 mg → 200 mg group) versus the placebo group (-1.23; $p < 0.0001$ and $p = 0.0005$ for the 200 mg → 100 mg and 400 mg → 200 mg groups, respectively, versus placebo);

- Significantly greater mean decreases from baseline in the log transformed fecal lactoferrin concentrations in the 200 mg →100 mg and the 400 mg → 200 mg groups (-0.30 and -0.49, respectively) versus the placebo group (-0.15; p = 0.0479 and p = 0.0002 for the 200 mg →100 mg and 400 mg → 200 mg groups, respectively, versus placebo) at Week 2, which were maintained through Week 6 in the 400 mg → 200 mg group;
- Significantly greater mean decreases from baseline in the log transformed fecal calprotectin concentration in the 200 mg →100 mg and the 400 mg → 200 mg groups (-0.31 and -0.34, respectively) compared with the placebo group (-0.13; p = 0.0013 and p = 0.0009 for the 200 mg →100 mg and 400 mg → 200 mg groups, respectively, versus placebo) at Week 2, which were maintained through Week 6 in the 400 mg → 200 mg group;
- Among subjects who consented to participate in tissue sample collection for histological scoring and had biopsies collected at baseline, smaller proportions of subjects in the placebo and golimumab groups had Grade 5 inflammation at Week 6 compared with baseline, with the largest decrease in the 400 mg → 200 mg group.

Results for patient reported outcomes at Week 6 in the primary analysis population were as follows:

- Significantly greater mean increases in the SF-36 physical component summary scores in the 200 mg → 100 mg and the 400 mg → 200 mg groups (4.51 and 3.78, respectively) compared with the placebo group (2.46; p = 0.0006 and p = 0.0471 for the 200 mg → 100 mg and 400 mg → 200 mg groups, respectively, versus placebo) and the SF-36 mental component summary scores in the 200 mg → 100 mg and the 400 mg → 200 mg groups (4.69 and 5.10, respectively) compared with the placebo group (1.60; p = 0.0009 and p < 0.0001 for the 200 mg → 100 mg and 400 mg → 200 mg groups, respectively, versus placebo);
- Significantly greater mean improvements in the EQ VAS scores in the 200 mg → 100 mg and 400 mg → 200 mg groups (11.7 and 10.9, respectively) compared with the placebo group (5.1; p = 0.0003 and p = 0.0010 for the 200 mg → 100 mg and 400 mg → 200 mg groups, respectively, versus placebo).

Results for the primary endpoint, the major secondary endpoints, clinical endpoints, biomarker endpoints, and patient reported outcomes were evaluated in other prespecified populations and were generally consistent with those of the primary analysis population.

At Week 6 in all subjects treated with golimumab, there was an apparent association between the median improvement from baseline in the Mayo score and serum golimumab concentration, with a greater median improvement in the Mayo score in the higher serum golimumab concentration quartiles (-1.0, -3.0, -3.0, and -4.0 in the < 1st quartile, ≥ 1st quartile and < 2nd quartile, ≥ 2nd quartile and < 3rd quartile, and ≥ 3rd quartiles, respectively). Higher proportions of subjects were in clinical response and clinical remission in the higher quartiles of serum golimumab concentrations at Week 6.

SAFETY RESULTS:
Safety analyses were conducted for all treated subjects (ie, Part 1 and Part 2 combined). Through Week 6, the proportions of subjects with AEs were generally consistent in the all golimumab and placebo groups (39.1% and 38.2%, respectively). The most frequently reported system-organ classes for golimumab-treated and placebo-treated subjects were Infections and infestations (12.0% and 10.9%, respectively) and Gastrointestinal disorders (10.5% and 12.4%, respectively). Through Week 6, the most frequently reported AEs in the placebo group were headache, colitis ulcerative, and nasopharyngitis (5.2%, 3.9%, and 3.3%, respectively). The most frequently reported AEs in the 200 mg → 100 mg and 400 mg → 200 mg groups were headache (3.0%, and 4.5%, respectively), nausea (0.9%, and 3.6%, respectively), pyrexia (1.8%, and 3.0%, respectively), and nasopharyngitis (3.3%, and 2.4%, respectively). There was 1 death through the final safety visit: a subject in the 400 mg → 200 mg group died due to an SAE of ischiorectal abscess.

Through Week 6, the proportions of treated subjects with SAEs were low overall (6.1% and 3.0% in the placebo and all golimumab groups, respectively) and similar in the 200 mg → 100 mg and 400 mg → 200 mg groups (2.7% and 3.3%, respectively). The most frequently reported SAE in the placebo, 200 mg

→ 100 mg, and 400 mg → 200 mg groups was colitis ulcerative (2.4%, 0.9%, and 1.2%, respectively). Few treated subjects in any treatment group discontinued study agent due to AEs. Through Week 6, the proportions of treated subjects with AEs identified as infections by the investigator were consistent in the placebo and all golimumab groups (12.1% and 12.0%, respectively) and similar in the 200 mg → 100 mg and 400 mg → 200 mg groups (11.8% and 12.3%, respectively). The proportions of treated subjects with infections requiring antimicrobial therapy were low overall and generally consistent in the placebo and all golimumab groups (7.0%, and 5.4% respectively).

SAEs identified by the investigator as infections were low in the placebo and all golimumab groups (1.8% and 0.5%, respectively) and similar in the 200 mg → 100 mg and 400 mg → 200 mg groups (0.3% and 0.9%, respectively). There were no cases of active TB reported through the duration of the study. Four opportunistic infections were reported through the final safety visit: 1 report of oesophageal candidiasis, 2 reports of CMV infection, and 1 report of a serious CMV infection. Through Week 6, the proportions of treated subjects with injection-site reactions were low overall (1.5% and 3.4% in the placebo and all golimumab groups, respectively) and similar in the 200 mg → 100 mg and 400 mg → 200 mg groups (3.3% and 3.0%, respectively). No injection-site reactions were serious. No AEs of possible delayed hypersensitivity reaction or possible anaphylactic reaction were reported. Two malignancies were reported: 1 subject in the 400 mg → 200 mg group had carcinoma in situ and colon cancer, and 1 subject in the placebo group had thyroid cancer. Neither malignancy was attributable to treatment with golimumab in this study.

Hematology and chemistry laboratory values were generally unremarkable. Results for treated subjects in Part 2 after the dose selection were generally consistent with those of all treated subjects.

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

CONCLUSION:
Golimumab SC regimens of 200 mg → 100 mg and 400 mg → 200 mg at Weeks 0 and 2, respectively, led to highly significant improvements in disease activity in subjects with moderately to severely active UC as measured by clinical response, clinical remission, mucosal healing, and improved health-related quality of life at Week 6. Higher serum golimumab exposures were associated with greater improvement in UC disease activity as measured by the Mayo score, and proportions of subjects in clinical response and clinical remission. Golimumab was generally well tolerated and the safety profile was similar to that observed with other anti-TNF therapies as well as with that of golimumab in other indications. Overall, the safety and efficacy data from this study support a positive benefit/risk profile for induction therapy with SC golimumab in the treatment of adults with moderately to severely active UC.