SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development
Name of Investigational Product	SIMPONI (golimumab)

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Status: Approved

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Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO148UCO2001

Title of Study: A Phase 2a Open-label Study to Evaluate Prediction of Response to Golimumab Using a Transcriptomic Profile in Subjects with Moderately to Severely Active Ulcerative Colitis

Study Name: PROgECT

EudraCT Number: 2013-002042-36

NCT No.: NCT01988961

Clinical Registry No.: CR102851

Coordinating Investigator: Dr. William Sanborn, University of California at San Diego Medical Center, [redacted], United States of America (USA).

Study Centers: Belgium (3), Bulgaria (3), Canada (5), Czech Republic (3), Germany (4), France (3), Hungary (3), Israel (1), Netherlands (3), Poland (4), Russia (3), Ukraine (3), and United States of America (17).

Publication (Reference): Not applicable.

Study Period: First subject entered: 10 February 2014 and last subject last visit: 29 January 2016
Database lock: 18 April 2016

Phase of Development: 2a

Objectives and Hypothesis:

This was a Phase 2a, open-label, multicenter study to evaluate the accuracy of a biomarker panel in predicting response to golimumab treatment in subjects with moderately to severely active ulcerative colitis (UC).

Primary Objective

The primary objective was to evaluate the accuracy of a subset of the length-109 (subsequently defined as the length-13) probe set panel in predicting mucosal healing (ie, improvement in the endoscopic appearance of the mucosa) at Week 6 as measured by the area under a Receiver Operating Characteristic (ROC) curve (AUC_{ROC}).

Secondary Objectives

The secondary objectives were:

- To evaluate the accuracy of a subset of the length-109 (subsequently defined as the length-13) probe set panel in predicting clinical response at Week 6 and at Week 30 as measured by the AUC_{ROC}
- To evaluate the accuracy of a subset of the length-109 (subsequently defined as the length-13) probe set panel in predicting clinical remission at Week 6 and at Week 30 as measured by the AUC_{ROC}
- To evaluate the accuracy of a subset of the length-109 (subsequently defined as the length-13) probe set panel in predicting mucosal healing at Week 30 as measured by the AUC_{ROC}

Overall safety was assessed.

Hypothesis:

The study hypothesis was that the accuracy of a subset of the length-109 (subsequently defined as the length-13) probe set panel in predicting mucosal healing at Week 6 as measured by the AUC_{ROC} would be significantly greater than 0.5 (ie, better than chance).

Methodology:

This was a Phase 2a, open-label, multicenter study that evaluated the accuracy of a subset of the length-109 (subsequently defined as the length-13) probe set panel in predicting response to golimumab treatment in subjects with moderately to severely active UC, defined by a baseline Mayo score of 6 to 12, inclusive, including an endoscopic subscore of ≥2 (based on the endoscopy subscore assigned by central readers). The planned total sample size was approximately 100 subjects.

All subjects enrolled in the study received the approved induction dose regimen of subcutaneous (SC) golimumab for UC: 200 mg at Week 0 and 100 mg at Week 2 (200 mg→100 mg). At Week 6 and thereafter through Week 50, subjects received the maintenance dose (50 mg every 4 weeks [q4w] or 100 mg q4w) of SC golimumab approved for UC in the country in which the study was conducted. In countries where there was no local labeling for golimumab, a maintenance dose of 100 mg q4w was used. Subjects were followed for safety through 8 weeks following their last administration of golimumab.

The safety data of the subjects in this study were reviewed on an ongoing basis by the medical monitor.

No interim analysis was performed. There were 3 database locks, at Weeks 6, 30, and 58 (end-of-study).

Number of Subjects (planned and analyzed):

A total of 103 subjects were enrolled in this study, and all subjects received golimumab induction (200 mg→100 mg). Of the 103 enrolled subjects, 3 subjects received no maintenance treatment, and 100 subjects received maintenance treatment as follows:

- 24 subjects received 50 mg q4w maintenance
- 76 subjects received 100 mg q4w maintenance

Diagnosis and Main Criteria for Inclusion/Exclusion:

To be eligible for the study, 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 (based on the endoscopy subscore assigned by central readers), with a clinical diagnosis of UC at least 3 months prior to screening. Subjects must have been treated with or had a failure

to respond to, or tolerate, oral 5-aminosalicylates (5-ASAs), oral corticosteroids, 6-mercaptopurine (6-MP), or azathioprine (AZA), 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, history of a fistula, an obstruction, or adenomatous colonic polyps that were not removed were ineligible for entry into the study.

Subjects with a history of active granulomatous infection (including histoplasmosis), or a predisposition to infections were ineligible for entry into the study. Subjects with a diagnosis or history of hepatitis C virus infection or human immunodeficiency virus, were ineligible for entry into the study. Subjects were screened for hepatitis B virus, and subject eligibility based on test results was determined as detailed in the protocol. Subjects with 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, systemic lupus erythematosus, or demyelinating disease were ineligible for entry into the study.

Subjects with prior exposure to biologic anti-tumor necrosis factor-alpha (TNFα) agents were ineligible for entry into the study.

Test Product, Dose and Mode of Administration, Batch No.:

Golimumab was supplied as a sterile liquid for SC injection in single-use prefilled syringes (PFS). Each PFS contained either 100 mg (1 mL fill of liquid) or 50 mg (0.5 mL fill of liquid) of golimumab, in addition to histidine, sorbitol and polysorbate 80 at pH 5.5. No preservatives were present. At study sites, all golimumab was to be stored at controlled temperatures ranging from 36°F to 46°F (2°C to 8°C).

Batch numbers for golimumab were: 4368120, 4368560, 4368561, 4370164, and 4370165.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Following an 8 week screening, the treatment phase of the study was 50 weeks, followed by a final safety visit at Week 58.

Study Evaluations:

Pharmacokinetics
Evaluations included venous blood samples for measuring serum golimumab concentrations.

Immunogenicity
Evaluations included venous blood samples for assessment of antibodies to golimumab.

Biomarkers
Evaluations included mucosal biopsy ribonucleic acid (RNA) and histology samples, serum samples for biomarkers, and whole blood total RNA.

Efficacy
Evaluations included the Mayo score and partial Mayo score, C-reactive protein (CRP), fecal lactoferrin, fecal calprotectin, and Ulcerative Colitis Endoscopic Index of Severity (UCEIS).

Safety
Evaluations included adverse events (AEs) and clinical laboratory data (hematology, serum chemistry, antinuclear antibody [ANA] and anti-double-stranded deoxyribonucleic acid [dsDNA] antibodies).

Statistical Methods:

Pharmacokinetics

Serum golimumab concentrations and the number of subjects who had lower limit of quantification (LLOQ) concentration over time were summarized. The relationship between biomarkers and serum golimumab concentration was explored.

Immunogenicity

The incidence and titers of antibodies to golimumab were summarized for all subjects who received at least 1 dose of golimumab and had appropriate samples for detection of antibodies to golimumab (ie, subjects with at least 1 sample obtained after their first dose of golimumab).

Biomarkers

Unless otherwise specified, biomarker analyses were based on the biomarker analysis set, which consisted of all treated subjects who had their biomarker measurement at baseline, excluding those from site PL00117.

Primary Endpoint

The primary endpoint was the AUC_{ROC} of the length-13 probe set panel in predicting mucosal healing at Week 6. Subjects who had a colectomy or ostomy, discontinued golimumab due to lack of therapeutic effect or an AE of worsening of UC disease, or had a protocol-prohibited medication change prior to the Week 6 visit were considered as not having achieved mucosal healing. In addition, subjects who had a missing endoscopy subscore at Week 6 were considered not to have achieved mucosal healing.

A predictive signature score was calculated for each subject using the expression of each of the predictive 13 genes as measured by polymerase chain reaction. The expression of each of the 13 genes were weighted and summed to yield a predictive signature score. The predictive signature score for each subject was then compared to the pre-specified threshold to determine whether that subject was a predicted mucosal healing responder or non-responder.

The ROC curve was constructed by plotting the sensitivity versus 1-specificity at various thresholds of the length-13 probe set panel based on the biomarker analysis set. The non-parametric approach was used to estimate the AUC_{ROC} by numerical integration of the area under the ROC curve. The estimated AUC_{ROC} along with its 1 sided 95% confidence interval (CI) and p-value were provided.

The diagonal line in the AUC_{ROC} figure represents an AUC of 0.5, ie, a hypothetical predictive gene panel that is not better than chance. Therefore, an AUC that is further above the diagonal line, has greater predictive performance than an AUC that is closer to the diagonal.

As part of the primary analysis, the sensitivity and specificity were calculated for all thresholds of the length-13 probe set panel. In addition, sensitivity along with its 1-sided 95% CI, p-value, and specificity were computed for 2 prespecified thresholds: -3.8234 (Threshold A) selected to achieve an optimal sensitivity, and 1.000 (Threshold B) selected to achieve an optimal balance between sensitivity and specificity for the primary endpoint. The analysis was not adjusted for multiplicity.

Major Secondary Endpoints

The major secondary endpoints were not controlled for multiplicity.

The estimated AUC_{ROC} values along with their 1-sided 95% CIs and nominal p-values were provided for the major secondary endpoints of the AUC_{ROC} of the length-13 probe set panel in predicting clinical response at Week 6 and clinical remission at Week 6, and in predicting clinical response, clinical remission and mucosal healing, all at Week 30.

For each major secondary endpoint, the sensitivity estimate along with its 1-sided 95% CI, p-value, and specificity were computed for Threshold A (-3.8234) and Threshold B (1.000) as was done for the primary endpoint. In addition, estimated AUC_{ROC} values (along with their 1-sided 95% CIs and nominal p-values) of the length-13 probe set panel in predicting mucosal healing at Week 30 were provided by golimumab maintenance doses of 50 mg q4w and 100 mg q4w.

Additional biomarker analyses (not stated in the SAP) were performed to determine the accuracy of the length-13 probe set panel as measured by the AUC_{ROC} in predicting sustained clinical response, sustained clinical remission, and sustained mucosal healing. Sustained response is defined as achieving the respective response criterion at both Week 6 and Week 30. The sustained clinical response and sustained clinical remission analyses were repeated for subjects in the biomarker analysis set who had non-missing Mayo score data at both Week 6 and Week 30. The sustained mucosal healing analyses were repeated for subjects who had non-missing endoscopy subscore data at both Week 6 and Week 30.

Other Planned Analyses

The estimated AUC_{ROC} values along with their 1-sided 95% CIs and nominal p-values were provided for AUC_{ROC} of the length-13 probe set panel in predicting partial Mayo response and partial Mayo remission at Week 50.

Pharmacogenomics and Epigenetics

Pharmacogenomics and epigenetic assessment were only performed for subjects who signed the consent form to participate in this assessment. The pharmacogenomics and epigenetic analyses were to evaluate drug metabolism and mechanistic responses that are directly related to golimumab.

Results of these analyses will be presented in a separate technical report.

Efficacy

Summaries are provided for:

1. The proportions of subjects who achieved clinical response at Week 6 and at Week 30
2. The proportions of subjects who achieved clinical remission at Week 6 and at Week 30
3. The proportions of subjects who achieved mucosal healing at Week 6 and at Week 30
4. The change from baseline in the Mayo score at Week 6 and at Week 30
5. The change from baseline in the partial Mayo score over time
6. The change from baseline in CRP concentration over time
7. The change from baseline in fecal lactoferrin concentration over time
8. The change from baseline in fecal calprotectin concentration over time
9. The UCEIS score at Week 0, Week 6 and Week 30 by the level of Mayo endoscopy score at the corresponding visit, to assess the association between the UCEIS score and Mayo endoscopy score
10. The proportions of subjects who achieved partial Mayo score response over time
11. The proportions of subjects who achieved partial Mayo score remission over time

The following additional analysis (not stated in the SAP) was performed: the proportion of subjects with sustained mucosal healing, sustained clinical response, and sustained clinical remission was summarized.

Efficacy and Pharmacokinetics

To assess the relationship between golimumab concentration and efficacy, the following analyses of efficacy endpoints by golimumab concentrations (<1st quartile, ≥1st quartile and <2nd quartile, ≥2nd quartile and <3rd quartile, and ≥3rd quartile) were performed.

- The proportions of subjects who achieved mucosal healing at Week 6 and at Week 30 were summarized by golimumab concentrations at Week 6 and at Week 30, respectively.
- The proportions of subjects who achieved clinical response at Week 6 and at Week 30 were summarized by golimumab concentrations at Week 6 and at Week 30, respectively.
- The following additional analysis (not stated in the SAP) was performed: the proportions of subjects who achieved clinical remission at Week 6 and at Week 30 was summarized by golimumab concentrations at Week 6 and at Week 30, respectively.

Efficacy and Immunogenicity

The proportions of subjects achieving mucosal healing and clinical response at Week 6 and at Week 30 by antibodies to golimumab status through Week 6 and through Week 30, respectively, were summarized.

Safety

Safety evaluations were based on subjects who received at least 1 injection of study agent, including partial injections. Safety was assessed by summarizing the frequency and type of AEs and examining changes in laboratory parameters (hematology and chemistry), and ANA and anti-dsDNA antibody measurements.

Safety data through Week 6, Week 30, and Week 58 were summarized.

RESULTS:

SUBJECT AND TREATMENT INFORMATION:

A total of 103 subjects were enrolled in this study, and all subjects received golimumab induction (200 mg→ 100 mg). Of the 103 subjects, 3 subjects received no maintenance treatment, and 100 subjects received maintenance treatment as follows

- 24 subjects received 50 mg q4w maintenance
- 76 subjects received 100 mg q4w maintenance

The clinical disease characteristics, baseline demographic and baseline UC-related concomitant medication usage were consistent with a population with moderately to severely active UC that was refractory to, intolerant of, or dependent on conventional UC medications. The 2 maintenance doses (50 mg q4w and 100 mg q4w) were not randomly assigned but followed regional posology guidelines in each country. Based on this, a greater proportion of subjects were assigned to receive 100 mg q4w than 50 mg q4w.

In total the proportion of subjects who discontinued study agent was 42.7%. The 2 most common reasons for discontinuation of study agent were unsatisfactory therapeutic effect and adverse event (AE) of worsening of UC.

BIOMARKER, PHARMACOKINETIC, AND IMMUNOGENICITY RESULTS:

Primary Endpoint

- The accuracy of the length-13 probe set panel in predicting mucosal healing at Week 6 as measured by the AUC_{ROC} was significantly greater than 0.5 (better than chance), indicating that the primary objective was met for this study (AUC_{ROC}: 0.688 [lower bound of 95% CI: 0.589; p-value=0.002]).
  - Results from sensitivity analysis based on non-missing data were consistent with that of the primary analysis.
  - Results from subgroup analyses were generally consistent with that of the primary analysis.

Major Secondary Endpoints

The accuracy of the length-13 probe set panel in predicting the specified endpoints is as follows:

- Mucosal healing at Week 30 as measured by the AUC_{ROC} was significantly greater than 0.5 (better than chance; AUC_{ROC}: 0.671 [lower bound of 95% CI: 0.569; nominal p-value=0.006]). The result was robust to prespecified changes in data handling rules.
- Clinical remission at Week 30 as measured by the AUC_{ROC} was numerically greater than 0.5, but it was not statistically significant (AUC_{ROC}: 0.633 [lower bound of 95% CI: 0.517; nominal p-value=0.059]).
  - The sensitivity analysis based on subjects with non-missing Mayo score data indicated that the accuracy of the length-13 probe set panel in predicting clinical remission at Week 30 was significantly greater than 0.5 (better than chance).
- Clinical response at Week 6, clinical remission at Week 6, and clinical response at Week 30 as measured by the AUC_{ROC} were not better than chance. Results from sensitivity analyses based on non-missing data yielded similar results.

Additional Endpoints

- The accuracy of the length-13 probe set panel in predicting partial Mayo response at Week 50 was not better than chance.
- The accuracy of the length-13 probe set panel in predicting partial Mayo remission at Week 50 was numerically greater than 0.5, but it did not meet statistical significance.
- The length-13 probe set panel had superior sensitivity and low specificity in predicting mucosal healing, clinical remission, clinical response, partial Mayo response, and partial Mayo remission, based on Threshold A (-3.8234) optimized for sensitivity and Threshold B (1.000) optimized for sensitivity and specificity.

Pharmacokinetics

The median serum golimumab concentration peaked at Week 6, decreased by Week 30 and then remained relatively stable through Week 50.

Immunogenicity

Of 101 subjects with appropriate samples for the assessment of antibodies to golimumab, 26 (25.7%) were positive for antibodies to golimumab at any time. The majority of these subjects who were positive for antibodies to golimumab had low antibody titers (<1:96); and almost half of them had neutralizing antibodies.

EFFICACY RESULTS:

- The proportions of subjects who achieved mucosal healing, clinical response, and clinical remission at Week 6 were 24.2%, 52.5%, and 13.1%, respectively.
- The proportions of subjects who achieved mucosal healing, clinical response, and clinical remission at Week 30 were 28.3%, 48.5%, and 22.2%, respectively.
- The proportions of subjects who achieved sustained mucosal healing, sustained clinical response, and sustained clinical remission were 14.1%, 30.3%, and 5.1%, respectively.
- Higher serum concentrations of golimumab were associated with higher proportions of subjects achieving mucosal healing, clinical response, and clinical remission.
- The decrease in the Mayo score achieved at Week 6 was maintained through Week 30.
- The decrease in the partial Mayo score achieved at Week 6 was maintained through Week 50.
- There were increases in the proportion of subjects who achieved partial Mayo score response and partial Mayo score remission from Week 2 through Week 18, and this was sustained through Week 50.
- There were no clinically relevant changes in CRP levels throughout the study.
- Fecal lactoferrin and fecal calprotectin concentrations decreased at Week 6 and the decreases were maintained through Week 50.
- A higher UCEIS score was associated with a higher Mayo endoscopy score.
- The proportions of subjects who achieved efficacy outcomes were numerically lower among those positive for antibodies to golimumab through Week 30 compared with those who were negative for antibodies to golimumab.

SAFETY RESULTS:

Subcutaneous induction doses of 200 mg→100 mg of golimumab at Week 0 and Week 2, followed by SC regimens of 50 mg maintenance or 100 mg maintenance treatment q4w between Week 6 and Week 50, were generally well tolerated.

- The proportion of subjects who discontinued study agent because of 1 or more AEs was 18.4% (19) through the final safety visit.
- The proportions of subjects with SAEs were low: 2.9% (3) through Week 6, and 10.7% (11) through the final safety visit.
- Colitis ulcerative was the most frequently reported AE (26.2% [27] of subjects) and serious adverse event (SAE; 6.8% [7] of subjects).
- There were no deaths reported.
- There was 1 report of an SAE of megacolon.
- One subject reported a serious infection of pneumonia through Week 6.
- There were 2 malignancies reported: 1 basal cell carcinoma of the skin, and 1 squamous cell carcinoma of the cervix.
- There was 1 report of nonserious opportunistic infections, and no reports of TB.

- There were no reports of systemic lupus erythematosus or lupus-like disorders.
- Markedly abnormal changes in hematology and chemistry laboratory values were uncommon.
- No relationship was identified between the development of antibodies to golimumab and injection-site reactions.

STUDY LIMITATIONS:

The 2 maintenance doses (50 mg q4w and 100 mg q4w) were not randomly assigned but followed regional posology guidelines in each country. Therefore, the interpretation of results was based on the total number of subjects treated, though results by dose groups are also presented in the tables. Caution should be exercised when comparing the 2 maintenance groups.

CONCLUSIONS:

- The accuracy of the length-13 probe set panel was better than chance in predicting mucosal healing at Week 6 and at Week 30. However, for other endpoints, the accuracy of the length-13 probe set panel was not better than chance.
- Golimumab was generally well tolerated in this population of adult subjects with moderately to severely active UC and the safety results were consistent with the known safety profile of golimumab in patients with UC.

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