Janssen Research & Development

Clinical Study Report Synopsis
[Protocol REMICADEUCO3001; Phase 3]

CNTO312 (infliximab)

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SYNOPSIS

Name of Sponsor/Company	Xi'an Janssen Pharmaceutical Ltd.
Name of Finished Product	REMICADE®
Name of Active Ingredient(s)	CNTO312 (infliximab)

Status: Approved
Date: 21 October 2014
Prepared by: Xi'an Janssen Pharmaceutical Ltd.

Protocol No.: REMICADEUCO3001

Title of Study: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Infliximab in Chinese Subjects With Active Ulcerative Colitis

NCT No.: NCT01551290

Clinical Registry No.: CR018769

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

Study Center(s): 12 centers in China.

Publication (Reference): None

Study Period: 26 March 2012 to 26 March 2014

Phase of Development: Phase 3

Objectives:

Primary Objective: The primary objective of this study was to evaluate the safety and efficacy of infliximab, in comparison with placebo, in subjects with active ulcerative colitis (UC). The primary efficacy endpoint was the proportion of subjects with a clinical response, defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1, at Week 8.

Secondary Objectives: The major secondary objectives were:

- To determine the proportion of subjects in clinical remission at Week 8, defined as a Mayo score of ≤2 points, with no individual subscore >1, at Week 8.
- To determine the proportion of subjects who demonstrated mucosal healing at Week 8.
- To determine the proportion of subjects with clinical response at Week 26.
- To determine the proportion of subjects in clinical remission at Week 26.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of infliximab in Chinese subjects with active UC. Subjects were to be randomized to receive either placebo or infliximab at 5 mg/kg in a 1:1 ratio. Induction dosing was to be given at Weeks 0, 2, and 6 via intravenous infusion; maintenance dosing was to be followed at Weeks 14

and 22. A subject was to be considered to have completed the study if he or she completed the study treatment through Week 22 and assessments at Week 26 in the main study.

Subjects completing treatment of Week 22, who, in the opinion of the investigator, might benefit from continued treatment, may enter a study extension from Week 30 to Week 60.

Number of Subjects (planned and analyzed): A total of 100 subjects were planned to be enrolled in the study, approximately. Actual number of subjects in each analysis set is presented as below:

Data Sets Analyzed
(REMICADEUCO3001: All Randomized Analysis Set)

	Placebo (N=49) n (%)	Infliximab (N=50) n (%)	Total (N=99) n (%)
All randomized subjects	49 (100)	50 (100)	99 (100)
Safety	49 (100)	50 (100)	99 (100)
Intent-to-Treat	49 (100)	50 (100)	99 (100)
Per-protocol	49 (100)	50 (100)	99 (100)

Note: Percentages calculated with the number of subjects in each group as denominator.
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Diagnosis and Main Criteria for Inclusion: Men or women aging 18 to 80 years old; active UC confirmed at baseline with Mayo score of 6 to 12, despite the therapy of corticosteroids, azathioprine, 6-mercaptopurine (6-MP) or 5-aminosalicylic acid (5-ASA).

Test Product, Dose and Mode of Administration, Batch No.: Infliximab for intravenous infusion at 5 mg/kg was to be given at Weeks 0, 2, 6, 14, and 22. Four batches were used in the main study: ADM32011, BLM99014, BHD61014, and DDM30014.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for intravenous infusion was also to be given at Weeks 0, 2, 6, 14, and 22. Two batches were used in the main study: AFX43013 and BFX39012.

Duration of Treatment: Treatment duration for the main study was 22 weeks with a follow-up visit on Week 26.

Criteria for Evaluation:

Efficacy Evaluations/Criteria: Clinical response at Weeks 8 and 26 were defined as a decrease from baseline in the Mayo score by ≥30% and ≥3 points, with a decrease in the rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1. Clinical remission at Weeks 8 and 26 were defined as a Mayo score of ≤2 points, with no individual subscore >1. Mucosal healing was defined as endoscopy subscore of 0 or 1.

The Mayo score was calculated according to the Truelove and Witts criteria.

Safety Evaluations: Safety evaluations included adverse events (AEs), clinical laboratory tests (hematology and serum chemistry), vital signs, physical examinations, signs and symptoms of active tuberculosis (TB). Adverse events were monitored throughout the study. Signs and symptoms of active TB were to be evaluated at each study visit.

Statistical Methods:

Sample Size Determination: Based on previously observed data, the expected clinical response rate (Week 8) of infliximab therapy was around 64.5% while that of placebo was 29.3%. With the allocation ratio of 1:1, a sample size of 40 subjects per group were to provide 90% power to demonstrate the

superiority at a two-sided significance level of 0.05. Considering 20% dropout rate, the suggested sample size was 50 subjects per treatment group and 100 subjects in total.

Analysis Sets: Intent-to-treat analysis set (ITT): included all randomized subjects who received at least 1 infusion of study agent, including partial infusion; Per protocol analysis set (PP): excluded subjects with at least 1 of the pre-specified major deviations; Safety analysis set (SS): included all randomized subjects who received at least 1 infusion of the study agent, including partial infusion.

Statistical Analyses: The demographic and baseline characteristics, efficacy assessment, and safety assessment were to be summarized and described by treatment groups. For categorical variables, descriptive statistics included frequency and percentage; for continuous variables, descriptive statistics included number of cases, mean, standard deviation, median, minimum, and maximum. In general, all hypothesis testing was to be conducted using a 2-sided test (α=0.05), and all interval estimations were to be reported using 2-sided 95% confidence interval (CI).

Efficacy Analyses: Cochran-Mantel-Haenszel (CMH) test was to be performed for between-group comparison, controlling for effects of baseline corticosteroid refractory status. If p-value was less than 0.05 (two sided), the difference between the 2 treatment groups was to be deemed as statistically significant.

Safety Analyses: Adverse events were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology (Version 16.0) and was to be categorized by system organ class (SOC) and preferred term (PT). All AEs were to be summarized by the following categories: treatment emergent adverse events (TEAEs), study agent related AEs, serious adverse events (SAEs), death, discontinuation of study agent due to an AE, AEs of interest. Descriptive analyses were to be performed on hematology, serum chemistry, physical examinations, and vital signs by treatment groups at each scheduled time point and change from baseline.

RESULTS:

This report covers the results of the main study (Week 0 - Week 26).

STUDY POPULATION:

A total of 99 subjects were enrolled in the study (infliximab group: 50 subjects; placebo group: 49 subjects). Overall, 94 subjects completed the main study and 5 subjects discontinued from the study, with the main reason of AE.

Subjects had a median age of 37 years. The median duration of UC was 3.7 years, 28 out of 99 subjects were refractory to corticosteroids, and the median total Mayo score was 8.0 at baseline. For concomitant medications, the proportion of subjects with baseline immunomodulatory agents and aminosalicylates were similar between the 2 treatment groups; whereas 60% of subjects in the infliximab group and 80% of subjects in the placebo group had baseline corticosteroids.

Thirteen subjects were reported to have at least 1 major protocol deviation: 6 subjects received prohibited concomitant treatment, 2 subjects entered the study but entry criteria not met, and 1 subject received the wrong treatment or incorrect dose. Seven subjects were reported with protocol deviation for "other" reasons (3 subjects' lab tests not done at screening, 1 subject skipped Week 6 infusion; 2 subjects had isoniazide treatment less than 6 months, 1 subject did not have baseline Mayo score).

All subjects received at least 1 dose of the study agent during the main study. Overall, 95 (96%) subjects (47 in the placebo group and 48 in the infliximab group) had received all 5 scheduled study agent infusions, and 4 (4%) subjects (2 in each group) had received 2 study agent infusions.

EFFICACY RESULTS:

Primary Efficacy Results: The number of subjects who achieved clinical response at Week 8 was higher in the infliximab group compared with the placebo group (32 [64%] subjects vs 16 [33%] subjects, p=0.0021). Four sensitivity analyses showed consistent results.

Secondary Efficacy Results:

Clinical Remission at Week 8 and Week 26: At Week 8, 11 (22%) subjects achieved clinical remission in the infliximab group and 5 (10%) subjects in the placebo group (p=0.1233). At Week 26, 14 (28%) subjects achieved clinical remission in the infliximab group and 5 (10%) subjects in the placebo group, with p-value of 0.0281.

Mucosal Healing at Week 8: At Week 8, 17 (34%) subjects achieved mucosal healing in the infliximab group compared with 8 (16%) subjects in the placebo group, with p-value of 0.0451.

Clinical Response at Week 26: At Week 26, 29 (58%) subjects achieved clinical response in the infliximab group and 26 (53%) subjects in the placebo group (p=0.6638).

Corticosteroid Related Endpoints: Among subjects who received corticosteroids at baseline, the proportion of subjects in clinical remission at Week 26 without corticosteroids for at least 1 month was higher in the infliximab group than the placebo group (17% [5/30] vs 3% [1/39], p=0.0428); the proportion of subjects in clinical response at Week 26 without corticosteroids was also higher in the infliximab group than the placebo group (33% [10/30] vs 5% [2/39], p=0.0026).

Mucosal Healing at Week 26: At Week 26, 20 (40%) subjects achieved mucosal healing in the infliximab group compared with 13 (27%) subjects in the placebo group (p=0.1781).

Sustained Response (clinical response at both Week 8 and Week 26): 27 (54%) subjects in the infliximab group and 12 (24%) subjects in the placebo group had sustained response (p=0.0032).

Sustained Remission (clinical remission at both Week 8 and Week 26): 7 (14%) subjects in the infliximab group compared with 2 (4%) subjects in the placebo group achieved sustained remission (p=0.0926).

C-reactive Protein: A notable decrease from baseline in the mean CRP concentration was observed in the infliximab group compared with the placebo group (-4.2 [median -1.8] vs 2.1 [median 0.0], respectively) at Week 2. At Week 8, the mean decrease from baseline in CRP concentration was significantly greater in the infliximab group than in the placebo group (-5.0 [median -1.3] vs -1.5 [median -0.2], respectively; p=0.0256). At Week 26, the mean decrease from baseline in CRP concentration was also greater in the infliximab group than in the placebo group (-1.6 [median -0.6] vs 2.4 [median 0.0], respectively, p=0.0896).

Quality of Life: The mean improvements of total IBDQ score in the infliximab group reached the threshold (clinical meaningful change) of 20 points and were greater than the placebo group at both Week 8 and Week 26.

SAFETY RESULTS:

Of all subjects enrolled, 64 subjects reported TEAEs (33 [66.0%] subjects in the infliximab group and 31 [63.3%] subjects in the placebo group). Study agent related TEAEs were reported in 8 (16.0%) subjects in the infliximab group and 5 (10.2%) subjects in the placebo group. The most commonly reported TEAEs by SOC were Gastrointestinal disorders (infliximab group: 11 [22.0%] subjects; placebo group: 18 [36.7%] subjects), followed by Blood and lymphatic system disorders (6 [12.0%] subjects vs 17 [34.7%] subjects), Infections and infestations (13 [26.0%] subjects vs 7 [14.3%] subjects), and Metabolism and nutrition disorders (7 [14.0%] subjects vs 10 [20.4%] subjects). The most frequently reported TEAE by

PT amongst Gastrointestinal disorders was Colitis ulcerative, which was reported in 6 (12.0%) subjects in the infliximab group and 16 (32.7%) subjects in the placebo group.

Seven (14.0%) subjects in the infliximab group and 4 (8.2%) subjects in the placebo group had treatment-emergent SAEs. The most frequently reported SAE by SOC was Gastrointestinal disorders (infliximab group: 4 [8.0%] subjects; placebo group: 3 [6.1%] subjects) and by PT was Colitis ulcerative (aggravation) (infliximab group: 3 [6.0%] subjects; placebo group: 3 (6.1%) subjects). All treatment-emergent SAEs were considered as not related to the study agent.

Four (8.0%) subjects in the infliximab group and 2 (4.1%) subjects in the placebo group had TEAEs resulting in study agent discontinuation. None were considered as related to the study agent.

Two subjects (one in each treatment group) had TEAE leading to study agent discontinuation after they completed the main study. The TEAE of optic ischemic neuropathy reported in subject [redacted] (infliximab group) was considered as possible related to the study agent.

During the main study, 14 (28.0%) subjects in the infliximab group and 8 (16.3%) subjects in the placebo group reported TEAEs of interest. The most frequently reported TEAEs of interest by SOC were infections and infestations and by PT was upper respiratory tract infection and nasopharyngitis. No reported infection was severe in intensity. No auto immune disease or malignancy was reported through the main study. No opportunistic infection included active TB was reported.

No deaths were reported during the main study.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

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