# SYNOPSIS

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| Name of Sponsor/Company | Janssen Korea |
| Name of Investigational Product | CNTO312  Infliximab |

**Status:** Approved

**Date:** 22 August 2019

**Prepared by:** Janssen Korea

**Protocol No.:** REMICADEBEC3001

**Title of Study:** An Interventional, Open-label, Single Arm, Multicenter Study to Evaluate Efficacy and Safety of Infliximab in Subjects with Moderate-to-Severe Refractory Intestinal Behçet's Disease

**Study Name:** BEGIN

**EudraCT Number:** NA

**NCT No.:** NCT02505568

**Clinical Registry No.:** CR107121

**Coordinating Investigator(s):** Jae hee Cheon, MD – Severance Hospital, ███ Korea

**Study Center(s):** 9 centers in Korea

**Publication (Reference):** None

**Study Period:** 17 Aug 2015 to 13 Jul 2018; database lock, 17 Dec 2018

**Phase of Development:** Phase 3

**Objectives:** The primary objectives of this study were to evaluate the efficacy of induction regimen of infliximab by assessing whether the mean of the decrease in Disease Activity Index for intestinal Behçet's disease (DAIBD) score from baseline to Week 8 is 20 or more in subjects with active intestinal Behçet's disease (BD) who are refractory to conventional therapies AND to evaluate the efficacy of the maintenance regimen of infliximab by assessing whether the mean of the decrease in DAIBD score from baseline to Week 32 is 20 or more.

The secondary objectives were to evaluate the efficacy and safety of infliximab including maintenance regimen in :

- Changing of Disease activity indexes
- Changing of C-reactive protein (CRP)
- Inducing Mucosal healing
- Safety

**Methodology:** This was a phase 3, interventional, open label, single arm study conducted at multiple sites in Korea that evaluated the clinical outcomes of infliximab in subjects with intestinal type of BD. The planned total sample size was 31 subjects.

This study consisted of a screening phase (within 4 weeks prior to Week 0), induction phase (Week 0 to Week 8), maintenance phase (Week 8 to Week 32) and safety follow up period (at Week 36 or approximately 6 weeks after the last infusion of infliximab).

Eligible subjects were enrolled in the induction phase, received 5mg/kg infliximab infusion at Week 0, Week 2, and Week 6 and were evaluated for the induction phase at Week 8. The subjects who completed the induction phase according to the protocol continued participation in the maintenance phase, irrespective of their clinical response at Week 8. They continued to receive 5mg/kg infliximab infusion at Week 14, Week 22, and Week 30 and clinical outcomes were evaluated for the maintenance phase at Week 32.

The data for efficacy evaluations were collected at every visit from Week 0 to Week 32 and the co-primary endpoints was assessed based on the data of Week 8 (induction phase) and Week 32 (maintenance phase). Subjects were to be followed up for adverse events (AEs) and serious adverse events (SAEs) at least 6weeks following their last infusion of infliximab (i.e., Week 36 or early termination). The end of study was defined as the time when the last subject completed the Week 32 visit.

**Diagnosis and Main Criteria for Inclusion:** The target population consisted of adult men or women 19 to 75 years of age at the time of informed consent with active intestinal BD defined as DAIBD score $\geq 40$ and endoscopy with evidence of active intestinal BD (defined as ulcerations in the ileum and/or colon). Subjects had to have demonstrated a failure of conventional therapy using oral corticosteroid or immunomodulators.

**Test Product, Dose and Mode of Administration, Batch No.:** Infliximab was supplied as a sterile, white, lyophilized powder for intravenous (IV) infusion. Following reconstitution with 10mL of Sterile Water for Injection (SWFI), the resulting pH was approximately 7.2. No preservatives were present. It was supplied in 100mg single-use vials containing the following formulation: 10.0mg infliximab, 50.0mg sucrose, 0.05mg polysorbate 80, 0.22mg monobasic sodium phosphate monohydrate and 0.61mg dibasic sodium phosphate dihydrate. Infliximab batch numbers were 4371080, 4372220, HEL23015.A: Subjects treated with infliximab received 5mg/kg infusion via IV administration at Week 0, Week 2, Week 6, Week 14, Week 22 and Week 30.

**Duration of Treatment:** Subjects received infliximab 5mg/kg for 8 weeks in the induction phase followed by infliximab 5mg/kg for additional 24 weeks in the maintenance phase. After completion of the maintenance phase, subjects completed 4 weeks of safety follow up period after the last evaluation at Week 32.

**Criteria for Evaluation:**

*Efficacy:* Co-Primary endpoints were the mean decrease in DAIBD score of 20 or more at Week 8 from baseline for induction phase and mean decrease in DAIBD score of 20 or more at Week 32 from baseline for maintenance phase. The secondary endpoints were the time to reach clinical remission at Week 32, the proportion of subjects with mucosal healing at Week 32, the proportion of subjects who achieve clinical response (DAIBD score change $\geq 20$) at Week 8 and Week 32, the proportion of subjects with clinical remission (DAIBD score $\leq 19$) at Week 8 and Week 32, the proportion of subjects achieving Crohn's disease activity index (CDAI) 70 response at Week 8 and Week 32, the change in CDAI score from baseline at Week 8 and Week 32, and the change in CRP concentration from baseline at Week 8 and Week 32. *Safety:* Safety evaluations included assessment of adverse events, clinical laboratory tests (hematology and serum chemistry at all visits and serology for HIV antibody, hepatitis B surface antigen (HBsAg), and HCV antibody at screening only), electrocardiogram, vital signs, physical examination, weight, concomitant medication review, infusion reactions, allergic reactions, infections, and tuberculosis (TB).

**Statistical Methods:** Descriptive summary statistics, number (n) and percentage of subjects in each category for categorical parameters, and n, mean, standard deviation (SD), median, minimum (min), and maximum (max) values were used to summarize data for continuous parameters.

The sample size was calculated under the fixed sequence method approach to evaluate the efficacy of infliximab induction regimen and maintenance regimen for 2 statistical tests. Each statistical testing was based on the assumption of achieving 99% statistical power with two-sided significance level 0.05 using two-sided one-sample test. The sample size was calculated to identify the mean of decrease of DAIBD score by 20 or more from baseline to Week 32 among subjects who achieved clinical response in the induction phase (evaluation for the efficacy of maintenance regimen), only if the mean decrease of DAIBD score was identified to be 20 or more from baseline to Week 8 and significant (evaluation for the efficacy of induction regimen). The assumption of clinical responder rate of 0.57 in the induction phase was from one retrospective BD study in Korea. With an expected drop-out rate 5% respectively in each phase (induction and maintenance), an overall sample of 31 patients was required.

Efficacy analyses and summaries of subject information were performed using the full analysis set 1 (FAS1; all subjects who received at least 1 dose of study agent and have both baseline and at least one post-baseline efficacy assessment for the induction regimen) for induction phase and full analysis set 2 (FAS2; all subjects who completed the induction phase and received at least 1 dose of study agent in the maintenance phase) for maintenance phase. Safety analyses were performed using the safety analysis set 1 (SS1; all subjects who received at least 1 dose of infliximab in the induction phase) for induction phase and safety analysis set 2 (SS2; all subjects who received at least 1 dose of infliximab in the maintenance phase). A full safety analysis set (all subjects who received at least 1 dose of infliximab) were used for the total safety analyses of the study.

**RESULTS:**

STUDY POPULATION:

A total of 50 subjects were screened and 33 subjects entered the induction phase and were treated with infliximab 5mg/kg IV. Of the 33 subjects whom completed the induction phase, 2 subjects did not continue to enter the maintenance due to adverse event and withdrawal of consent, respectively. Thirty-one subjects continued to receive 5mg/kg infliximab in the maintenance phase regardless of their clinical response to the induction regimen. Of the 31 subjects, 2 subjects withdrew during the maintenance phase due to loss of response to the study agent and AE, respectively.

INDUCTION PHASE

The mean age at baseline of the 33 subjects in the induction phase 50.8±12.27 years. The mean duration of intestinal BD was 5.39±4.787 years, with all 'typical ulcer' type. For the type of intestinal BD, 26 (78.8%) subjects had 'definite' type and 7 (21.2%) subjects had 'probable' type.

MAINTENANCE PHASE

The mean age at baseline of the subjects in the maintenance phase was 52.2±12.70 years. The mean duration of intestinal BD was 5.39±5.452 years, with all 'typical ulcer' type. For the type of intestinal BD, 19 (73.1%) subjects had 'definite' type and 7 (26.9%) subjects had 'probable' type.

EFFICACY RESULTS:

INDUCTION PHASE

Induction with infliximab 5mg/kg IV at Week 0, 2, and 6 demonstrated statistically significant efficacy outcome in subjects with moderate-to-severe refractory intestinal BD. From analysis of primary endpoint at Week 8, the mean of decrease in DAIBD score was more than 20 from Week 0. The infliximab treated

subjects also showed improvement in the secondary endpoints; clinical response, clinical remission, change of CDAI score from baseline, CDAI 70 response and change in the CRP concentration.

Primary Endpoint at Week 8

*20 or more decrease of the mean DAIBD score*

- The mean DAIBD score changed from 90.8±40.12 at baseline to 40.3±36.44 at Week 8 in the subjects treated with infliximab 5mg/kg IV, with a statistically significant mean change of 50.5±36.43 (95% C.I. = [37.54, 63.37], p<0.0001). Sensitivity analyses confirmed the robustness of the results.

- In subgroup analyses, the biggest mean decrease of DAIBD score was in the subjects with 'probable' type of intestinal BD, which was 69.3±35.87. Whereas the smallest mean decrease was observed in subjects that had disease duration less than 5 years which was 26.9±24.78.

Secondary Endpoints at Week 8

*Clinical response (DAIBD score change ≥ 20), and clinical remission (DAIBD score ≤ 19)*

- The proportion of subjects with clinical response was shown to be 75.8% at Week 2 and 78.8% at Week 8.

- The proportion of subjects with clinical remission was 15.2% at Week 2 and 30.3% at Week 8.

*CDAI 70 response and CDAI score change*

- The proportion of subjects whose CDAI score decreased by more than 70 points was 72.7% at Week 8.

- The mean change of CDAI score from baseline to Week 8 was 110.7±87.86.

*Change in CRP concentration*

- The mean change of the CRP concentration from baseline to Week 8 was 15.68±34.309mg/L.

MAINTENANCE PHASE

Maintenance therapy with infliximab 5mg/kg IV demonstrated efficacy in the of moderate-to-severe refractory intestinal BD subjects with clinical response to infliximab 5mg/kg IV at Week 8 in the induction phase of this study. In the efficacy analyses of the 24-week maintenance phase, infliximab 5mg/kg IV infusion at Week 14, 22 and 30 showed a statistically significant change in DAIBD score of 20 or more at Week 32. Infliximab maintenance therapy also showed improvement in the secondary endpoints including clinical response, clinical remission, change of CDAI score, CDAI70 response and change of CRP concentration.

Primary Endpoint at Week 32:

*20 or more decrease of the mean DAIBD score*

- The mean DAIBD score of the subjects included in the maintenance phase was 94.2±37.81 at Week 0 and 32.7±32.10 at Week 32, with a statistically significant mean change of 61.5±38.49 (95% C.I. = [45.99, 77.09], p<0.0001) from Week 0 to Week 32. Sensitivity analyses confirmed the robustness of the results.

- In subgroup analyses, the largest mean decrease in the DAIBD score was 85.0±28.46 in the subject with disease duration of 5 years or more. Whereas the smallest mean decrease was reported as 16.3±31.98 in the subject with disease duration less than 5 years.

Secondary Endpoints at Week 32:

*Mucosal healing*

- The longest mean diameter of open ulcer at Screening and Week 32 were 2.95±1.840cm and 0.85±0.963cm, respectively, both in the terminal ileum/ileocecal valve. The mean reduction ratio of open ulcer from Week 0 to Week 32 was 0.651±0.4058. By predefined mucosal healing grade, 37.5% of subjects were evaluated to achieve mucosal healing.

*Clinical response (DAIBD score change ≥ 20), and clinical remission (DAIBD score ≤ 19)*

- The proportion of subjects with clinical response was 92.3% at Week 32.

- The proportion of subjects who experienced clinical remission during the study was 53.8% and the mean time to first clinical remission was 65.4±62.18 days.

- The proportion of subjects with clinical remission was 30.8% at Week 14 and 38.5% at Week 32.

*CDAI 70 response and CDAI score change*

- The proportion of subjects that had 70 or more reduction in CDAI score was 84.6% at Week 32.

- The mean change of CDAI score from Week 0 to Week 32 was 151.3±83.34.

*Change in CRP concentration*

- The mean change of the CRP concentration from Week 0 to Week 32 was 16.13±35.748mg/L.

SAFETY RESULTS:

INDUCTION PHASE

Infliximab 5mg/kg IV at Weeks 0, 2, and 6 to subjects with intestinal BD was generally well tolerated through Week 8, the induction phase.

Overall 15 subjects (45.5%) reported 33 events of AEs through Week 8. All 15 subjects reported 26 events of treatment emergent adverse events (TEAEs) and 1 subject (3.0%) reported 1 event of adverse drug reaction (ADR). Two subjects (6.1%) reported 2 events of treatment emergent SAEs which were not ADRs.

- Overall, gastrointestinal disorders were the system organ class (SOC) in which the highest proportion of subjects reported TEAEs which was 21.2% (7 subjects) and the most common TEAE was abdominal pain in 9.1% (3 subjects) of subjects.

- One subject had 1 event (3.8%) of severe TEAE which was asthenia and other TEAEs were mild (80.8%) and moderate (15.4%) in intensity.

- No subject had TEAEs with fatal outcome and most of the TEAEs were recovered. Three TEAEs, asthenia, neurodermatitis and arthralgia were not recovered during the induction phase.

- Most of the TEAEs were assessed as 'not related' (96.2%) to the study agent. Only 1 TEAE event, urticaria was assessed to be 'possible' in causality to the study agent.

- No death reported during the induction phase.

- Two subjects reported 2 events of treatment-emergent SAEs, abdominal pain and asthenia. Both treatment-emergent SAEs required hospitalization and were assessed as 'not related' to the study agent, thus there were no serious ADRs during the induction phase.

- Seven subjects (21.2%) reported 12 events of intestinal BD related TEAEs. Abdominal pain was the most commonly reported intestinal BD related TEAE in 2 subjects (6.1%) with 1 event each and 1 of the events was considered as a treatment emergent SAE.

- Treatment emergent AEs that were infections occurred in 3 subjects (9.1%) with 3 events. All 3 infections, clostridium difficile infection, nasopharyngitis and onychomycosis were reported as not related to the study agent.

- There were no infusion reactions during the induction phase.

- Tuberculosis assessments were not performed because there no subjects suspected for TB infection through the TB evaluation during the maintenance phase.

MAINTENANCE PHASE

Overall 16 subjects (51.6%) reported 54 events of AEs in the maintenance phase. Of these AEs, 42 events in 14 subjects (45.2%) were TEAEs. There were 7 events in 5 subjects (16.1%) with ADRs. Four subjects (12.9%) reported 6 events of SAEs which were all treatment-emergent SAEs and none were assessed as serious ADRs.

- Overall gastrointestinal disorders were the SOC in which the highest proportion of TEAEs were reported with 19.4%. Of the gastrointestinal disorders, abdominal pain was the most common TEAE with 9.7%.

- One subject experienced severe TEAE of abdominal pain and other TEAEs were assessed as mild (73.8%) and moderate (23.8%) in intensity.

- No TEAEs with fatal outcome. Among reported TEAEs, 61.9% were recovered and 23.8% were not recovered.

- Most of the TEAEs were assessed as 'not related' (83.3%) to the study agent.

- Adverse drug reactions were reported for 5 subjects (16.1%) in 7 events; 2 events of rash and 1 event each in dyspnoea, pruritis, paraesthesia, liver function test increased and arthralgia.

- No death was reported during the maintenance phase.

- Treatment-emergent SAEs occurred in 4 subjects (12.9%) with 6 events. All SAEs required hospitalization and were reported as not related to the study agent. The most common SAE was abdominal pain in 3 subjects (9.7%) with 4 events.

- No serious ADR occurred during the maintenance phase.

- Two subjects discontinued the study agent due to AEs, which were breast cancer and pruritis. Both AEs were reported as not related to the study agent.

- Intestinal BD related TEAEs occurred in 7 subjects (22.6%) with 19 events. Abdominal pain was the most commonly reported intestinal BD related TEAE in 3 subjects (9.7%) with 6 events.

- Treatment emergent AEs that were infections occurred in 6 subjects (19.4%) with 6 events. The infections were nasopharyngitis in 4 subjects (12.9%), and anal abscess and cystitis each in 1 subject (3.2%).

- Two subjects (6.5%) experienced 1 or more infusion reactions. The infusion reaction TEAEs were pruritus, rash, paraesthesia and dyspnoea.

- Tuberculosis assessments were not performed because there no subjects suspected for TB infection through the TB evaluation during the maintenance phase.

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