SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	CNTO1275 USTEKINUMAB

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Status: Approved

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Prepared by: CTI Clinical Trial & Consulting Services Portugal, Unipessoal LDA

Protocol No.: CNTO1275CRD3006

Title of Study: AN EARLY ACCESS PROGRAM FOR USTEKINUMAB IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE CROHN'S DISEASE

Study Name: EAP STELARA

EudraCT Number: NA

NCT No.: NA

Clinical Registry No.: NCT03362736 (clinicaltrials.gov identifier) and CR108395 (Other Study ID number)

Coordinating Investigator(s): NA

Study Center(s): 6 sites in Brazil

Publication (Reference): Not applicable

Study Period: 17 October 2017 (Date first subject signed informed consent) to 12 November 2019 (Date of last observation for last subject recorded as part of the database)

Phase of Development: EAP

Objectives:

The objective(s) of this study were:

1) to provide early access to ustekinumab where it was commercially unavailable for the treatment of patients with moderately to severely active Crohn's disease who had failed treatment with conventional Crohn's disease therapy (e.g., immunomodulators or corticosteroids) and TNFα antagonist therapy (e.g., infliximab, adalimumab, certolizumab pegol, or their biosimilars), or who were intolerant to, or have a contraindication to these treatments. During the course of this EAP, through the reporting of SAEs and non-serious ADRs by participating physicians, information on the safety and tolerability of ustekinumab was captured.

2) To observe the effectiveness of ustekinumab for the treatment of moderately to severely active Crohn's disease among patients who had failed treatment with conventional Crohn's disease therapy (e.g.,

immunomodulators or corticosteroids) and TNFα antagonist therapy (e.g., infliximab, adalimumab, certolizumab pegol, or their biosimilars), or who were intolerant to, or had a contraindication to these treatments. The impact of ustekinumab on Crohn's disease was assessed by measuring clinical response and clinical remission in response to ustekinumab treatment with clinician reported instruments that are typically used in clinical practice, such as CDAI and the Harvey-Bradshaw Index (HBI). In addition, the impact of ustekinumab on Crohn's disease was also assessed by measuring CRP and fecal calprotectin.

Methodology:

This was a multicenter, open-label, early access treatment program of a single agent, ustekinumab, in adult patients suffering from moderately to severely active Crohn's disease who resided in Brazil. This EAP captured pertinent and relevant information on the safety of ustekinumab in order to ensure the safe and appropriate use of ustekinumab on patients. The expected total sample size was approximately 50 patients.

Number of Subjects (planned and analyzed): A total of 47 patients were screened for this study. From those, 38 (80.9%) were eligible, six (12.8%) were not eligible but proceed for the induction period visit (IPV) and three (6.4%) were screening failures. Thirty-four (77.3%) patients completed the EAP study and ten (22.7%) were early discontinued. Overall, 44 (93.6%) patients were included in the safety population.

Diagnosis and Main Criteria for Inclusion:

The target population consisted of men or women ≥18 years of age at the time of informed consent with moderately to severely active Crohn's disease (of at least 3 months duration), who had failed treatment with conventional Crohn's disease therapy (e.g., immunomodulators or corticosteroids) and TNFα antagonist therapy (e.g., infliximab, adalimumab, certolizumab pegol, or their biosimilars), or who were intolerant to, or had a contraindication to these treatments. Patients must have had colitis, ileitis, or ileocolitis previously confirmed at any time in the past by radiography, histology, and/or endoscopy.

The TNFα antagonist therapies, infliximab, adalimumab, and certolizumab pegol have been shown to reduce signs and symptoms and induce and maintain response and/or remission in the majority of patients for whom they are indicated. However, the populations treated with ustekinumab in Phase IIb and Phase III studies had previously failed to respond, lost response, or had been intolerant to one or more of these TNFα antagonist therapies or conventional Crohn's disease therapies. Therefore the proposed population in this EAP is one that lacks good therapeutic alternatives.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab is formulated as a sterile liquid for intravenous (IV) administration in a glass vial during induction, followed by a maintenance dose administered subcutaneously (SC) with a single-use pre-filled syringe (PFS). For the most comprehensive nonclinical and clinical information regarding ustekinumab, refer to the latest version of the Investigator's Brochure and Addenda for ustekinumab (CNTO1275 IB Ed 18, 13 April 2017) and the Summary of Product Characteristics (SmPC) for Stelara® in Brazil (Stelara® SmPC, 2017).

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

Duration of Treatment: The program was conducted in two phases: a Screening Phase (approximately 30 days prior to administration of first dose) and a Program Treatment Phase (including the induction period - week 0 - and maintenance period – week 8 to week 80) to continue until safety follow-up visit. A patient was automatically withdrawn from the program for any of the following reasons: lost to follow-up; withdrawal of consent; death; sponsor decision; an AE or lack of clinical response to treatment; discontinuation of program treatment for any reason.

Criteria for Evaluation: Safety was evaluated by the participating physician. The sponsor's safety team was provided on a routine basis with safety data collected locally, and assessed for new signals. New safety findings were communicated to all sites, following local regulations and Sponsor procedures.

Safety was evaluated based on:

- Adverse events
- Clinical laboratory tests (hematology, chemistry, urinalysis, stool sample, serology)
- Physical examinations
- ECGs
- Vital sign measurements
- Concomitant medication review
- Infusion reactions
- Injection site reaction
- Allergic reactions
- Additional assessments: tuberculosis (TB) infection

Additional evaluations:

- Crohn's Disease Activity index (CDAI)
- Harvey-Bradshaw index (HBI)
- C-reactive protein (CRP)
- Fecal calprotectin
- Colonoscopy
- Effectiveness: clinical response, clinical remission, normalization of CRP and fecal calprotectin

Statistical Methods: The sample size for this program was not determined according to statistical calculations. It was expected that approximately 50 patients would be enrolled.

Data is summarized using descriptive statistics for all patients who signed the ICF, and that received at least one dose of ustekinumab. Continuous variables are summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical variables are summarized using the number of observations and percentages as appropriate.

RESULTS:

Of the 47 patients screened for this study, 3 (6.4%) were screening failures. Thirty-four (77.3%) patients completed the EAP study and ten (22.7%) were early discontinued. Overall, 44 (93.6%) patients were included in the safety population.

Patients' mean age was 39.93±13.81 years, 52.3% were female and all reported at least one medical condition. At induction period, all patients received ustekinumab intravenously with mean dose of 387.05 mg for approximately 75 minutes of duration. At week 8, 65.9% of patients were allocated to a 8-week medication regimen and during the maintenance period all patients received subcutaneous ustekinumab, except for two patients. All patients were exposed to the same ustekinumab subcutaneous dosage (90 mg), across all study visits.

Activity of disease was assessed by Crohn's disease activity index (CDAI) and Harvey-Bradshaw index (HBI). The higher mean score for CDAI disease activity was observed in the screening visit (287.67 points), decreasing until week 32 to 85.65 points. At week 40/44 the mean score slightly increased to 99.63 points. Again decreasing until the last visit at week 80 (60.70 points). The same was observed for the disease activity assessed by HBI, with mean score of 11.54 points at screening decreasing constantly throughout visits at weeks 8, 16/20, 40/44, 64/68 and 80 (2.18 points).

Effectiveness was assessed by clinical response, endoscopic improvement, normalization of CRP and normalization of fecal calprotectin at weeks 16/20, 40/44 and 80. At week 16/20, 73.7% of patients [95%CI: 56.9%-86.6%] had clinical response assessed by CDAI, 74.3% [95%CI: 56.7%-87.5%] had clinical

response assessed by HBI, 76.3% of patients [95%CI: 59.8%-88.6%] achieved clinical remission, 38.1% of patients [95%CI: 23.6%-54.4%] had normalized CRP and 24.2% [95%CI: 11.1%-42.3%] had normalized fecal calprotectin. At the end of study, 93.8% [95%CI: 79.2%-99.2%] had clinical response in CDAI and 100.0% [95%CI: 88.8%-100.0%] in HBI, clinical remission was achieved by 87.9% of patients [95%CI: 71.8%-96.6%], and respectively 50% [95%CI: 31.9%-68.1%] and 41.4% of patients [95%CI: 23.5%-61.1%] had normalization of CRP and fecal calprotectin.

SAFETY RESULTS:

The primary endpoint results for this study were assessed through the reporting of SAEs and non-serious ADRs. Fifty-one SAEs or non-serious ADRs were reported by 23 patients, corresponding to 53.5% (95% confidence interval: 38.6% to 68.4%). The most frequent SAEs or non-serious ADRs were gastrointestinal disorders and infections and infestations, both in 25% of patients.

A total of 41 patients (93.2%; 95%CI: 85.7%-100.0%) reported at least one AE, in an overall number of 249 AEs reported. Fourteen SAEs were reported by 9 patients (20.5%; 95%CI: 8.5%-32.4%). Overall, gastrointestinal disorders were the adverse events with higher incidence (75.0%) in the study—36.4% abdominal pain, 22.7% Crohn's disease, 20.5% diarrhea—followed by infections and infestations (54.5%) and musculoskeletal and connective tissue disorders (31.8%). Overall, 171 (68.7%) AEs were mild, 69 (27.7%) were moderate and nine (3.6%) were severe. About 6% of the AEs were classified as "serious" by the investigators and all required inpatient hospitalization or prolongation of existing hospitalization. For 114 AEs no action was taken with the patients. However, pharmacological treatment was required for 108 AEs (43.4%) and for 13 (5.2%) there was hospitalization/prolongation of existing hospitalization. Seven (2.8%) AEs caused a temporary drug discontinuation, in six (2.4%) AEs there was dose adjustment and three (1.2%) led to permanent drug discontinuation.

The most frequent SAEs were infections and infestations (5 SAEs in 4 patients)—liver abscess (2), pneumonia, systemic viral infection and urinary tract infection—and gastrointestinal disorders (4 SAEs in 4 patients)—Crohn's disease, diarrhea, gastrointestinal hypermotility and intestinal obstruction. All SAEs reported had equal incidence of 2.3%, all occurring in 1 patient.

ADRs reported were aggravated infections and infestations (25.0%) and gastrointestinal disorders (20.5%)—aggravated Crohn's disease in 5 patients (11.4%), abdominal pain in 3 (6.8%). One drug hypersensitivity reaction was reported by one patient (2.3%).

Serology assessment was performed across all study visits. HIV, hepatitis B, hepatitis C and syphilis were tested and no positive results were found in these serologic assessments. Tuberculosis was not suspected in any subject throughout the study period.

The most frequent concomitant pharmacologic medications reported were from the alimentary tract and metabolism (75.0% of patients), antineoplastic and immunomodulating agents (70.5%) and nervous system (70.5%) groups.

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

CONCLUSION(S):

In conclusion, ustekinumab was considered safe, tolerable and effective for Crohn's disease. Adverse events reported were mostly mild or moderate and most of them not related to the study drug. Main ADRs reported were related with Crohn's disease. The effectiveness of the study drug was confirmed with the results achieved in the end of study, with clinical response in almost all patients and clinical remission in most of the sample.

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