SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Investigational Product	STELARA® (ustekinumab)

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Status: Approved

Date: 13 October 2015

Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1275CRD3002

Title of Study: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Safety and Efficacy of Ustekinumab Induction Therapy in Subjects with Moderately to Severely Active Crohn's Disease

Study Name: UNITI-2

EudraCT Number: 2010-022759-42

NCT No.: NCT01369342

Clinical Registry No.: CR018418

Coordinating Principal Investigator(s): Brian Feagan, MD - London Health Sciences Centre University Hospital, [redacted], Canada

Study Center(s): 175 sites in North America, South America, Eastern Europe, Western Europe, Asia Pacific, and South Africa.

Publication (Reference): None

Study Period: 23 Jun 2011 to 28 Oct 2014; database lock, 9 Sep 2014

Phase of Development: 3

Objectives: Primary: To evaluate the efficacy of intravenous (IV) induction regimens of ustekinumab in inducing clinical response in subjects with moderately to severely active Crohn's disease and to evaluate the safety of IV induction regimens of ustekinumab in subjects with moderately to severely active Crohn's disease. Secondary: To evaluate the efficacy of IV induction regimens of ustekinumab in inducing clinical remission; to evaluate the efficacy of IV induction regimens of ustekinumab in improving disease-specific health-related quality of life; to evaluate the pharmacokinetics and pharmacodynamics of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other pharmacodynamic biomarkers; and to provide, along with induction study CNTO1275CRD3001, the target study population to be evaluated in the maintenance study CNTO1275CRD3003.

Methodology: In this randomized, double-blind, placebo-controlled, parallel-group, multicenter study, subjects were randomized in a 1:1:1 ratio at Week 0 to receive a single IV administration of either placebo or 1 of 2 induction doses of ustekinumab (ustekinumab 130 mg or weight-range-based [hereafter referred to as "tiered"] ustekinumab doses approximating ustekinumab 6 mg/kg [~6 mg/kg]: ustekinumab 260 mg [weight ≤55 kg], 390 mg [weight >55 kg and ≤85 kg], or 520 mg [weight >85 kg]). At Week 6, all subjects were evaluated for the primary endpoint of clinical response. At Week 8, subjects who had been randomized to ustekinumab induction therapy at Week 0 and had been induced into clinical response at Week 8 were eligible to enter the maintenance study, CNTO1275CRD3003, as the primary efficacy population. Subjects who were not in clinical response to ustekinumab induction therapy, as well as all subjects who were initially receiving placebo (both in clinical response and not in clinical response), at Week 8 were eligible to enter the CNTO1275CRD3003 study, but were not included in the primary efficacy population. Subjects who did not enter the maintenance study were to have a safety follow-up visit approximately 20 weeks after the Week 0 study agent administration.

An independent Data Monitoring Committee (DMC) monitored subject safety data throughout the study. No interim analysis was conducted.

Number of Subjects (planned and analyzed): Per protocol, 600 subjects (200 per treatment group) were planned. The Sponsor temporarily suspended dosing of subjects in November 2011 because a stability issue was identified with the batch of the IV drug used in the study (130 mg ustekinumab in 26 mL [5 mg/mL]). Because knowledge of the stability issue could potentially bias the assessments, data from the 12 subjects who were randomized before the study was temporarily suspended were not used in the planned analyses. To maintain the originally planned sample size of 600 subjects, which was needed to power the primary endpoint analysis, the planned enrollment in the Statistical Analysis Plan was prospectively changed to 612 (600+12) subjects.

A total of 640 subjects were randomly assigned to receive study agent. Unless otherwise specified, all planned analyses were based on the 628 subjects who were randomized after the study was restarted: 210 in the placebo group, 209 in the ustekinumab 130 mg group, and 209 in the ustekinumab ~6 mg/kg group. Data for 1 subject were retrospectively excluded from the efficacy analyses because the Sponsor was unable to determine the accuracy and validity of the subject's data due to Good Clinical Practice concerns identified at the study site. The efficacy analyses were therefore based on 627 subjects. However, as a conservative approach, because this subject was confirmed to have received study agent, all available data were included in the safety and pharmacokinetic (PK) analyses. Safety and PK analyses were based on the 627 subjects who were randomly assigned and received the Week 0 dose of study agent (1 subject in the placebo group was randomized but did not receive study agent).

Diagnosis and Main Criteria for Inclusion: Eligible subjects had to be ≥18 years of age and have moderately to severely active Crohn's disease (of at least 3 months' duration), defined as a Crohn's Disease Activity Index (CDAI) score of ≥220 and ≤450 and at least 1 of the following: 1) an abnormal CRP (>3.0 mg/L); 2) fecal calprotectin >250 mg/kg at screening; 3) endoscopy (within 3 months prior to baseline) with evidence of active Crohn's disease. Subjects had to have colitis, ileitis, or ileocolitis previously confirmed at some time in the past by radiography, histology, and/or endoscopy. Subjects must have failed conventional therapy and must not have previously demonstrated inadequate response or intolerance to 1 or more tumor necrosis factor (TNF) antagonist therapies (ie, infliximab, adalimumab, or certolizumab pegol).

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab for IV administration was supplied as a single-use, sterile solution in glass vials with 2 dose strengths (ie, 90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume) (bulk lot numbers BHS49, CAS4C00, CGS3400). Each 1 mL of ustekinumab solution contained 90 mg ustekinumab. In addition to ustekinumab, each vial contained L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for IV administration was supplied as a single-use, sterile solution in a glass vial (bulk lot numbers BDS2S00, CAS5300, CFS50, DCS4H00). Each vial contained L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present.

Duration of Treatment: All subjects were randomized at Week 0 to receive a single IV dose of placebo, 130 mg ustekinumab, or ~6 mg/kg ustekinumab at Week 0. Subjects were evaluated at Week 6 for the primary endpoint of clinical response. At Week 8, eligible subjects could enter the maintenance study, CNTO1275CRD3003. Subjects who did not enter the maintenance study were to have a safety follow-up visit approximately 20 weeks after the Week 0 study agent administration.

Evaluations:

- Pharmacokinetics: Serum ustekinumab concentration.
- Immunogenicity: Antibodies to ustekinumab.
- Pharmacodynamics / biomarkers: Serum-based biomarkers, peripheral blood messenger ribonucleic acid (RNA) expression, RNA expression and histologic assessment of disease and healing in mucosal biopsies, analysis of whole blood DNA.
- Efficacy: CDAI assessment, CRP concentrations, fecal lactoferrin and fecal calprotectin concentrations, fistula assessment, pyoderma gangrenosum (PG) assessment, ileocolonoscopy (in subjects who consented to the procedure at selected clinical study centers).
- Patient-reported outcomes: Inflammatory Bowel Disease Questionnaire (IBDQ), 36-Item Short-form Health Survey (SF-36).
- Health economics: Resource utilization, productivity visual analog scale (VAS), Work Limitations Questionnaire (WLQ).
- Safety: Adverse events (AEs), serious adverse events (SAEs), vital signs, AEs that occurred during or within 1 hour of the administration of study agent (hereafter referred to as infusion reactions), hematology and chemistry parameters, physical examinations, 12-lead electrocardiograms (ECGs).

Analyses of mucosal healing, as assessed by ileocolonoscopy in subjects who consented to participate in that substudy, will be presented in a separate report

Statistical Methods:

Primary endpoint: Clinical response at Week 6, defined as a reduction from baseline in the CDAI score of ≥100 points. Subjects with a baseline CDAI score of ≥220 to ≤248 were considered to be in clinical response if a CDAI score of <150 was attained.

Major secondary endpoints, listed in the order in which they were tested:

- Clinical remission at Week 8, defined as a CDAI score of <150 points at Week 8;
- Clinical response at Week 8, defined as a reduction from baseline in the CDAI score of ≥100 points at Week 8. Subjects with a baseline CDAI score of ≥220 to ≤248 were considered in clinical response if a CDAI score of <150 was attained.
- 70-point response at Week 6, defined as a reduction from baseline in the CDAI score of ≥70 points at Week 6.
- 70-point response at Week 3, defined as a reduction from baseline in the CDAI score of ≥70 points at Week 3.

Demographic and baseline disease characteristics were summarized; these analyses were based on the 628 subjects who were randomly assigned after the study was restarted. Efficacy analyses were based on 627 subjects; data for 1 subject randomized after study restart were retrospectively excluded from the efficacy analyses because the Sponsor was unable to make a determination of the accuracy and validity of the subject's data. The proportion of subjects in clinical response at Week 6 (primary endpoint) was summarized and compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi-square test, stratified by study region (Asia, Eastern Europe, or rest of world) and CDAI score (≤300 or >300), at a significance level of 0.05. The study was considered positive if the ustekinumab high-dose group was significantly different from the placebo group for the primary endpoint. Global and US-specific multiple testing procedures were prespecified to control the overall Type I error rate at the 0.05 level in this study. Safety analyses were based on the 627 subjects who were randomly assigned (after the study was restarted) and received the Week 0 dose of study agent (1 subject in the placebo group was randomized but did not receive study agent). Safety was assessed by summarizing the frequency and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry analyses.

RESULTS:

STUDY POPULATION:

A total of 628 subjects were randomized after the study was restarted: 210 in the placebo group, 209 in the ustekinumab 130 mg group, and 209 in the ustekinumab ~6 mg/kg group. Among these subjects, 52.9% were women and 83.8% were white; the median age was 37.0 years and median weight was 70.8 kg. Baseline demographic characteristics were generally similar across the treatment groups. Among the 23 subjects (3.7%) who terminated their study participation, most (2.2%, n=14) did so before Week 8: 4.3%, 1.4%, and 1.0% in the placebo, ustekinumab 130 mg, and ustekinumab ~6 mg/kg groups, respectively. The most common reason for termination before Week 8 was withdrawal of consent.

Baseline disease characteristics were representative of a population of subjects with moderate to severe Crohn's disease who had previously failed or were intolerant to conventional systemic therapy, and were generally well balanced across the 3 treatment groups: median CDAI score, 292.5; median CRP concentration, 8.05 mg/L. Of the 628 randomized subjects, the majority (91.0%, 92.3%, and 92.8% in the placebo group, ustekinumab 130 mg group and ustekinumab ~6 mg/kg group, respectively) had an abnormal CRP (>3.0 mg/L), highly elevated fecal calprotectin (>250 mg/kg), or abnormal fecal lactoferrin (>7.24 micrograms/g) at baseline. Median disease duration was slightly greater in the placebo group at baseline (8.28 years) compared with the ustekinumab groups (5.61 and 6.21 years in the 130 mg and ~6 mg/kg groups, respectively); in light of the balanced nature of all other demographic and clinical measures, this difference is unlikely to have impacted the study results.

Consistent with the study entry criteria, 99.4% of subjects previously had failed either corticosteroids or immunomodulators. Subjects in the study were allowed to have previously received TNF antagonists, but they were not to have demonstrated inadequate response or intolerance to them. A total of 31.4% of subjects had previously received TNF antagonists and 98.5% of these subjects had not demonstrated failure or intolerance to them, per study entry criteria. Conversely, 68.6% of subjects were anti-TNF naïve. Additionally, 77.9% of subjects were receiving 1 or more concomitant medications for Crohn's disease at baseline and the proportions of subjects receiving each class of Crohn's disease medication at baseline was similar across the 3 treatment groups. Approximately 39% of subjects were receiving corticosteroids (including budesonide) at baseline and approximately 35% of subjects were receiving immunomodulators (6-mercaptopurine, azathioprine, and methotrexate).

EFFICACY RESULTS

Ustekinumab induced clinical response and clinical remission in a population of Crohn's disease patients with moderately to severely active disease who had previously failed or were intolerant to conventional systemic therapy.

- Based on the prespecified global and US-specific multiple testing procedures, statistical significance can be claimed for both ustekinumab doses (~6 mg/kg and 130 mg) for the primary endpoint as well as all 4 major secondary endpoints.
  - The proportions of subjects in clinical response at Week 6 were significantly greater in both the ~6 mg/kg (55.5%) and 130 mg (51.7%) ustekinumab groups than in the placebo group (28.7%, p<0.001 for both).
    - The effect of ustekinumab on inducing clinical response was generally consistent across subgroups (including the anti-TNF naïve subjects) and was robust to prespecified changes in data-handling rules.
  - The proportions of subjects in clinical remission at Week 8 were significantly greater in both the ~6 mg/kg (40.2%) and 130 mg (30.6%) ustekinumab groups than in the placebo group (19.6%, p<0.001 and p=0.009, respectively).
    - The effect of ustekinumab on inducing clinical remission was generally consistent across subgroups (including the anti-TNF naïve subjects).
  - The proportions of subjects in clinical response at Week 8 were significantly greater in both the ~6 mg/kg (57.9%) and 130 mg (47.4%) ustekinumab groups than in the placebo group (32.1%, p<0.001 for both).
  - The proportions of subjects in 70-point response at Week 6 were significantly greater in both the ~6 mg/kg (64.6%) and 130 mg (58.9%) ustekinumab groups than in the placebo group (38.8%, p<0.001 for both).
  - The proportions of subjects in 70 point response at Week 3 were significantly greater in both the ~6 mg/kg (50.7%) and 130 mg (49.3%) ustekinumab groups than in the placebo group (31.6%; p<0.001 for both).
- Early response to ustekinumab was evident across multiple efficacy endpoints and was seen as early as the first postbaseline visit (Week 3). In addition to the major secondary endpoint of 70-point response at Week 3, the proportions of subjects in clinical response at Week 3 were significantly greater in the ustekinumab treatment groups than in the placebo group. Although the proportions of subjects in clinical remission at Week 3 were higher in the ustekinumab treatment groups compared with placebo, this difference was only significant for the ~6 mg/kg ustekinumab dose group.
- Median reductions from baseline in the CDAI score over time were significantly greater in both ustekinumab groups compared with the placebo group.
- Significantly greater mean reductions from baseline in CRP and significantly greater proportions of subjects with normalized CRP were observed in both ustekinumab groups compared with the placebo group over time.
- At Week 6, significantly greater median reductions from baseline in fecal lactoferrin and fecal calprotectin, and significantly greater proportions of subjects with normalized fecal lactoferrin and fecal calprotectin, were observed in both ustekinumab groups compared with the placebo group.
- A greater magnitude of effect with the ustekinumab ~6 mg/kg dose compared with the ustekinumab 130 mg dose was observed for the following key analyses of clinical endpoints:
  - Clinical remission at Week 8: the treatment effect for the ~6 mg/kg dose group (20.6%) was nearly twice that seen in the 130 mg group (11.0%)
  - Clinical response at Week 8: the treatment effect was larger for the ~6 mg/kg group (25.8%) than for the 130 mg group (15.3%)
  - 70 point response at Week 8: the treatment effect was larger for the ~6 mg/kg group (22.5%) than for the 130 mg group (13.9%)

  - Change from baseline in CDAI score at Week 8: the treatment effect was larger for the ~6 mg/kg group (−65.0) than for the 130 mg group (−41.0)

- A greater magnitude of effect with the ~6 mg/kg ustekinumab dose compared with the 130 mg ustekinumab dose was observed for the following objective markers of inflammation:
  - Change from baseline in mean CRP concentration. For example, the treatment effect at Week 8 was larger for the ~6 mg/kg group (−8.42) than for the 130 mg group (−3.83)
  - Change from baseline in median fecal lactoferrin concentration at Week 6: the treatment effect was larger for the ~6 mg/kg group (−25.93) than for the 130 mg group (−10.35)
  - Change from baseline in median fecal calprotectin concentration at Week 6: the treatment effect was larger for the ~6 mg/kg group (−106.32) than for the 130 mg group (−55.03)
- Greater proportions of subjects were in clinical remission at Week 8 in the higher quartiles of serum ustekinumab concentrations; however, this trend was not apparent for clinical response at Weeks 6 and 8, or for change in CDAI at Week 6. In the 130 mg treatment group, a trend towards lower CRP levels at Week 6 was associated with increasing serum ustekinumab concentrations. Although such a trend was not as clear in the ~6 mg/kg treatment group, CRP at Week 6 was highest in the lowest serum ustekinumab concentration quartile.

PHARMACOKINETIC RESULTS AND IMMUNOGENICTY RESULTS

- Following a single IV administration of the 130 mg ustekinumab fixed dose or tiered doses approximating 6 mg/kg ustekinumab, median serum ustekinumab concentrations were approximately dose proportional and were detectable at all sampling timepoints through Week 8. Median peak serum ustekinumab concentrations 1 hour after the Week 0 infusion were 39.81 μg/mL and 124.37 μg/mL for the 130 mg and ~6 mg/kg dose groups, respectively. At the end of induction at Week 8, median serum ustekinumab concentrations were 2.0 μg/mL and 6.3 μg/mL for the 130 mg and ~6 mg/kg dose groups, respectively.
- Among subjects who received tiered ustekinumab doses approximating 6 mg/kg, median serum ustekinumab concentrations tended to be higher as the absolute ustekinumab dose increased. Among subjects who received the same ustekinumab 130 mg IV induction dose, comparable serum ustekinumab concentrations were attained regardless of body weight. The relationship between serum ustekinumab concentration and body weight does not appear to be linear across the body weight range of subjects in this 8-week study.
- Among the 411 ustekinumab-treated subjects with appropriate samples for the assessment of antibodies to ustekinumab, only 1 (0.2%) subject was positive for antibodies to ustekinumab through the final safety visit at Week 20.

PATIENT-REPORTED OUTCOMES RESULTS AND HEALTH ECONOMICS RESULTS

- At Week 8, the mean change from baseline in the IBDQ score was significantly greater in both ustekinumab groups compared with the placebo group. In addition, significantly greater proportions of subjects in both ustekinumab groups had a clinically meaningful (≥16-point) improvement from baseline in the IBDQ at Week 8 compared with the placebo group, indicating greater improvement in disease-specific health-related quality of life. The treatment effect for ≥ 16-point improvement from baseline in the IBDQ at Week 8 was larger for the ~6 mg/kg ustekinumab dose (27.0%) than for the 130 mg ustekinumab dose (17.6%).
- At Week 8, significantly greater proportions of subjects in the ustekinumab treatment groups compared with the placebo group showed improvement in the Physical Component Summary (PCS), Mental Component Summary (MCS), and all 8 scale scores of the SF-36. In addition, significantly greater proportions of subjects in both ustekinumab groups achieved a clinically meaningful (≥ 5-point) improvement from baseline in both PCS and MCS scores indicating greater improvement in

general health-related quality of life; the treatment effect was larger for the ~6 mg/kg group (18%) than for the 130 mg group (12.8%).

- No significant differences were observed between the ustekinumab groups and placebo for the following health economic analyses: Crohn's disease-related hospitalizations and surgeries; time lost from work; and work limitations. However, the median change from baseline in daily productivity (VAS) at Week 8 was significantly greater for both ustekinumab groups compared with placebo.

SAFETY RESULTS

- Intravenous ustekinumab at both 130 mg and ~6 mg/kg was well-tolerated through Week 8 with a safety profile generally comparable with placebo through Week 8.
- The proportions of subjects experiencing at least one AE were similar across all the treatment groups through Week 8; gastrointestinal disorders and infections and infestations were the system-organ classes in which the highest proportions of subjects experienced AEs.
- Study discontinuations due to AEs occurred at a low frequency and in a similar proportion of subjects in the placebo and ustekinumab treatment groups combined. More subjects in the 130 mg ustekinumab group discontinued due to an AE compared with the ~6 mg/kg group. Crohn's disease was the most common AE leading to discontinuation.
- Serious AEs occurred at a low frequency overall and in similar proportions of subjects in all treatment groups through Week 8. Except for anal abscess, intestinal obstruction, and Crohn's disease, no individual SAE was reported in more than 1 subject in any treatment group.
- Proportions of subjects with infections and serious infections were similar in all treatment groups through Week 8; there were no opportunistic infections in either ustekinumab treatment group and no cases of tuberculosis were reported.
- There were no deaths or major adverse cardiovascular events reported in any treatment group during the study. Of note, 1 nonserious event of basal cell carcinoma in a placebo-treated subject was reported to the sponsor.
- Infusion reactions were non-serious and occurred in a similar proportion of subjects in all treatment groups. No individual infusion reaction occurred in >1% of subjects in any treatment group and no infusion reactions were assessed to represent anaphylaxis.
- The only markedly abnormal changes in hematology laboratory values occurring in more than 1 subject on more than 1 occasion in any treatment group through Week 8 were decreased lymphocytes; the proportions of subjects experiencing decreased lymphocytes was <6% across all treatment groups.
- There were no markedly abnormal changes in chemistry laboratory values observed in more than 1 subject on more than 1 occasion in any treatment group through Week 8.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Study CNTO1275CRD3002 provided consistent and definitive evidence that ustekinumab was effective at inducing clinical response and clinical remission, at both induction doses studied, in adult subjects with moderate to severe Crohn's disease who had previously failed conventional therapy.

- Single IV induction dosing of ustekinumab at doses of up to 6 mg/kg was generally well tolerated over 8 weeks in this population of adult subjects with moderate to severe Crohn's disease.
- The safety and efficacy data from this study support a positive benefit/risk profile for IV ustekinumab induction therapy. In this population of adults with moderate to severe Crohn's disease, a greater benefit was seen in the ~6 mg/kg dose, without any corresponding incremental safety risk.