

SYNOPSIS

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

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Status: Approved
Date: 17 September 2015
Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1275CRD3001

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 Who Have Failed or Are Intolerant to TNF Antagonist Therapy

Study Name: UNITI-1

EudraCT Number: 2010-022758-18

NCT No.: NCT01369329

Clinical Registry No.: CR018415

Principal Investigator(s): William J. Sandborn, MD, University of California San Diego and UC San Diego Health System, La Jolla, CA, USA

Study Center(s): 178 sites in North America, Europe, the Asia-Pacific region, Israel, South Africa, and Brazil

Publication (Reference): None

Study Period: 23 June 2011 to 03 July 2013; database lock, 16 Aug 2013

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 who have failed or are intolerant to 1 or more tumor necrosis factor (TNF) antagonist therapies, and to evaluate the safety of IV induction regimens of ustekinumab in subjects with moderately to severely active Crohn’s disease who have failed or are intolerant to 1 or more TNF antagonist therapies. 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 CNTO1275CRD3002, 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 [\sim 6 mg/kg]: ustekinumab 260 mg (weight \leq 55 kg), 390 mg (weight $>$ 55 kg and \leq 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 initially received placebo (both in clinical response and not in clinical response), were also eligible to enter Study CNTO1275CRD3003 at Week 8, 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, 675 subjects (225 subjects 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 (130 mg ustekinumab in 26 mL [5 mg/mL; 27 mL fill of liquid]) used in the study. Because knowledge of this could potentially bias the assessments, data from the 28 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 675 subjects, which was needed to power the primary endpoint analysis, the planned enrollment in the Statistical Analysis Plan was prospectively changed to 703 (675+28) subjects.

A total of 769 subjects were randomly assigned to receive study agent; unless otherwise specified, all planned analyses were based on the 741 subjects who were randomized after the study was restarted: 247 in the placebo group, 245 in the ustekinumab 130 mg group, and 249 in the ustekinumab \sim 6 mg/kg group. Safety analyses were based on the 740 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 \geq 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 \geq 220 but \leq 450, who had received infliximab (REMICADE®), adalimumab (HUMIRA®), or certolizumab pegol (CIMZIA®) at a dose approved for the treatment of Crohn’s disease, and have been documented to have not responded initially, responded initially but then lost response, or been intolerant to the medication. Subjects had to have colitis, ileitis, or ileocolitis previously confirmed at some time in the past by radiography, histology, and/or endoscopy, and had to allow washout period of at least 8 weeks for prior TNF antagonist use.

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. 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. 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 \sim 6 mg/kg ustekinumab at Week 0. Subjects were evaluated at Week 6 for the primary endpoint of clinical response and 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 (PK): Serum ustekinumab concentration.
- Immunogenicity: Antibodies to ustekinumab.
- Pharmacodynamics (PD)/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 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, 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 electrocardiogram.

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 and the efficacy analyses were based on the 741 subjects who were randomly assigned after the study was restarted. 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), CDAI score (≤ 300 or > 300), and initial response to TNF antagonist therapy (yes or no), 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 1 error rate at the 0.05 level in this study. Safety analyses were based on the 740 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 741 subjects were randomized after the study was restarted: 247 in the placebo group, 245 in the ustekinumab 130 mg group, and 249 in the ustekinumab ~6 mg/kg group. Among these subjects, 57.2% were women and 84.1% were white; the median age was 36.0 years and median weight was 67.0 kg. Baseline demographic characteristics were generally similar across the treatment groups. Among the 33 subjects (4.5%) who terminated their study participation, most (3.1%, n=23) did so before Week 8: 2.8%, 2.9%, and 3.6% in the placebo, 130 mg ustekinumab, and ~6 mg/kg ustekinumab 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 intractable moderate to severe Crohn's disease that was refractory to available therapies, specifically TNF antagonists, and were generally well balanced across the 3 treatment groups: median duration of disease at baseline, 10.14 years; median CDAI score, 317; median CRP concentration, 9.88 mg/L. Subjects had to have previously failed at least 1 TNF antagonist: 78.8% of subjects had failed infliximab, 59.8% had failed adalimumab, and 22.1% had failed certolizumab pegol. Additionally, 72.5% 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 were similar across the 3 treatment groups. A total of 340 subjects (45.9%) were receiving corticosteroids (including budesonide); 233 (31.4%) of subjects were receiving immunomodulators (AZA, 6-MP, or methotrexate).

EFFICACY RESULTS:

Ustekinumab induced clinical response and clinical remission. 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 proportion of subjects in clinical response at Week 6 (the primary endpoint) was significantly greater in both the ~6 mg/kg (33.7%) and 130 mg (34.3%) ustekinumab groups than in the placebo group (21.5%; p=0.003 and p=0.002, respectively).
 - The effect of ustekinumab on inducing clinical response was generally consistent across subgroups.
 - The effect of ustekinumab on inducing clinical response was robust to prespecified changes in data-handling rules.
- The proportion of subjects in clinical remission at Week 8 was significantly greater in both the ~6 mg/kg (20.9%) and 130 mg (15.9%) ustekinumab groups than in the placebo group (7.3%; p<0.001 and p=0.003, respectively), with a greater proportion of subjects in remission in the ~6 mg/kg group than in the 130 mg group.
 - The effect of ustekinumab on inducing clinical remission was generally consistent across subgroups.
- The proportion of subjects in clinical response at Week 8 was significantly greater in both the ~6 mg/kg (37.8%) and 130 mg (33.5%) ustekinumab groups compared with the placebo group (20.2%; p<0.001 and p=0.001, respectively).
- The proportion of subjects in 70-point response at Week 6 was significantly greater in both the ~6 mg/kg (43.8%) and 130 mg (46.1%) ustekinumab groups compared with the placebo group (30.4%; p=0.002 and p<0.001, respectively).

- The proportion of subjects in 70-point response at Week 3 was significantly greater in both the ~6 mg/kg (40.6%) and 130 mg (38.4%) ustekinumab groups compared with the placebo group (27.1%; $p=0.001$ and $p=0.009$, respectively).
- Median reductions from baseline in the CDAI score were significantly greater in both the ~6 mg/kg and 130 mg ustekinumab groups compared with the placebo group at Weeks 3, 6, and 8 ($p<0.001$ for all comparisons).
 - At Week 3, the median reductions in the CDAI score were 53.0 and 50.0 in the ~6 mg/kg and 130 mg ustekinumab groups, respectively, compared with 22.0 in the placebo group.
 - Further reductions in the CDAI score were observed in all groups at Week 6 (median reductions of 59.0, 63.0, and 32.0 in the ~6 mg/kg ustekinumab, 130 mg ustekinumab, and placebo groups, respectively).
 - At Week 8, the treatment effect in the change from baseline in the CDAI score was greater for both ustekinumab groups than the placebo group, with the ~6 mg/kg ustekinumab group having a numerically greater median reduction in the CDAI score than the 130 mg ustekinumab group (69.0 and 55.0, respectively), compared with the placebo group (17.0).
- At Weeks 3, 6, and 8, 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.
- 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.
- Greater proportions of subjects were in clinical remission at Week 8 in the higher quartiles of serum ustekinumab concentrations; however, this trend was not as apparent for clinical response at Weeks 6 and 8, or for change in CDAI at Week 6. A trend toward lower CRP levels was associated with increasing serum ustekinumab concentrations.

PATIENT-REPORTED OUTCOMES RESULTS AND HEALTH ECONOMICS RESULTS:

- At Week 8, the mean change from baseline in the IBDQ score was significantly greater in the ~6 mg/kg (22.1) and 130 mg (18.1) ustekinumab groups compared with the placebo group (11.9; $p<0.001$). In addition, significantly greater proportions of subjects in both ustekinumab groups had a ≥ 16 -point improvement from baseline in the IBDQ at Week 8 (54.8% and 46.9% in the ~6 mg/kg and 130 mg groups, respectively) compared with the placebo group (36.5%), indicating better health-related quality of life; a greater proportion of subjects in the ~6 mg/kg group had a ≥ 16 -point improvement than in the 130 mg group.
- At Week 8, numeric improvements in the PCS and MCS of the SF-36 were noted in ustekinumab-treated subjects compared with placebo, particularly in the 6 mg/kg group for MCS in both change from baseline ($p=0.006$) and the proportion of subjects achieving 5-point improvement ($p=0.007$).
- Crohn's disease-related hospitalizations and surgeries were low across all treatment groups through Week 8; fewer subjects in the ustekinumab treatment groups had Crohn's disease-related surgeries through Week 8 compared with subjects in the placebo group.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

- Following a single IV administration of the 130 mg ustekinumab fixed dose or tiered doses ~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 43.6 µg/mL and 129.1 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 2.1 µg/mL and 6.4 µg/mL for the 130 mg and ~6 mg/kg dose groups, respectively.
- Among subjects who received tiered doses approximating 6 mg/kg ustekinumab, 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 484 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.

SAFETY RESULTS:

- Intravenous ustekinumab administered in a 130 mg or ~6 mg/kg ustekinumab dose was well tolerated, with a safety profile generally comparable with placebo through Week 8.
- Fourteen (5.7%) subjects in the placebo group discontinued due to an AE compared with 3 (1.2%) in the 130 mg and 7 (2.8%) in the ~6 mg/kg ustekinumab groups. An AE of Crohn's disease was the most common event that led to discontinuation in all treatment groups: 11 subjects in the placebo group and 2 and 1 subjects in the 130 mg and ~6 mg/kg ustekinumab groups, respectively.
- SAEs were uncommon in all treatment groups through Week 8 and, except for Crohn's disease, no SAE occurred in more than 1 subject in either ustekinumab dose group.
- No deaths and no investigator-reported major adverse cardiovascular events were reported. After the Week 20 safety follow-up visit, 1 malignancy, a multiple myeloma, was reported in a subject in the ~6 mg/kg ustekinumab group.
- The proportions of subjects with infections were similar across all treatment groups through Week 8; more SAEs of infection were reported in subjects in the ~6 mg/kg ustekinumab group than in the 130 mg ustekinumab or placebo groups.
- No subjects developed active TB during the study. One opportunistic infection (*Listeria meningitis*; ~6 mg/kg ustekinumab group) was reported.
- No anaphylaxis or serum-sickness-like reactions were reported. Infusion reactions, although uncommon and nonserious, occurred at a slightly higher rate in the ustekinumab groups compared with placebo. No specific infusion reaction occurred in ≥1% of subjects in the combined ustekinumab groups.
- Markedly abnormal changes in hematology laboratory values were observed in some subjects; the most common markedly abnormal change that occurred on more than 1 occasion in more than 1 subject was decreased absolute lymphocyte count (5.3%, 2.9%, and 4.0% in the placebo, 130 mg, and ~6 mg/kg ustekinumab groups). The only markedly abnormal change in chemistry values that was observed in more than 1 subject on more than 1 occasion in any treatment group was decreased albumin (2 [0.8%] subjects in the placebo group and no subjects in the ustekinumab groups).

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Study CNTO1275CRD3001 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 or were intolerant to TNF antagonist 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 at both doses studied in this population of adults with moderate to severe Crohn's disease.

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