SYNOPSIS

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

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Status: Approved

Date: 9 November 2015

Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1275CRD3003

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

Study Name: IM-UNITI

EudraCT Number: 2010-022760-12

NCT No.: NCT01369355

Clinical Registry No.: CR018421

Principal Investigator(s): William J. Sandborn, MD, University of California San Diego and UC San Diego Health System, [redacted], USA

Study Center(s): 260 sites in North America, Europe, the Asia-Pacific region, Israel, South Africa, Australia, New Zealand, and Brazil.

Publication (Reference): None

Study Period: 13 September 2011 to 10 June 2015; database lock 8 July 2015

Phase of Development: 3

Objectives: Primary: To evaluate clinical remission for the 2 subcutaneous (SC) maintenance regimens of ustekinumab in subjects with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in the induction studies, CNTO1275CRD3001 and CNTO1275CRD3002 and to evaluate the safety of 2 SC maintenance regimens of ustekinumab in subjects with moderately to severely active Crohn's disease. Secondary: To evaluate the efficacy of ustekinumab in maintaining clinical response in subjects induced into clinical response; to evaluate the efficacy of ustekinumab in maintaining clinical remission in subjects induced into clinical remission; to evaluate the efficacy of ustekinumab in achieving corticosteroid free remission; to evaluate the pharmacokinetics (PK), immunogenicity, and pharmacodynamics (PD) of ustekinumab therapy, including changes in C-reactive protein (CRP), fecal calprotectin, fecal lactoferrin, and other PD biomarkers; and to evaluate the effect of ustekinumab on health-related quality of life (QOL).

Methodology: In this randomized, double-blind, placebo-controlled, parallel-group, multicenter study, subjects with moderately to severely active Crohn's disease induced into clinical response with ustekinumab in induction studies CNTO1275CRD3001 or CNTO1275CRD3002 were randomized in a 1:1:1 ratio at Week 0 to receive a SC administration of either placebo or 1 of 2 maintenance regimens of ustekinumab (ustekinumab 90 mg every 12 weeks [q12w] through Week 36 or ustekinumab 90 mg every 8 weeks [q8w] through Week 40). This population of subjects is considered the primary population in this study. At Week 44, subjects were evaluated for the primary endpoint of clinical remission.

Randomized subjects who subsequently met loss of response (LOR) criteria at any time between Week 8 and Week 32 of the study were eligible to have a single dose adjustment to ustekinumab 90 mg q8w. Subjects who had a dose adjustment were evaluated 16 weeks after adjustment and were discontinued from study agent if not in clinical response.

Subjects who were not in clinical response to ustekinumab at Week 8 of the induction studies, as well as all subjects who initially received placebo (both in clinical response and not in clinical response), were also eligible to enter the study, but were not included in the primary population. Subjects in clinical response to placebo intravenous (IV) induction continued to receive SC placebo throughout the maintenance study. Subjects not in clinical response to IV placebo induction received ustekinumab 130 mg IV administration at Week 0. Subjects who achieved clinical response at Week 8 initiated ustekinumab 90 mg SC at Week 8 and then q12w thereafter through Week 32; otherwise they were discontinued from further study agent administration. Subjects who were not in clinical response to ustekinumab IV induction received ustekinumab 90 mg SC at Week 0 of this maintenance study. Subjects who achieved clinical response at Week 8 continued to receive ustekinumab 90 mg SC q8w through Week 40; otherwise they were discontinued from further study agent administration.

A long term extension will continue up to Week 272 for eligible subjects.

An independent Data Monitoring Committee (DMC) monitored subject safety data during the blinded period of the study (through Week 44). No interim analysis was conducted.

Number of Subjects (planned and analyzed): Per protocol, approximately 1,275 subjects were anticipated to be enrolled in the 2 inductions studies (CNTO1275CRD3001 and CNTO1275CRD3002). 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 induction studies (130 mg ustekinumab in 26 mL [5 mg/mL; 27 mL fill of liquid]). To maintain the originally planned sample size in each of the induction studies, an additional 40 subjects were to be enrolled in the induction studies. Because knowledge of the stability issue could potentially bias the assessments, data from subjects who were enrolled before this study was temporarily suspended (9 randomized subjects and 17 nonrandomized subjects) were not used in the planned efficacy analyses.

A total of 1,281 subjects who completed the ustekinumab induction studies were enrolled in this study. The numbers of subjects in each population were as follows:

- 397 subjects (31.0%) were in the primary population (ie, were in clinical response to ustekinumab IV induction at Week 8 of an induction study; randomized subjects):
  - 133 subjects randomized to placebo
  - 132 subjects randomized to ustekinumab 90 mg q12w
  - 132 subjects randomized to ustekinumab 90 mg q8w
- 884 subjects (69.0%) were enrolled but not randomized (ie, nonrandomized subjects):
  - 123 placebo induction responders who continued to receive placebo

- 285 placebo induction nonresponders who received an ustekinumab 130 mg IV infusion at Week 0. Subjects who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q12w (subsequent induction responders).
- 476 ustekinumab induction nonresponders who received ustekinumab 90 mg at Week 0. Subjects who achieved clinical response by Week 8 of maintenance continued to receive ustekinumab 90 mg q8w (delayed responders).

Diagnosis and Main Criteria for Inclusion: Eligible subjects were required to have received study agent at Week 0 in study CNTO1275CRD3001 or CNTO1275CRD3002 and completed the Week 8 Crohn's Disease Activity Index (CDAI) score evaluation. Induction study CNTO1275CRD3001 included subjects with moderately to severely active Crohn's disease had who previously failed or were intolerant to 1 or more tumor necrosis factor (TNF)-antagonist therapies. Induction study CNTO1275CRD3002 included subjects with moderately to severely active Crohn's disease with evidence of active inflammation who failed conventional therapy (ie, corticosteroids and immunomodulators).

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab for SC administration was supplied as a sterile liquid for SC injection in a single-use prefilled syringe (PFS). Each single-use PFS contained 90 mg (1 mL fill of liquid) ustekinumab; bulk lot numbers 11K032, 10M032, 13A052, 10C052, 11C052, 13F052, 14E022. In addition to ustekinumab, each PFS contained L-histidine, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present.

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 CAS4C00, CGS3400, DJS6B00. 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.: The placebo for SC injection was supplied as a sterile liquid at a fill volume of 1.0 mL in a single use PFS; bulk lot numbers 11J042, 10M042, 10E012, 13D042, EJSSL. Each PFS contained L-histidine, sucrose, and polysorbate 80 at pH 6.0.

Duration of Treatment: Duration of treatment in the main study was 44 weeks. The long-term extension will continue through Week 272.

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.
- 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 participating sites).
- Patient-reported outcomes: Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form (SF)-36.
- Safety: AEs, serious adverse event (SAE)s, clinical laboratory test results, vital signs, infusion and injection-site reactions, and physical examinations.
- Health economics: Resource utilization, productivity Visual Analog Scale (VAS), Work Limitations Questionnaire (WLQ).

Statistical Methods:

Analysis populations: Efficacy analyses were based on the primary analysis population (ie, subjects in clinical response to ustekinumab at Week 8 from 1 of the induction studies CNTO1275CRD3001 and CNTO1275CRD3002 excluding the subjects who were randomized prior to study restart). All subjects who received at least 1 dose of ustekinumab either in this study or in one of the induction studies, were included in the PK analyses. The safety analyses included all subjects who received study agent at Week 0.

Primary endpoint: Clinical remission at Week 44, defined as a CDAI score of <150 points.

Major secondary endpoints, listed in hierarchical order:

- Clinical response at Week 44, defined as a reduction from Week 0 of induction study CNTO1275CRD3001 or CNTO1275CRD3002 in the CDAI score of ≥100 points.
- Clinical remission at Week 44 among subjects in clinical remission to ustekinumab at Week 0 of maintenance.
- Corticosteroid-free remission at Week 44.
- Clinical remission at Week 44 in the subset of subjects who were refractory or intolerant to TNF antagonist therapy (ie, subjects from induction study CNTO1275CRD3001).

Demographic and baseline disease characteristics were summarized.

The proportion of subjects in clinical remission at Week 44 was compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran Mantel Haenszel chi-square test, stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinumab 6 mg/kg), and the induction study (CNTO1275CRD3001 or CNTO1275CRD3002) at a significance level of 0.05. The study was considered positive if the 90 mg q8w ustekinumab group was significantly different from placebo.

The major secondary endpoints were compared between each of the ustekinumab treatment groups and the placebo group using a 2-sided Cochran-Mantel-Haenszel chi square test, stratified by clinical remission status at Week 0 (yes or no), ustekinumab induction dose (130 mg or tiered dosing approximating ustekinumab 6 mg/kg), and the induction study (CNTO1275CRD3001 or CNTO1275CRD3002) at a significance level of 0.05.

Global and US-specific multiple testing procedures were prespecified to control the overall Type 1 error rate at the 0.05 level over the primary and major secondary endpoints in this study. All statistical testing was performed at the 2-sided 0.05 significance level. Nominal p-values are presented.

Safety analyses were assessed by summarizing the frequency and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry analyses. Safety summaries are provided for randomized subjects (ie, the primary population) to provide a balanced comparison across treatment groups, and for all treated subjects, including both randomized and nonrandomized subjects, to provide overall safety across the placebo and ustekinumab groups.

RESULTS:

Results through Week 44 of this maintenance study are presented in this document.

STUDY POPULATION:

Randomized Subjects:

A total of 397 subjects were randomized in the study: 133 in the placebo group, 132 in the ustekinumab 90 mg q12w group, and 132 in the ustekinumab 90 mg q8w group. Among these subjects, 56.4% were women and 84.9% were white; the median age was 36.0 years and median weight was 69.0 kg. Baseline demographic characteristics were generally similar across the treatment groups. The proportions of randomized subjects who discontinued study agent were similar across treatment groups (23.3%, 22.0%, and 22.7% in the placebo SC, ustekinumab 90 mg SC q12w, and q8w groups, respectively). The most common reasons for discontinuation of study agent among subjects in the primary population were lack of efficacy or an adverse event. Among randomized subjects, 9.8%, 6.8%, and 10.6% in the placebo, ustekinumab 90 mg q12w, and ustekinumab 90 mg q8w groups, respectively, terminated study participation prior to Week 44. The most common reason for termination 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 and were generally well balanced across the 3 treatment groups: median duration of disease at baseline, 7.57 years; median CDAI score, 311.0; median CRP concentration, 9.27 mg/L.

Of the randomized subjects in this study, 44.8% were TNF antagonist refractory, 15.6% had received TNF antagonists and had not demonstrated failure or intolerance, and 39.5% had not received any TNF antagonist therapy prior to study participation. Additionally, 79.3% 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 181 subjects (45.6%) were receiving corticosteroids (including budesonide); 143 (36.0%) subjects were receiving immunomodulators (azathioprine [AZA], 6-mercaptopurine [6-MP], or methotrexate [MTX]).

Nonrandomized Subjects:

A total of 884 subjects were enrolled but not randomized: 123 placebo induction responders, 285 placebo induction nonresponders, and 476 ustekinumab induction nonresponders. Baseline demographic characteristics were generally similar to those noted for randomized subjects.

A total of 455 (51.5%) nonrandomized subjects discontinued study agent. The most common reason for discontinuation of study agent was lack of efficacy. Among nonrandomized subjects, 14.6%, 15.8%, and 20.6% in the placebo induction responder, placebo induction nonresponder and ustekinumab induction nonresponder groups, respectively, terminated study participation prior to Week 44. The most common reason for termination 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: median duration of disease at baseline, 9.19 years; median CDAI score, 298.0; median CRP concentration, 8.1 mg/L.

Of the nonrandomized subjects in this study, 57.6% were TNF antagonist refractory, 14.3% had received TNF antagonists and had not demonstrated failure or intolerance, and 28.2% had not received any TNF antagonist therapy prior to study participation. Concomitant medication use for Crohn's disease was comparable in nonrandomized subjects compared with the randomized subject population. The proportions of subjects with a prior history of corticosteroid and immunomodulator use were also comparable to the proportions seen in the randomized subjects.

EFFICACY RESULTS:

Study CNTO1275CRD3003 was a positive study demonstrating efficacy in the maintenance of clinical response and remission at Week 44 for both the ustekinumab SC 90 mg q12w and 90 mg q8w dose

regimens. The totality of the data, including robustness of the primary endpoint, supports q8w dosing as the primary regimen. This q8w regimen had larger treatment effects than the q12w regimen across many of the endpoints.

Clinical Efficacy Among Subjects in Clinical Response to Ustekinumab Induction

Primary Endpoint

- A significantly greater proportion of subjects in the ustekinumab 90 mg q12w and q8w ustekinumab groups were in clinical remission at Week 44 (48.8% and 53.1%, respectively) compared with the placebo group (35.9%; p=0.040, p=0.005, respectively).
  - Sensitivity analyses were robust for the q8w dosing regimen (ie, all but the worst-case analysis were significant); however, while treatment effects were in the same direction and of generally similar magnitude to those in the primary analysis, the sensitivity analyses for the q12w regimen were generally not significant.
  - The treatment effect of ustekinumab on clinical remission in maintenance was generally consistent across subgroups. However, these analyses suggest that weight and CRP may be covariates that impact dosing.

Major Secondary Endpoints

- A significantly greater proportion of subjects in the ustekinumab 90 mg q12w and q8w groups maintained clinical response at Week 44 (58.1% and 59.4%, respectively) compared with the placebo group (44.3%; p=0.033 and p=0.018, respectively).
- Among the approximately 60% of subjects who were in clinical remission at baseline, a significantly greater proportion of subjects in the ustekinumab 90 mg q8w group maintained clinical remission at Week 44 (66.7%) compared with the placebo group (45.6%; p=0.007). The remission rate in the ustekinumab 90 mg q12w group (56.4%) was numerically higher than the placebo group (45.6%), however the result did not achieve statistical significance (p=0.189).
- A greater proportion of subjects in the ustekinumab 90 mg q12w and q8w groups were in corticosteroid-free remission at Week 44 (42.6% and 46.9%, respectively) compared with the placebo group (29.8%). While the nominal p-values for the comparisons of each of the ustekinumab groups with placebo were <0.05 for this endpoint, only the ustekinumab 90 mg q8w regimen can be considered as significantly different from placebo (p=0.004) within the global testing procedure. Under the US-specific testing procedure, neither of the two ustekinumab groups was considered as statistically significant.
- Among the subset of subjects who were refractory to TNF-antagonist therapy, remission rates at Week 44 were numerically greater (38.6% and 41.1%) in the ustekinumab 90 mg q12w and q8w dose groups, respectively, compared with the placebo group (26.2%). While the treatment effects were similar to those in the overall population, there was not sufficient power to detect a significant difference from placebo as only 44.8% of the subjects in the primary population of this study were in this subpopulation.

Other Clinical Outcomes

The following analyses of secondary endpoints have not been adjusted for multiplicity. Statements of statistical significance for these endpoints are based on nominal p-values.

Sustained Remission and Response

- A significantly greater proportion of subjects in the ustekinumab 90 mg q12w and q8w groups were in sustained clinical remission (40.3% and 46.1%, respectively) compared with placebo (26.0%; p=0.023 and p<0.001 for the q12w and q8w groups, respectively).
- A significantly greater proportions of subjects in the q12w and q8w groups (53.5% and 53.1%, respectively) were in sustained clinical response compared with the placebo group (38.2%; p=0.019 for both the q12w and q8w comparisons).

Dose Adjustment

- In subjects assigned to ustekinumab 90 mg q12w who subsequently met LOR criteria, dose adjustment to 90 mg q8w provided additional clinical benefit over subjects who did not dose adjust (q8w→q8w).
- Treatment strategy analysis (which suspends LOR criteria preserving initial randomization) suggests that initiating subjects on 90 mg q12w dosing with adjustment to 90 mg q8w dosing when needed by LOR ultimately results in similar rates of clinical response and remission to subjects who receive 90 mg q8w throughout.

Additional Corticosteroid Endpoints

- The proportions of subjects in clinical remission at Week 44 who were not receiving concomitant corticosteroids for at least 90 or 30 days prior to Week 44 were significantly greater in ustekinumab groups compared with the placebo group.
- The proportions of subjects who were in clinical response at Week 44 and not receiving concomitant corticosteroids at Week 44 were significantly greater in the ustekinumab 90 mg q12w and q8w groups compared with the placebo group (51.2% and 50.8%, and 36.6%, respectively).
- Among subjects who were receiving corticosteroids at baseline, a significantly greater proportion of these subjects in the combined ustekinumab group were able to achieve clinical remission or clinical response at Week 44 and not be receiving corticosteroids at Week 44 compared with the placebo group. In addition, a higher proportion of subjects in the ustekinumab 90 mg q12w and q8w groups were able to eliminate corticosteroid use by Week 44 compared with the placebo group.

Other Endpoints

- Over time analyses of clinical efficacy were generally similar for the ustekinumab q12w and q8w dose groups with separation from placebo as early as Week 20.
- At Week 44, subjects in the ustekinumab groups had maintained their improvement in CDAI attained during induction, while subjects in the placebo group worsened. The median change from maintenance baseline in CDAI scores were −10.0 and −6.0 for subjects in the ustekinumab 90 mg q12w and q8w groups, respectively, compared with 74.0 in the placebo group (p=0.030 and p<0.001 for the q12w and q8w groups, respectively).
- Among TNF antagonist-naive subjects (from induction study CNTO1275CRD3002), remission rates were generally higher than for subjects who were refractory to TNF antagonists. The proportion of TNF antagonist-naïve subjects in remission at Week 44 was significantly greater in the ustekinumab 90 mg q8w group (65.4%) and numerically greater in the q12w group (56.6%) compared with the placebo group (49.0%; p=0.041 for the ustekinumab q8w group).
- After Week 16, there was no evidence of a carryover effect from the induction dose received.
- At Week 44, 80.0% (n=12/15) of subjects in the combined ustekinumab groups had a fistula response compared with 45.5% (n=5/11) in the placebo group.

Inflammatory Markers

- The median decrease in CRP concentrations from Week 0 of an induction study observed at Week 0 of this study was significantly maintained through Week 44 by both ustekinumab maintenance dose regimens compared with the placebo group. Over time there was more consistent control of inflammation with the ustekinumab q8w regimen than the q12w regimen.
- The decreases in the fecal lactoferrin and fecal calprotectin at Week 0 of this maintenance study were maintained at Week 20 and significantly maintained at Week 44 in the both ustekinumab dose groups compared with the placebo group.
  - The proportions of subjects with normalized fecal lactoferrin concentrations remained stable or increased slightly over time in both ustekinumab dose groups and were significantly greater at Week 44 compared with placebo, where the proportion of normalized subjects decreased over time.
  - The proportions of subjects with fecal calprotectin levels ≤250 μg/g or ≤100 μg/g at Week 44 were significantly greater in both ustekinumab groups compared with placebo.

Patient-Reported Outcomes and Health Economics

Patient-Reported Outcomes

- At Week 44, the median change in IBDQ scores from Week 0 of this study was significantly smaller in the ustekinumab 90 mg q12w and q8w dose groups (-2.5 and -2.0, respectively), compared with the placebo group (-14.5; $p<0.001$ and $p=0.003$, respectively).
- The median changes in all 4 of the IBDQ dimension scores at Week 44 were significantly smaller in both ustekinumab groups compared with placebo.
- At Week 44, the proportions of subjects with at least a 16-point improvement in IBDQ score were 61.3% and 67.9% for the ustekinumab 90 mg q12w and q8w groups, respectively, compared with 50.4% of subjects in the placebo group ($p=0.140$ and $p=0.014$, respectively).
- The mean change (±SD) from baseline of this maintenance study in the SF-36 Physical Component Summary (PCS) score for the ustekinumab q8w group (-0.93±7.139) was significantly smaller compared with the placebo group (-3.56±9.326, $p=0.003$), and numerically, but not significantly smaller for the ustekinumab q12w group (-2.30±9.311) compared with the placebo group at Week 44. The mean (±SD) change from baseline of this maintenance study in the Mental Component Summary (MCS) score in the ustekinumab q12w (-1.89±12.679) and ustekinumab q8w groups (-1.67 ± 9.759) was significantly smaller compared with the placebo group (-4.38 ± 11.058) at Week 44.
- A significantly greater proportion of subjects in the ustekinumab q8w group achieved clinically meaningful (≥5-point) improvement from baseline of an induction study in SF-36 PCS than placebo, and significantly greater proportions of subjects in both ustekinumab q12w and q8w groups achieved clinically meaningful (≥5 points) improvement in SF-36 MCS than placebo at Week 44.
- At Week 44, the mean changes from Week 0 across the SF-36 dimension scores were generally smaller in the ustekinumab 90 mg q8w groups compared with the placebo group (p values<0.05 except for general health [$p=0.055$] and role emotional ($p=0.058$)]).

Health Economics

- At Week 44 the median change from baseline in work productivity (VAS) was significantly smaller in both the ustekinumab 90 mg q12w (0.0) and q8w (0.1) groups compared with the placebo group (1.4; $p=0.006$ and $p=0.017$ for the q12w and q8w groups, respectively).

- Healthcare utilization (ie, hospitalizations and surgeries) through Week 44 of the maintenance study was low and did not differentiate across the treatment groups.

Nonrandomized Subjects

- For subjects not in clinical response following ustekinumab IV induction dosing, after being given an additional SC dose of ustekinumab 90 mg, more than half achieved clinical response 8 weeks later. Of those subjects who continued and received a ustekinumab 90 mg q8w maintenance regimen, 68.1% maintained clinical response and 50.2% were in clinical remission at Week 44.
- For subjects not in clinical response following placebo IV induction dosing, after being given an IV infusion of ustekinumab, more than half achieved clinical response 8 weeks later. Of those subjects who continued and received a ustekinumab 90 mg q12w maintenance regimen, 66.7% maintained clinical response and 49.7% were in clinical remission at Week 44.

Efficacy and Pharmacokinetics/Immunogenicity

- In general, during maintenance, a positive association was observed between serum ustekinumab concentration and the clinical efficacy outcomes of clinical response and clinical remission. In addition lower levels of inflammation, as measured by CRP, were observed in subjects with higher serum ustekinumab concentrations.
- Greater proportions of subjects were in clinical remission at Week 24 as trough serum ustekinumab concentrations at Week 24 increased. In the lowest serum ustekinumab concentration quartile where the lowest remission rates were observed, a substantial majority of subjects in that quartile were receiving the q12w regimen.
- Among subjects receiving maintenance ustekinumab, no apparent impact on clinical efficacy was observed following the development of antibodies to ustekinumab. Because of the limited number of subjects who were positive for antibodies to ustekinumab, these analyses should be interpreted with caution.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

- Following maintenance treatment with ustekinumab 90 mg SC q8w or q12w, steady-state was reached at approximately 8 or 12 weeks after subjects began receiving ustekinumab 90 mg SC q8w, or ustekinumab 90 mg SC q12w maintenance doses, respectively. Median steady-state trough serum ustekinumab concentrations over time were 3-fold greater in the ustekinumab q8w group (1.97 µg/mL to 2.24 µg/mL) than in the q12w group (0.61 µg/mL to 0.76 µg/mL).
- Following maintenance doses of ustekinumab 90 mg SC q8w or q12w, serum ustekinumab concentrations were sustained through Week 44 in almost all subjects, with a smaller proportion of subjects with undetectable trough concentrations in the 90 mg q8w group (3.2% to 4.9%) compared to those in the 90 mg q12w group (11.1% to 19.1%).
- The impact of the different IV induction doses on serum ustekinumab concentrations during maintenance appears to have completely diminished by Week 16 of this maintenance study.
- In the ustekinumab 90 mg q12w group, median trough serum ustekinumab concentrations were lowest in the highest body weight group. No consistent pattern in serum ustekinumab concentrations was observed in relation to body weight for the ustekinumab 90 mg q8w group.
- Subjects who lost response and who needed dose adjustment had lower serum ustekinumab concentrations compared to those subjects who did not lose response. An increase in average trough serum ustekinumab concentrations was observed following an increase in the dose frequency from 90 mg SC q12 to 90 mg SC q8w.

- After receiving an additional 90 mg SC dose of ustekinumab at Week 0 of this study, ustekinumab delayed responders achieved similar serum ustekinumab concentrations compared with concentrations observed in initial ustekinumab induction responders (randomized subjects).
- Among 1,154 treated subjects with appropriate samples for the assessment of antibodies to ustekinumab, 27 (2.3%) were positive for antibodies to ustekinumab through 52 weeks of treatment, the majority with antibody titers ≤1:800. Of the 27 treated subjects who were positive for antibodies to ustekinumab in this maintenance study, 17 (63.0%) were positive for neutralizing antibodies.

SAFETY RESULTS:

- Subcutaneous maintenance regimens of ustekinumab 90 mg administered q12w or q8w through Week 44 were generally well tolerated. Among all treated subjects, the overall safety profile was generally consistent with that observed in the randomized population.
- There were similar proportions of randomized subjects across the treatment groups with 1 or more treatment emergent AEs, SAEs, and infections through Week 44 or up to the time of dose adjustment. In the placebo, ustekinumab 90 mg q12w, and q8w groups, the proportions of subjects with:
  - treatment emergent AEs were 83.5%, 80.3%, and 81.7%, respectively.
  - treatment emergent SAEs were 15.0%, 12.1%, and 9.9%, respectively.
  - infections were 49.6%, 46.2%, and 48.1%, respectively.
- No additional notable differences were seen in the pattern of AEs observed in treatment groups when events after the time of dose adjustment were included in the analyses.
- Crohn's disease was the most frequently reported SAE across randomized treatment groups, and was reported for 5.3%, 3.8%, and 3.1% of subjects in the placebo, ustekinumab 90 mg SC q12w, and ustekinumab 90 mg SC q8w groups, respectively.
- Adverse events leading to discontinuation of study agent were 6.0%, 7.6%, and 3.1% in the placebo, ustekinumab 90 mg SC q12w, and ustekinumab 90 mg SC q8w groups, respectively and the overall number was low.
- No deaths or major adverse cardiovascular events (MACE) were reported through Week 44.
- The proportions of randomized subjects with serious infections through Week 44 were 2.3%, 5.3%, and 2.3% in the placebo, ustekinumab 90 mg q12w, and q8w groups, respectively and comparable results were observed for all treated subjects.
- One case of presumed primary active pulmonary TB was reported through Week 44 in a subject who was randomized to placebo SC in this study approximately 10 months after exposure to IV ustekinumab.
- There was one opportunistic infection: a nonserious AE of esophageal candidiasis in a nonrandomized subject who was an ustekinumab IV induction nonresponder receiving ustekinumab 90 mg q8w in this study and had received infliximab at the time of diagnosis.
- Two malignancies, both basal cell carcinomas, were reported in the randomized population through Week 44, 1 each in the placebo group and ustekinumab 90 mg q8w group. Eight additional malignancies were reported among the nonrandomized population, 6 non melanoma skin cancer (NMSC) in 3 subjects (2 subjects in the ustekinumab groups and 1 subject in the placebo group) and 2 other malignancies (metastatic adenocarcinoma of the small bowel and incidental carcinoid tumor) in 1 subject receiving ustekinumab 90 mg q12w.

- A small proportion of all treated subjects reported injection-site reactions (1.7% and 3.0% of subjects reported a placebo or ustekinumab injection-site reaction, respectively); however, there were no serious injection-site reactions through Week 44.
- No serious infusion reactions, possible anaphylactic reactions, or possible delayed hypersensitivity reactions to ustekinumab were reported in this study through Week 44.
- No relationship between the development of antibodies to ustekinumab and injection-site reactions was identified in this study.
- Markedly abnormal post baseline changes in hematology and chemistry laboratory values were infrequent, and the proportions of subjects with markedly abnormal changes in hematology and chemistry laboratory values were generally comparable across treatment groups.
- The safety profile of ustekinumab was generally consistent in subjects above and below the median body weight of this study.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- Study CNTO1275CRD3003 provided consistent and definitive evidence that the ustekinumab 90 mg SC q12w and q8w dose regimens were both effective at maintaining clinical response and clinical remission in adult subjects with moderate to severe Crohn's disease.
- The ustekinumab q8w regimen more dependably demonstrated efficacy than the q12w regimen across the range of endpoints, especially at higher level measures of efficacy
- Maintenance dosing with ustekinumab SC dose regimens of 90 mg q12w and 90 mg q8w was generally well-tolerated over 44 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 ustekinumab SC maintenance therapy.