
SYNOPSIS**Issue Date:** 25 Oct 2011

<u>Name of Sponsor/Company</u>	Janssen Research & Development
<u>Name of Finished Product</u>	STELARA
<u>Name of Active Ingredient(s)</u>	Ustekinumab

Protocol No.: C0743T26**Title of Study:** A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of Ustekinumab Therapy in Subjects with Moderately to Severely Active Crohn's Disease Previously Treated with TNF Antagonist Therapy**Study Name:** CERTIFI (Crohn's Evaluation of Response to Ustekinumab anti-IL12/23 for Induction)**EudraCT Number:** 2008-000649-77**NCT No.:** NCT00771667**Clinical Registry No.:** CR015238**Principal Investigator:** William J. Sandborn, MD, Mayo Clinic, Rochester, MN, USA**Study Centers:** 153 sites in North America, Europe, and Australia**Publication (Reference):** None**Study Period:** 21 Oct 2008—09 Dec 2010**Phase of Development:** 2b

Objectives: Primary: To evaluate the efficacy of ustekinumab in inducing clinical response, and to evaluate the safety of ustekinumab in subjects with moderately to severely active Crohn's disease who had received treatment with 1 or more TNF antagonists and had not responded initially, responded and then lost response, or were intolerant to this therapy at a dose approved for Crohn's disease. Secondary: To evaluate the efficacy of ustekinumab in inducing clinical remission, fistula response, and mucosal healing; to obtain data to support selection of a maintenance dose regimen for continued clinical development; to explore the pharmacokinetics and pharmacodynamics of ustekinumab therapy; and to evaluate the efficacy of ustekinumab in achieving delayed clinical response.

Methodology: In this randomized, double-blind, placebo-controlled, parallel-group, dose-ranging, Phase 2b study, all subjects were randomized at Week 0 to receive intravenous (IV) induction therapy with placebo or 1, 3, or 6 mg/kg ustekinumab. At Week 6, all subjects were evaluated for the primary endpoint of clinical response. At Week 8, based on their clinical response status at Week 6, subjects who had been randomized to ustekinumab induction therapy at Week 0 were rerandomized to receive subcutaneous (SC) maintenance doses of ustekinumab or placebo at Week 8 and Week 16. Subjects who responded to ustekinumab induction therapy were rerandomized separately from subjects who did not respond to ustekinumab induction therapy. Subjects who responded to IV placebo induction therapy were to receive SC placebo maintenance at Week 8 and Week 16; subjects who did not respond to IV placebo induction therapy were to receive SC ustekinumab injections at Week 8 and Week 16.

All subjects underwent the same safety and efficacy study evaluations regardless of the treatment received and all were to continue in the study, whether or not they were in clinical response at Week 6. Safety and efficacy evaluations were performed through Week 36.

An interim analysis was conducted after all subjects had completed the Week 6 visit (to direct the choice of induction dose(s) in the Phase 3 ustekinumab studies in Crohn's disease); no adjustments were made to the overall Type I error rate (0.05) for the primary analysis. An interim analysis was also conducted after all subjects had completed the Week 22 visit (to facilitate the choice of the maintenance dose regimen for use in the Phase 3 ustekinumab studies in Crohn's disease). An independent Data Monitoring Committee (DMC) monitored unblinded safety data throughout the duration of the study.

Number of Subjects (planned and analyzed): Approximately 500 subjects were planned to be enrolled at approximately 170 investigational sites; 526 subjects were randomized at 153 investigational sites. All 526 subjects were included in the efficacy and safety analyses; 394 subjects who received at least 1 dose of ustekinumab were included in the pharmacokinetic analyses.

Diagnosis and Main Criteria for Inclusion: Eligible subjects had to be ≥ 18 years of age, have moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score ≥ 220 but ≤ 450) for at least 3 months, with colitis, ileitis, or ileocolitis as confirmed by radiography and/or endoscopy, and have received infliximab, adalimumab, or certolizumab pegol at a dose approved for the treatment of Crohn's disease and either did not respond initially, responded initially but then lost response, or were intolerant to the medication. Subjects also had to meet criteria for concomitant medication stability, screening laboratory test results, and tuberculosis (TB) history and testing results.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab for IV administration (1, 3, or 6 mg/kg) was supplied as a single-use, sterile solution in glass vials (lot numbers 8GS04, 8IS53, 9CS2S, 9IS27). Ustekinumab for SC administration was supplied in prefilled syringes as a single-use, sterile solution (ie, ustekinumab 90 mg in 1 mL nominal volume [lot numbers 07M012, 08F012, 09E012]).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for SC administration was supplied in prefilled syringes as a single-use, sterile solution (ie, 1 mL of placebo [lot numbers 07C092, 08H022, 09E022]).

Duration of Treatment: All subjects were randomized at Week 0 to receive IV induction therapy with placebo or 1, 3, or 6 mg/kg ustekinumab. At Week 6, all subjects were evaluated for the primary endpoint of clinical response. At Week 8, based on their clinical response status at Week 6, subjects who had been randomized to ustekinumab induction therapy at Week 0 were rerandomized to receive SC maintenance doses of ustekinumab (90 mg) or placebo at Week 8 and Week 16. Subjects who responded to ustekinumab induction therapy were rerandomized separately from subjects who did not respond to ustekinumab induction therapy. Subjects who responded to IV placebo induction therapy received SC placebo maintenance at Week 8 and Week 16; subjects who did not respond to IV placebo induction therapy receive SC ustekinumab injections at Week 8 (270 mg) and at Week 16 (90 mg).

Criteria for Evaluation:

- **Pharmacokinetics (PK):** Serum ustekinumab concentration.
- **Immunogenicity:** Antibodies to ustekinumab.
- **Pharmacodynamics (PD):** Serum-based biomarkers, peripheral blood messenger ribonucleic acid [mRNA] expression, analysis of whole blood DNA.
- **Efficacy:** CDAI scores, ability to discontinue corticosteroid therapy, CRP concentrations, fecal lactoferrin and fecal calprotectin concentrations, fistula assessment, PG assessment, ileocolonoscopy.

- **Patient-reported outcomes:** Inflammatory Bowel Disease Questionnaire (IBDQ), Jenkins Sleep Evaluation Questionnaire (JSEQ).
- **Health economics:** Resource utilization.
- **Safety:** Adverse events (AEs), serious adverse events (SAEs), vital signs, infusion and injection site reactions, hematology and chemistry parameters, physical examinations, 12-lead ECGs.

Statistical Methods: Demographic and baseline disease characteristics were summarized for all randomized subjects. The proportion of subjects in clinical response at Week 6 (primary endpoint) was summarized and compared between treatment groups (ustekinumab 6 mg/kg vs placebo, ustekinumab 3 mg/kg vs placebo, and ustekinumab 1 mg/kg vs placebo) using a 2-sided 0.05 level Cochran-Mantel-Haenszel chi-square test, stratified by initial response to TNF antagonist therapy (yes or no). A fixed-sequence testing procedure was to be employed to control the Type I error rate at the 0.05 level. The study was to be considered positive if the test involving the highest ustekinumab dose (6 mg/kg) was positive, regardless of the test for all the other ustekinumab doses (3 mg/kg and 1 mg/kg). A fixed-sequence testing procedure was also employed to control the overall Type I error rate at the 2-sided 0.05 significance level over the major secondary endpoints of clinical remission at Week 6, clinical response at Week 4, and clinical remission at Week 22 among subjects randomized as responders to ustekinumab induction. In particular, the endpoints of clinical remission at Week 6 and clinical response at Week 4 were to be tested in sequential order if the primary endpoint was positive; the endpoint of clinical remission at Week 22 was also to be tested if the primary endpoint was positive. The analyses of the other secondary endpoints were not controlled for multiplicity; statements of statistical significance for these endpoints are based on nominal p-values.

The primary analysis was based on an intent-to-treat principle. Therefore, the efficacy data for each subject randomly assigned to a treatment group were to be analyzed according to the assigned treatment regardless of the actual treatment received.

Safety was assessed by summarizing the incidence and type of AEs and changes from baseline in clinical laboratory parameters for hematology and chemistry analyses. Safety evaluations were based on subjects who were treated with at least 1 administration of study agent (partial or complete) in the study.

RESULTS:

STUDY POPULATION:

In the induction phase, 526 subjects were randomly assigned in a 1:1:1:1 ratio to receive IV ustekinumab 1, 3, or 6 mg/kg or placebo. A total of 49 subjects (9.3%) discontinued study agent, slightly more than half due to unsatisfactory therapeutic effect or an AE of Crohn's disease and 17 for reasons classified as "other" (eg, withdrawal of consent, visit noncompliance, or not meeting inclusion/exclusion criteria); 477 subjects (90.7%) did not end their participation in the study.

In the maintenance phase, IV ustekinumab responders were randomized to SC ustekinumab (72 subjects) or SC placebo (73), IV ustekinumab nonresponders were randomized to SC ustekinumab (109) or SC placebo (110), IV placebo responders received SC placebo (28), and IV placebo nonresponders received 270/90 mg SC ustekinumab (85). A total of 63 subjects (13.2%) discontinued study agent, more in the SC placebo groups than in the SC ustekinumab groups; the most common reasons for discontinuation were unsatisfactory therapeutic effect and AE (the majority of which were an AE of Crohn's disease). A total of 336 subjects (70.4%) did not end their participation in the study.

Of the 526 subjects randomized in the induction phase, 309 (58.7%) were women; 490 (93.2%) were Caucasian. The median age was 38.0 years and median weight was 69.0 kg. Baseline demographic characteristics were generally similar across the 4 induction treatment groups, and in the maintenance treatment groups. Baseline disease characteristics were representative of a population of subjects with

moderate to severe Crohn's disease that was refractory to available therapies: median duration of Crohn's disease, 10.34 years; median CDAI score, 316.0; median IBDQ score, 116.0. Disease characteristics were generally similar across the 4 induction treatment groups and between the SC placebo and SC ustekinumab groups in the maintenance phase. Approximately 50% of subjects were receiving corticosteroids at baseline.

All 526 subjects initially randomized received at least 1 dose of study agent.

EFFICACY:

- Ustekinumab induced clinical response:
 - The proportion of subjects in clinical response at Week 6 (primary endpoint) was significantly greater in the 6 mg/kg ustekinumab group (39.7%) than in the placebo group (23.5%, $p = 0.005$). The proportions of subjects in clinical response at Week 6 in the 1 and 3 mg/kg ustekinumab groups were 36.6% and 34.1%, respectively.
 - The effect of ustekinumab on inducing clinical response was generally consistent across the subgroups.
 - In particular, subjects with an inadequate initial response to a TNF antagonist (ie, primary nonresponders), those who had a response followed by a loss of response (ie, secondary nonresponders), and those who were intolerant to a TNF antagonist had a clinical response consistent with that seen in all subjects.
 - Compared with Week 6, the proportions of subjects in clinical response were higher at Week 8 in the 6 mg/kg group and lower in the 1 and 3 mg/kg groups, suggesting a dose response.
- There were no significant differences among the treatment groups in the proportion of subjects in clinical remission at Week 6.
 - The proportions of subjects in clinical remission were higher at Week 8 than Week 6, particularly in the 6 mg/kg group (18.3% vs 12.2%).
- A greater proportion of subjects in the 6 mg/kg ustekinumab group had a fistula response at Week 6 (47.1%) compared with the other groups (15.8%, 10.0%, and 21.4%, respectively, in the ustekinumab 1 mg/kg and 3 mg/kg groups and the placebo group).
- At Week 6, reduction in CDAI, improvement in IBDQ, normalization of CRP, and reductions in fecal lactoferrin and fecal calprotectin were greater in all of the ustekinumab treatment groups compared with placebo and were significantly greater in the 6 mg/kg ustekinumab group.
- Among a subset of subjects with lesions at baseline, a greater proportion of subjects in the combined ustekinumab groups had mucosal healing at Week 6 (19.5%) compared with the placebo group (11.1%). Proportions were similar among the 3 ustekinumab groups.
- **Maintenance:** In subjects randomized as responders to ustekinumab induction, ustekinumab maintained clinical remission and clinical response:
 - The proportion of subjects in clinical remission at Week 22 was significantly greater in the SC ustekinumab group (41.7%) than in the SC placebo group (27.4%, $p = 0.029$).
 - The proportion of subjects in clinical response at Week 22 was significantly greater in the SC ustekinumab group (69.4%) than in the SC placebo group (42.5%, $p < 0.001$).
 - Among ustekinumab induction responders who were randomized to SC ustekinumab, no appreciable differences in the proportion of subjects in clinical response were observed at Week 22 based upon induction dose received; among those randomized to SC placebo,

however, the proportion of subjects in clinical response declined earlier among those who received lower induction doses.

- The proportion of subjects in sustained clinical response through Week 22 was significantly greater in the SC ustekinumab group (55.6%) than in the SC placebo group (32.9%, $p = 0.005$).
- Among subjects who were in remission at Week 6, 78.6% remained in clinical remission at Week 22 in the SC ustekinumab group, compared with 53.3% in the SC placebo group ($p = 0.056$).
- Additional measures of efficacy (ie, IBDQ, CRP, CDAI, fecal lactoferrin and fecal calprotectin) supported these findings.
- There was no evidence that additional treatment with ustekinumab in nonresponders was efficacious.
- In subjects who were nonresponders to placebo induction and who received 270 mg SC ustekinumab at Week 8, the proportions of subjects in clinical response and clinical remission 8 weeks after treatment were generally consistent with those observed with IV induction; in the absence of a control, however, these data are difficult to interpret.

PHARMACOKINETICS AND IMMUNOGENICITY:

- After a single IV administration of 1, 3, or 6 mg/kg ustekinumab, serum ustekinumab concentrations were proportional to dose and were detectable in almost all subjects through Week 8. Median peak serum ustekinumab concentrations, 1 hour after the infusion at Week 0, were 24.3 µg/mL, 71.6 µg/mL, and 144.1 µg/mL for the 1, 3, and 6 mg/kg induction treatment groups, respectively. At the end of induction (Week 8), median serum ustekinumab concentrations were 0.8 µg/mL, 3.1 µg/mL, and 7.0 µg/mL for the 1, 3, and 6 mg/kg induction treatment groups, respectively. The lowest ustekinumab dose group (1 mg/kg) had the highest proportion of subjects (10.3%) without detectable concentrations at Week 8.
- Despite the administration of different IV ustekinumab induction doses, subjects who received 90 mg SC maintenance doses reached similar ustekinumab concentration levels about 12 weeks after starting the SC maintenance regimen.
- At Week 22 (6 weeks after the last SC dose at Week 16), subjects who received SC ustekinumab had sustained levels of ustekinumab during maintenance, in contrast with subjects who received SC placebo maintenance.
- Among 427 ustekinumab-treated subjects with appropriate samples for the assessment of antibodies to ustekinumab, 3 (0.7%) subjects were positive for antibodies to ustekinumab through the final study visit at Week 36. All 3 had low antibody titers (1:10 to 1:80) and were positive for neutralizing antibodies.

PATIENT-REPORTED OUTCOMES:

- For the 1, 3, and 6 mg/kg IV ustekinumab doses, mean improvement from baseline in IBDQ at Week 6 (19.9, 22.7, and 24.8, respectively) was statistically significant compared with that seen in the placebo group (11.8; $p < 0.05$ for all comparisons).
- At Week 6, a greater proportion of subjects randomized to the ustekinumab 1, 3, and 6 mg/kg treatment groups (45.0%, 47.7%, and 54.7%, respectively) had a ≥ 16 -point improvement from baseline in IBDQ scores compared with the placebo group (33.1%).
- At Week 22, mean IBDQ scores in Week 6 ustekinumab responders were significantly higher for subjects receiving SC ustekinumab compared with SC placebo.

- At Week 22, mean IBDQ dimension scores in Week 6 ustekinumab responders were significantly higher for subjects receiving SC ustekinumab compared with SC placebo ($p < 0.05$ for all comparisons).
- Among subjects randomized as responders, a significantly greater proportion of subjects in the SC ustekinumab group (68.1%) had a ≥ 16 -point improvement from baseline in the IBDQ score at Week 22 compared with the SC placebo group (44.9%, $p = 0.005$).
- Among subjects randomized as responders who had at least 16-point improvement at Week 6 from baseline, 71.9% in the SC ustekinumab group had a ≥ 16 -point response at Week 22 compared with 54.9% in the SC placebo group; at Week 36, 43.9% in the SC ustekinumab group had a ≥ 16 -point response compared with 27.5% in the SC placebo group.

HEALTH ECONOMICS:

- All 3 ustekinumab induction treatment groups achieved significant improvement in productivity compared with the placebo group at Week 6 ($p < 0.05$ for each ustekinumab group vs placebo).
- The 1 mg/kg ustekinumab group and the combined ustekinumab groups achieved significant decreases in Crohn's disease-related hospitalizations at Week 6 ($p < 0.05$ for ustekinumab group vs placebo). No significant differences were observed in the 3 and 6 mg/kg ustekinumab groups.
- No notable differences were observed among all ustekinumab groups compared with placebo for Crohn's disease-related surgeries at Week 6.
- No notable differences in change from Week 6 in productivity at Week 22 and Week 36 were observed among the maintenance treatment groups.

SAFETY:

AEs and SAEs: Induction Phase

- Intravenous ustekinumab at 1, 3, and, 6 mg/kg was well tolerated, with a safety profile generally comparable with placebo through Week 8.
- SAEs were uncommon in all treatment groups in the induction phase through Week 8, and except for Crohn's disease, no individual SAE was reported in more than 1 subject in any IV ustekinumab dose 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 placebo or 1 or 3 mg/kg ustekinumab groups.
- Infusion reactions were uncommon and nonserious, and occurred at a similar rate in all treatment groups.

AEs and SAEs: Maintenance Phase

- Among subjects randomized as responders and nonresponders, SC ustekinumab was also well tolerated, with a safety profile similar to SC placebo.
- The regimen of 270 mg SC ustekinumab at Week 8 followed by 90 mg at Week 16 was also well tolerated.
- SAEs occurred at a similar frequency with SC placebo and SC ustekinumab groups. Gastrointestinal (GI) disorder system organ class SAEs, particularly events of Crohn's disease, were reported most frequently across the treatment groups. No non-GI SAEs occurred in more than 1 subject in any dose group in the maintenance phase.

- There were no deaths, serious opportunistic infections, or cases of TB. One skin malignancy of basal cell carcinoma was reported.
- The proportions of subjects with infections were similar across all treatment groups in the maintenance phase. SAEs of infection were uncommon and similar in frequency across treatment groups.
- No major adverse cardiovascular events occurred.
- Injection site reactions were uncommon and nonserious, and occurred at a similar rate in all treatment groups.

Laboratory Test Results

- Markedly abnormal changes in hematology laboratory values were observed in some subjects during both the induction and maintenance phase, with the most common being a decrease in absolute lymphocyte counts in the placebo group.
- No markedly abnormal changes in chemistry laboratory values were observed in more than 1 subject on more than 1 occasion in any treatment group during the induction phase; in the maintenance phase, decreased phosphate occurred in 2 subjects on more than 1 occasion in the combined SC ustekinumab group.

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

CONCLUSIONS:

Study C0743T26 provided clinically important evidence that in subjects with moderate to severe Crohn's disease who had previously failed TNF antagonist therapy, ustekinumab was effective at inducing and maintaining clinical response. Specifically, in this 36-week study of ustekinumab administered at 1, 3, or 6 mg/kg IV at Week 0 and then at 90 mg SC at Week 8 and Week 16:

- Ustekinumab induced clinical response:
 - The proportion of subjects in clinical response at Week 6 was significantly greater in the 6 mg/kg ustekinumab group (39.7%) than in the placebo group (23.5%, $p = 0.005$). The proportions of subjects in clinical response at Week 6 in the 1 and 3 mg/kg ustekinumab groups were 36.6% and 34.1%, respectively.
 - The effect of ustekinumab on inducing clinical response was generally consistent across the subgroups, including in TNF antagonist primary and secondary nonresponders and in those who were intolerant to a TNF antagonist.
 - Compared with Week 6, the proportions of subjects in clinical response were higher at Week 8 in the 6 mg/kg group and lower in the 1 and 3 mg/kg groups, suggesting a dose response.
- There were no significant differences between the treatment groups in the proportion of subjects in clinical remission at Week 6.
- Additional measures of efficacy (ie, IBDQ, CRP, CDAI, fistula response, fecal lactoferrin and fecal calprotectin) supported these findings.

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- In subjects randomized as responders to ustekinumab induction, SC ustekinumab maintained clinical remission and clinical response:
 - The proportions of subjects in clinical remission and clinical response at Week 22 were significantly greater in the SC ustekinumab group than in the SC placebo group.
 - Among subjects who were in remission at Week 6, a greater proportion of subjects in the SC ustekinumab group remained in clinical remission at Week 22 compared with the SC placebo group.
 - Ustekinumab was generally well tolerated in this population, with a safety profile consistent with that reported in other indications.
 - The safety of IV ustekinumab was comparable to placebo through Week 8.
 - Subcutaneous ustekinumab was similarly well tolerated in the maintenance phase, with a safety profile similar to SC placebo.
 - The proportions of subjects with infections were similar across all ustekinumab and placebo treatment groups through Week 8 as well as in the maintenance phase. In the induction phase, more SAEs of infection were reported in the 6 mg/kg ustekinumab treatment group. In the maintenance phase, SAEs of infection were uncommon and similar in frequency across treatment groups.
 - There were no deaths, serious opportunistic infections, or cases of TB in the study. One skin malignancy of basal cell carcinoma was reported, and there were no major adverse cardiovascular events.
 - Infusion reactions and injection site reactions were uncommon and nonserious, and occurred at a similar rate in all treatment groups.
 - Three subjects who received ustekinumab were positive for antibodies to ustekinumab through the final study visit at Week 36.

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