SYNOPSIS

Issue Date: 17 May 2012

Name of Sponsor/Company	Janssen Research and Development
Name of Finished Product	STELARA®
Name of Active Ingredient(s)	Ustekinumab

Protocol No.: C0743T09

Title of Study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Efficacy and Safety of Ustekinumab in the Treatment of Subjects with Moderate to Severe Plaque-type Psoriasis

Study Name: PHOENIX 2

EudraCT Number: 2005-003530-17

NCT No.: NCT00307437

Clinical Registry No.: CR006325

Principal Investigator: Prof. Kristian Reich - SCIderm GmbH Stephansplatz 5 Hamburg, Germany

Study Center(s): 70 investigative sites: 3 sites in Austria, 19 sites in Canada, 1 site in France, 10 sites in Germany, 2 sites in Switzerland, 3 sites in the United Kingdom, and 32 sites in the United States.

Publication (Reference): Papp KA, Langley RG, Lebwohl M, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2). *Lancet*. 2008;371(9625):1675-1684.

Study Period: 03 Mar 2008 – 10 Oct 2011

Phase of Development: 3

Objectives: The primary objective of this study was to evaluate the efficacy and safety of ustekinumab in the treatment of subjects with moderate to severe plaque psoriasis. Secondary objectives were to: (1) Evaluate dosing interval adjustment in subjects who inadequately respond to their starting dose regimen and (2) Evaluate the impact of ustekinumab on quality of life. The results of the primary and secondary endpoints were presented in the 28-Week and 52-Week Clinical Study Reports (CSR). The focus of this report is the analyses of the efficacy data during the long-term extension (LTE) period from Week 52 through Week 244 and cumulative safety of long-term dosing and dose adjustment with ustekinumab through Week 264 (Year 5). In addition, the results of a vaccine substudy conducted between Weeks 184-240 comparing T-cell dependent and independent immune responses in psoriasis subjects treated with long term ustekinumab are also presented.

Methodology: This was a multicenter, randomized, placebo-controlled, double-blind, parallel, 3-arm study of subcutaneous (SC) injections of ustekinumab 45 mg (Group 1), ustekinumab 90 mg (Group 2), and placebo (Group 3) in subjects with moderate to severe plaque psoriasis. The study was designed to evaluate safety and efficacy of 2 dosing regimens of ustekinumab: 45 mg at Week 0 and Week 4, followed by 45 mg q12week (w) maintenance therapy (45 mg q12w regimen), and 90 mg at Week 0 and Week 4, followed by 90 mg q12w maintenance therapy (90 mg q12w regimen). The safety and efficacy of these 2 regimens were evaluated during 4 study periods occurring over approximately 5 years: a 12-week placebo-controlled period; a subsequent 16-week placebo crossover and active treatment period; a randomized dose interval adjustment period beginning at Week 28; and a LTE period beginning at Week 52 for an additional 4 years.

An open-label non-randomized parallel design vaccine substudy was implemented to examine immune responses to tetanus toxoid and *Streptococcus pneumoniae* in subjects who received long-term treatment with ustekinumab. Two groups (approximately 60 subjects each) were to receive single administrations of the tetanus, diphtheria and acellular pertussis (Tdap) and pneumococcal vaccines and then were followed for safety and vaccine responses for 4 weeks. The first group (Group 1) included subjects at 10 sites in Canada who were enrolled in the C0743T09 study and received either 45 mg or 90 mg ustekinumab. The second group (Group 2) was comprised of subjects with moderate to severe chronic plaque psoriasis who were not currently receiving systemic therapy for psoriasis.

Number of Subjects (planned and analyzed): 1200 planned (400 subjects per group); 1230 subjects were randomized to treatment and analyzed for efficacy and for safety; 1212 subjects were analyzed for pharmacokinetics of ustekinumab.

Diagnosis and Main Criteria for Inclusion: Men or women ages 18 years or older with moderate to severe plaque psoriasis who were candidates for systemic therapy or phototherapy and had a Psoriasis Area and Severity Index (PASI) ≥ 12, and at least 10% of their total body surface area (BSA) involved.

Test Product, Dose and Mode of Administration, Batch No.: 45 or 90 mg ustekinumab (0.5 or 1.0 mL, respectively) was administered by SC injection. Subjects randomized to the 45 or 90 mg ustekinumab groups were to receive ustekinumab at Weeks 0, 4, and 16. Subjects randomized to placebo, were to receive 45 mg or 90 mg ustekinumab at Weeks 12 and 16. Subsequent dosing regimens were to be determined by each subject's response status according to the study design. Four lots of ustekinumab (D05PE7427, D05PE7428, 6DS50, and 6DS4Z) were used for liquid in vial (LIV) and 2 lots of ustekinumab (06J091, and 06J092) were used for pre-filled syringes (PFS). The following lots of ustekinumab were used from Week 208 through Week 264 (all supplied in PFS): 09G041, 09G042, 09H031, and 09H052.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was administered by SC injection. Subjects randomized to placebo were to receive 2 placebo injections (0.5 mL and 1.0 mL) at Weeks 0 and 4. Subjects randomized to the ustekinumab groups were to receive 2 placebo injections (0.5 mL and 1.0 mL) at Week 12. To maintain the blind associated with ustekinumab dose administration, each injection of ustekinumab was given with a placebo injection through the Week 52 database lock: 45 mg administration included a 1.0 mL placebo injection and 90 mg administration included a 0.5 mL placebo. Four lots of placebo (D05PE7429, D05PE7430, 6DS4I, and 6DS4R) were used.

Vaccine Therapy, Dose and Mode of Administration, Batch No.: The following two approved non-live vaccines were used as part of the vaccine substudy: ADACEL® (Sanofi-Pasteur) Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine Adsorbed (Tdap) vaccine was supplied as a sterile liquid suspension of tetanus with diphtheria toxoids and acellular pertussis components adsorbed onto aluminum phosphate, for intramuscular administration. Each dose of ADACEL vaccine (0.5 mL) is provided in a pre-filled syringe. One lot of ADACEL (C3125AC) was used for the entire substudy. PNEUMOVAX®23 (Merck-Frost) vaccine was supplied as a clear, sterile solution supplied in a single-dose vial (0.5-mL dose) administered intramuscularly. One lot of PNEUMOVAX23 vaccine (1573Y) was used for the entire substudy.

Duration of Treatment: First to last administration of study agent was either 240 weeks (subjects maintained on q8w dosing), or up to 244 weeks (subjects adjusted to q12w dosing); efficacy, pharmacokinetic and immunogenicity data were evaluated through Week 244 and safety data were evaluated through Week 264 (Year 5).

Criteria for Evaluation: All randomized subjects were summarized in the description of the study population. All randomized subjects were included in the primary efficacy, and selected secondary analyses; subjects were analyzed according to the assigned treatment group. Secondary efficacy analyses were based on all randomized subjects or on the subset of subjects with available outcome measurements

according to their randomized group. Safety evaluations were based on subjects who received at least 1 administration of study agent; subjects were analyzed according to the actual treatment received. Subjects that received vaccines as part of the vaccine substudy were included in immune response analyses and the safety analyses for the vaccine substudy.

Pharmacokinetics/Pharmacodynamics: Blood samples were collected from all subjects at selected timepoints through Week 244, for the determination of serum ustekinumab concentration as well as antibodies to ustekinumab.

Efficacy: Efficacy evaluations in this CSR included the Psoriasis Area and Severity Index (PASI) and the Physician's Global Assessment (PGA). In addition, the relationship between efficacy and antibodies to ustekinumab was examined.

Safety: Safety evaluations for the overall population included the following: 1) AE and SAE assessment, infections, and injection-site reaction evaluation; 2) tuberculosis evaluation; 3) changes in routine laboratory analyses (ie, complete blood count, blood chemistry); 4) evaluation of weight and 5) skin examination.

Statistical Methods: Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, maximum, and minimum for continuous variables, and counts and percentages for discrete variables were used to summarize most data. In addition to statistical analyses, graphical data displays and subject listings were also used to summarize the data. For data displays (tables and figures), the number (n) of subjects evaluated at each timepoint is provided. Efficacy through Year 5 in this report was primarily evaluated for the overall population and the subjects who dose adjusted during the LTE. Safety through Year 5 in this report was primarily evaluated by 2 sets of analyses: safety data in the overall population who received at least 1 injection of ustekinumab; and safety in subjects who were dose adjusted as compared with those who were not dose adjusted.

RESULTS:

STUDY POPULATION RESULTS:

The demographic characteristics of the overall study population were discussed in the 28-Week CSR. Demographic characteristics were generally well balanced across treatment groups for subjects who were randomized at Week 0. The population of subjects enrolled in this study was consistent with other studies of biologic drugs in subjects with psoriasis:[7,4]

- approximately twice as many men (68.3%) as women (31.7%)
- majority of subjects were Caucasian (91.7%)
- median age was 47.0 years
- median weight was 88.6 kg

PHARMACOKINETIC RESULTS:

- An approximate dose-proportionality in trough serum concentrations of ustekinumab was observed in subjects who continued q12w maintenance dosing through Week 244.
- Trough serum ustekinumab concentrations were generally maintained at steady state over time through Week 244 in subjects who continued q12w maintenance dosing through Week 244.
- The overall incidence of antibodies to ustekinumab through Year 5 was 5.4%. Antibody responses to ustekinumab were predominantly low titers.
- There were no additional subjects who became positive for antibodies to ustekinumab after Week 52 through Year 5.

- The majority of subjects who were positive for antibodies to ustekinumab had antibodies that were able to neutralize the bioactivity of ustekinumab in vitro.

EFFICACY RESULTS:

- Over 244 weeks, approximately 70% of subjects continued to receive study agent through the last scheduled dose, with a similar high retention rate in both the 45 and 90 mg groups.
- In a setting where dose adjustment was allowed at the investigator's discretion, PASI 50, PASI 75, and PASI 90 response rates in the originally randomized population were maintained or increased through Week 244 in both the 45 mg and 90 mg groups.
  - During the LTE (Week 52 through Week 244), PASI 50, PASI 75, and PASI 90 response rates were generally sustained. At Week 244, the PASI 75 response rate for the 45 mg and 90 mg groups was 76.5% and 78.6%, respectively, and the PASI 90 response rate was 50.0% and 55.5% for 45 mg and 90 mg groups, respectively.
  - During the LTE, a PGA of cleared or minimal was achieved at Week 244 by 54.0% and 58.6% of subjects in the 45 mg and 90 mg groups, respectively.
- During the LTE (Week 52 through Week 244), PASI 50, PASI 75, and PASI 90 response rates were generally sustained when analyzed by weight. Despite a higher proportion of subjects in the >100 kg strata who dose adjusted, response rates tended to be higher in subjects weighing ≤ 100 kg.
- During the LTE, 552 dose adjustments were made (349 adjustments from q12w to q8w and 203 adjustments from 45mg q8w to 90 mg q8w) of which PASI assessments were available for 454 at the time of dose adjustment; 50.7% (230/454) of dose adjustments were made when subjects had at least a PASI 75 response and 89.9% were made when subjects had at least a PASI 50 response.
- During the LTE, among subjects with <PASI 75 response at time of dose adjustment
  - 78.6% (66/84) in the 45 mg group and 71.6% (48/67) in the 90 mg group achieved PASI 75 response 48 weeks after dose adjustment from q12w to q8w.
  - 56 subjects dose adjusted from 45 mg q8w to 90 mg q8w. At 48 weeks after dose adjustment, 68.6% (35/51) had achieved PASI 75 response.

SAFETY RESULTS:

Overall, ustekinumab was generally well tolerated through 5 years of continuous therapy. Through Week 264 (Year 5), 1212 subjects received least 1 dose of ustekinumab for a total of 5037 patient years of follow-up. The average number of administrations was 20.8 in the combined ustekinumab group, and the median total dose was 1800 mg.

Adverse Events

- The rate and types of AEs through Year 5 were generally comparable across both dose groups. For both dose groups, the rates generally decreased over time in the by-year analyses and the types of AEs remained consistent over time. The types of events were consistent with that observed in previous reports.
- Through Year 5, the proportion of subjects reporting AEs was comparable for those who never dose adjusted (remained on q12w) vs. those who ever dose adjusted (required dose adjustment to q8w).
- Through Year 5, 10.0% of subjects discontinued ustekinumab due to an adverse event, with similar rates between 45 (9.1%) and 90 mg (10.9%) groups. The rate of discontinuation due to adverse event was stable in the by-year analyses.

- Through Year 5, the proportion of subjects who discontinued ustekinumab due to an adverse event was slightly higher for subjects who remained on q12w (10.8%) vs. those who required dose adjustment to q8w (7.6%).

Serious Adverse Events

- Through Year 5, a total of 12 (1.0%) subjects died while participating in the study:
  - By randomized assignment, 5 (0.8%) subjects in the 45 mg group died (0.20 per 100 subject years) and 7 (1.2%) subjects in the 90 mg group died (0.28 per 100PY) for overall rate of 0.24 events per 100 subject years.
  - By dose received, 3 subjects died while receiving 45 mg (0.15 per 100PY) and 9 subjects died while receiving 90 mg (0.29 per 100 subject years).
  - Based upon medical review, the 12 deaths do not reveal an unusual pattern in the causes of death and the causes of death were consistent with that expected in a psoriasis population
- Through Year 5, the rate and types of SAEs were generally comparable across both treatment groups. The 3 SOCs in which SAEs were most commonly reported were Cardiac disorders, Infections and infestations, and Neoplasms benign, malignant, and unspecified (including cysts and polyps).
- When SAEs were examined in the by-year analyses, substantial increases in SAE rates were not observed. Rates were generally stable and comparable in the 45 mg and 90 mg dose groups.
- Through Year 5, the proportion of subjects reporting SAEs was comparable for those who remained on q12w vs. those who dose adjusted to q8w.

Infections

- The rate and type of infections through Year 5 were generally comparable across both treatment groups. For both 45 mg and 90 mg dose groups, the types of infections remained consistent over time while the rates generally decreased over time in the by-year analysis.
- The overall rate of serious infections was comparable between 45 mg and 90 mg either by dose randomized or dose received. The rate of serious infections was stable in the by-year analyses.
- Through Year 5, the proportion of subjects reporting infection or serious infection was comparable for those who remained on q12w vs. those who dose adjusted to q8w.
- Through Year 5, the pattern of serious infections was consistent with that observed in previous reports. There were no opportunistic infections, or cases of active TB, atypical mycobacterial infection, or systemic fungal infection.

Injection Site Reactions and Possible Anaphylactic or Serum-like Sickness

- Through Year 5, ustekinumab administrations were generally well tolerated.
- The most commonly reported injection-site reaction was injection-site erythema, which trended toward a higher rate with 90 mg administrations compared to 45 mg administrations as was also observed in previous reports.
- No cases of possible anaphylaxis or serum sickness-like reactions to ustekinumab were reported.
- Overall, there was no association between the development of antibodies to ustekinumab and the development of injection-site reactions.

Malignancies

- The rate and pattern of non-melanoma skin cancer (NMSC) were generally comparable across both treatment groups over 5 years of treatment. For the 45 mg group, the rate of NMSC was stable over time and in the 90 mg group, the rate of NMSC decreased from Year 1 through Year 5 in the by-year analysis. The overall ratio of BCC to SCC remained stable at 3:1.
- The rate of other malignancies was slightly higher in the 90 mg group (19/606 subjects) than the 45 mg group (14/606 subjects) by dose randomized. This was also true for the 90 mg group (23 subjects) vs. 45 mg group (10 subjects) for dose received. While there was some year to year variability observed, the rate of other malignancies generally remained stable over time in both the 45 mg and 90 mg groups.
- The pattern of malignancies was comparable to that observed through Year 4 and no cases of lymphoma were reported in this study.
- The rates of both NMSC and other malignancies were slightly lower in subjects who dose adjusted compared to those who remained on q12w dosing.

Cardiovascular Events

- The proportion of subjects reporting cardiac disorder AEs was comparable for both dose groups. No consistent pattern of cardiovascular AEs was observed.
- The rate of cardiac disorder SAEs was comparable across both the 45 mg and 90 mg groups and remained stable over time.
- The overall rate of major adverse cardiovascular events (MACE) was slightly lower in the 90 mg group vs. the 45 mg group both by dose randomized and by dose received. The rate of MACE was stable in the by-year analyses.
- The overall rate of MACE for subjects who ever dose adjusted vs. never dose adjusted was comparable for subjects in the 90 mg group and higher in subjects who never dose adjusted in the 45 mg group.

Adverse Events of Psoriasis

- The rate of psoriasis AEs was comparable between the 45 mg and 90 mg groups and generally comparable to that observed through Year 4.

Laboratory Test Results

- Therapy with ustekinumab over 5 years did not produce any clinically meaningful changes from baseline in hematology or chemistry values.
- The pattern and rate of markedly abnormal changes in hematology and chemistry values through Year 5 was generally comparable across both treatment groups.

VACCINE RESPONSES:

- Response to tetanus toxoid and pneumococcal vaccinations was comparable between subjects treated with long-term ustekinumab and subjects with moderate to severe psoriasis who were not receiving systemic therapy.
- Immune responses were similar between the subjects treated with long-term ustekinumab and subjects with moderate to severe psoriasis who were not receiving systemic therapy, regardless of the baseline antibody status (eg, protective vs. not protective at baseline).
- The rate of adverse events was higher in the long-term ustekinumab-treated group (26.7%) than the control group (8.9%), and was primarily driven by a higher rate of injection site reactions to vaccinations in the ustekinumab-treated subjects. Injection site reactions to vaccinations were generally mild.

STUDY LIMITATIONS: The following considerations should be taken into account when interpreting the results:

1. After the Week 52 database lock, the study was open label; subjects and investigators were unblinded to the dose group they were in.
2. Dose adjustment (dosing interval and/or dose level) was conducted in a non-randomized fashion after Week 28.
3. After the Week 52 database lock, subjects could dose adjust 45 mg to 90 mg at the investigator discretion.

The above limitations could result in confounding of the following:

1. Assessment of safety and efficacy of dose response,
2. Assessment of safety and efficacy of dose adjustment.

CONCLUSION(S):

- Continuous dosing with both 45 and 90 mg ustekinumab maintained high levels of clinical response.
- Due to flexible study design during the long-term extension, dose adjustment occurred frequently, even in subjects with PASI 75 response.
- Dose adjustment in this setting improved clinical response, especially in the 45 mg group.
- Response to tetanus toxoid and pneumococcal vaccinations was comparable between subjects treated with long-term ustekinumab and subjects with moderate to severe psoriasis who were not receiving systemic therapy.
- With 5 years of continuous dosing with approximately 5000 subject years of exposure, the safety profile of ustekinumab from this trial remains consistent with that observed in other ustekinumab psoriasis studies and supports a favorable benefit-risk profile in this population.

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