SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	STELARA®
Name of Active Ingredient(s)	ustekinumab

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Status: Approved

Date: 16 December 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1275PSA3001

Title of Study: A Phase 3 Multicenter, Randomized, Double-blind, Placebo controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects with Active Psoriatic Arthritis

Study Name: PSUMMIT I

EudraCT Number: 2009-012264-14

NCT No.: NCT01009086

Clinical Registry No.: CR016315

Principal Investigator(s): [redacted] MD, [redacted] Scotland

Study Center(s): 104 study sites

Publication (Reference): McInnes IB, Kavanaugh A, Gottlieb AB, et al, on behalf of the PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet; 2013 Aug 31;382(9894):780-9. doi: 10.1016/S0140-6736(13)60594-2. Epub 2013 Jun 13.

Study Period: 30 November 2009 (first informed consent) to 30 May 2013 (last study-related procedure for Week 108); database lock (DBL), 11 July 2013

Phase of Development: 3

Objectives: The primary objectives of this study were to evaluate the efficacy of ustekinumab in subjects with active psoriatic arthritis (PsA) by assessing the reduction in signs and symptoms of PsA and to evaluate the safety of ustekinumab in this population.

The secondary objectives of this study were to evaluate the efficacy of ustekinumab in improving physical function; improving psoriatic skin lesions; and inhibiting the progression of structural damage.

Methodology: This was a randomized, double-blind, placebo-controlled, parallel, multicenter, 3-arm study (with early escape at Week 16) of ustekinumab in subjects with active PsA. A total of 615 subjects were randomized to receive treatment with subcutaneous (SC) injections of ustekinumab 45 mg (45 mg group), ustekinumab 90 mg (90 mg group), or placebo at Weeks 0 and 4, followed by dosing every

12 weeks (q12w), with the last dose at Week 88. Subjects randomized to placebo were eligible for crossover to receive ustekinumab 45 mg at Weeks 24 and 28, followed by q12w dosing, with the last dose at Week 88. The expected duration of exposure to study agent was 100 weeks. Subjects were followed for efficacy through Week 100 and for safety through Week 108. Investigative study sites and subjects remained blinded to treatment assignment until the last enrolled subject completed the Week 108 evaluations and the database was locked.

Number of Subjects (planned and analyzed): A target of 600 subjects was planned (200 subjects in each group) and 615 subjects were randomly assigned: 205, 204, and 206 subjects in the 45 mg, 90 mg, and placebo groups, respectively. At Week 0, 614 randomized subjects received their assigned treatment (1 subject in the placebo group withdrew consent and was never treated) and were included in the analysis.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women between 18 and 99 years of age, with a diagnosis of active PsA for at least 6 months before the first administration of study agent and with 5 or more swollen and tender joints at screening and at baseline. At screening, subjects had to have C-reactive protein (CRP) ≥0.3 mg/dL (modified to ≥0.3 mg/dL from ≥0.6 mg/dL with Protocol Amendment 3 dated 27 Oct 2010; upper limit of normal 1.0 mg/dL), at least 1 of the PsA subsets, and active plaque psoriasis or a documented history of plaque psoriasis.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab was supplied in a prefilled syringe as a single-use, sterile solution in a BD Hypak™ 1 mL, type 1 glass syringe with a 27-gauge, ½-inch fixed needle. There were 2 dose strengths (ie, 90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume). Each 1 mL of ustekinumab solution contained 90 mg ustekinumab, L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present. Eight lots of ustekinumab (batch numbers: 08F011, 08F012, 09G041, 09G042, 10C051, 10C052, 11C051, and 11C052) were used in the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was supplied in a prefilled syringe as a single-use, sterile solution in a BD Hypak™ 1 mL, type 1 glass syringe with a 27-gauge, ½-inch fixed needle. There were 2 dose volumes (ie, 1 mL nominal volume or 0.5 mL nominal volume). Each 1 mL of placebo solution contained L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present. Six lots of placebo (batch numbers: 08H021, 08H022, 09E021, 09E022, 10E011, and 10E012) were used in the study.

Duration of Treatment: A total of 615 subjects was randomized in a 1:1:1 ratio to 1 of the 3 groups and received treatment with ustekinumab 45 mg, ustekinumab 90 mg, or placebo SC at Weeks 0 and 4 followed by a q12w dose regimen, with the last dose at Week 88. At Week 16, subjects with <5% improvement from baseline in both tender and swollen joint counts were eligible for early escape; subjects in the 45 mg and placebo groups began to receive ustekinumab 90 mg and 45 mg, respectively, and subjects randomized to 90 mg remained on 90 mg. Subjects randomized to placebo who did not qualify for early escape were to crossover to receive ustekinumab 45 mg at Weeks 24 and 28 followed by q12w dosing, with the last dose at Week 88. Subjects were followed for efficacy through Week 100 and for safety through Week 108. The first and second DBLs occurred at Week 24 and Week 52, respectively, and the results were reported in the CNTO1275PSA3001 24-week Clinical Study Report (CSR) and CNTO1275PSA3001 52-week CSR. Results for the radiographic endpoints through Week 52 were presented in a separate report according to the prespecified integrated analysis of the combined radiographic data from the similarly designed CNTO1275PSA3001 and CNTO1275PSA3002 studies. This 108-week CSR presents the data from the final 108-week DBL, including radiographic data collected for CNTO1275PSA3001 at Week 100.

Criteria for Evaluation:

Pharmacokinetics: Serum ustekinumab concentrations were summarized through Week 88 for subjects treated with ustekinumab. Serum ustekinumab concentrations were also summarized by methotrexate (MTX) use at baseline and by subject weight at baseline (≤100 kg versus >100 kg). The relationships of serum ustekinumab concentrations and selected efficacy parameters were also assessed.

Immunogenicity: The incidence of antibodies to ustekinumab during the study was summarized for all subjects who had appropriate serum samples for antibody detection. The relationships of antibodies to ustekinumab with serum ustekinumab concentrations and selected efficacy and safety measures were also assessed.

Efficacy: Efficacy data were summarized primarily after Week 52 through Week 100 and included PsA and psoriasis response evaluations. PsA response evaluations included American College of Rheumatology (ACR) responses (which include joint assessments, the Disability Index of the Health Assessment Questionnaire [HAQ-DI], and visual analog scales [VAS] for the patient's assessment of pain and for patient and physician global assessments of disease activity), the Disease Activity Index Score 28 using CRP (DAS28), assessments of dactylitis and enthesitis, imaging evaluations (radiographs of hands and feet at Week 100), the modified Psoriatic Arthritis Responder Criteria (PsARC), and the 36-item Short Form Health Survey (SF-36). Psoriasis evaluations included the proportions of subjects with Psoriasis Area and Severity Index (PASI) responses and improvements from baseline in the Dermatology Life Quality Index (DLQI). The potential pharmacoeconomic benefit of ustekinumab treatment was also assessed.

Safety: Safety data were summarized through Week 108 for subjects treated with ustekinumab. Safety evaluations were monitored for all subjects and included assessment of adverse events (AEs) and injection-site reactions, vital sign measurements (heart rate and blood pressure), and physical evaluations (waist circumference and weight). Tuberculosis (TB) evaluations were performed, including the QuantiFERON®-TB Gold Test and the Mantoux tuberculin skin test (in countries where QuantiFERON®-TB Gold Testing was not licensed). Samples for routine laboratory analyses were collected.

Statistical Methods: Descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum and maximum for continuous variables, and counts and percentages for categorical variables were used to summarize data. Graphical presentations of the data were also used.

RESULTS:

STUDY POPULATION

Baseline demographic and disease characteristics were described in the CNTO1275PSA3001 24-Week CSR. In summary, subjects' demographic characteristics at baseline were generally well balanced across treatment groups; 53.7% were men and 96.6% were Caucasian, with a median age of 48.0 years and median weight of 86.0 kg. Baseline disease characteristics were generally comparable across the treatment groups and indicative of subjects with PsA of moderate to severe activity and significant psoriatic skin involvement, with a substantial negative impact on quality of life.

- Through Week 108, 20.3% of subjects discontinued study agent across the randomized treatment groups, including 6.5% due to lack of efficacy and 5.4% due to withdrawal of consent. The proportions of subjects who discontinued study agent through Week 108 were higher in the 45 mg group than the 90 mg group: 5.4% versus 3.9%, respectively, discontinued study agent due to AEs, and 7.3% versus 4.4%, respectively, discontinued study agent due to lack of efficacy.
- Among subjects initially randomized to placebo (including those who qualified for early escape at Week 16 or crossed over at Week 24), the proportions of subjects who discontinued study agent

through Week 108 were similar to those in the 45 mg group: 5.8% discontinued study agent due to an AE and 7.8% discontinued study agent due to lack of efficacy.

PHARMACOKINETIC RESULTS

Pharmacokinetics

- Dose proportionality in serum ustekinumab concentration was observed when comparing mean serum ustekinumab concentrations between the 45 mg only and 90 mg groups through Week 88.
- Steady state was achieved at Week 28 for both the 45 mg only and 90 mg groups, and trough serum ustekinumab concentrations were maintained at steady state through Week 88.
- There was no evidence of accumulation in serum ustekinumab concentrations over time.
- A higher proportion of subjects with trough serum ustekinumab concentrations below the lowest quantifiable sample concentration of the assay (BQL) was observed in the 45 mg only group compared with the 90 mg group through Week 88.
- Within each treatment group, mean trough serum ustekinumab concentrations through Week 88 in subjects who received concomitant MTX appeared to be slightly higher than those in subjects who did not receive concomitant MTX.
- Heavier-weight subjects (>100 kg) had generally lower mean serum ustekinumab concentrations compared with lighter-weight subjects (≤100 kg). Notably, mean steady-state trough serum ustekinumab concentrations were generally comparable between subjects >100 kg in the 90 mg group and subjects ≤100 kg in the 45 mg only group.

Immunogenicity

- The incidence of antibodies to ustekinumab was generally comparable between the combined 45 mg group (8.4%, n=17) and the 90 mg group (8.0%, n=16) through Week 108; across all treatment groups, the combined incidence of antibodies to ustekinumab was 8.3% (n=49).
- The incidence of antibodies to ustekinumab was lower in subjects receiving concomitant MTX (4.5%) than in subjects not receiving concomitant MTX (11.8%).
- The majority (65.3%) of subjects who were positive for antibodies to ustekinumab had antibodies that were able to neutralize the bioactivity of ustekinumab in vitro.
- Subjects who were positive for antibodies to ustekinumab had lower mean serum ustekinumab concentrations than subjects who were negative for antibodies to ustekinumab.
- Lower serum ustekinumab concentrations appeared to be associated with a higher incidence of antibodies to ustekinumab. Specifically, the incidence of antibodies to ustekinumab in subjects with BQL trough serum ustekinumab levels was higher than that in subjects with quantifiable trough serum ustekinumab levels (20.7% vs 4.6%, respectively) and the incidence of antibodies to ustekinumab was higher in subjects >100 kg than in subjects ≤100 kg (13.5% vs 6.5%, respectively).

EFFICACY RESULTS

- At Week 100, the mean changes in total modified vdH-S scores observed between Week 52 and Week 100 for the ustekinumab groups were similar to those observed between Week 0 and Week 52, indicating that the impact of ustekinumab on the inhibition of structural damage was maintained through Week 100.
- Subjects who were initially randomized to placebo and began treatment with ustekinumab 45 mg at Week 16 or Week 24 demonstrated a reduction in the amount of radiographic progression between

Week 52 and Week 100 compared with the amount of radiographic progression observed between Week 0 and Week 52.

- The proportion of subjects who achieved an ACR response was maintained from Week 52 through Week 100. At Week 100, the proportions of subjects who achieved an ACR 20 response were 56.7% and 63.6% in the 45 mg group and 90 mg groups, respectively. ACR 50 response was achieved by 38.8% and 46.0% and ACR 70 response by 24.7% and 22.2% of subjects in the 45 mg and 90 mg groups, respectively, at Week 100.
- The percent improvements from baseline in the numbers of swollen and tender joints were maintained from Week 52 through Week 100: 80.0% and 85.7% for swollen joints and 65.0% and 67.5% for tender joints in the 45 mg and 90 mg groups, respectively, at Week 100.
- The improvement from baseline in HAQ-DI was maintained from Week 52 through Week 100: −0.25 and −0.38 for the 45 mg and 90 mg groups, respectively, at Week 100. The proportions of subjects who achieved clinically meaningful improvement (HAQ-DI ≥0.3) in HAQ-DI at Week 100 were 47.8% and 51.7% in the ustekinumab 45 mg and 90 mg groups, respectively.
- The proportions of subjects who achieved a PsARC response were maintained from Week 52 through Week 100: 70.8% and 74.4% of subjects in the 45 mg and 90 mg groups, respectively, at Week 100.
- The proportions of subjects who achieved a DAS28 response were maintained from Week 52 through Week 100: 71.9% and 76.7% of subjects in the 45 mg and 90 mg groups, respectively, achieved a DAS28 good or moderate response at Week 100.
- Among subjects with dactylitis at baseline, the proportions of subjects with 1 or more digits with residual dactylitis continued to improve from Week 52 to Week 100, with 32.2% and 31.4% of subjects in the 45 mg and 90 mg groups, respectively, having digits with dactylitis at Week 100; the median percent improvement in dactylitis score at Week 100 remained 100% for both dose groups.
- Among subjects with enthesitis at baseline, the proportions of subjects with residual enthesitis continued to improve from Week 52 to Week 100, with 48.7% and 46.9% of subjects in the 45 mg and 90 mg groups, respectively, having enthesitis at Week 100; the median percent improvement in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) index improved to 100% for both dose groups at Week 100.
- PASI responses were generally maintained from Week 52 through Week 100. The proportions of subjects with ≥3% BSA skin involvement with psoriasis at baseline who achieved PASI 75 response at Week 100 were 72.5% and 71.3% in the 45 mg and 90 mg groups, respectively.
- The proportions of subjects with ≥3% BSA at baseline who achieved both a PASI 75 response and an ACR 20 response continued to improve from Week 52 through Week 100, at 51.3% and 58.7% of subjects in the 45 mg and 90 mg groups, respectively, at Week 100.
- The median change from baseline in DLQI score was generally maintained from Week 52 through Week 100: -5.00 and -6.00 in the 45 mg and 90 mg groups, respectively, at Week 100.
- Among subjects weighing ≤100 kg, ACR 20 responses at Week 100 were similar in the 45 mg and 90 mg groups, at 61.5% and 63.5%, respectively. Among subjects weighing >100 kg, ACR 20 responses at Week 100 were higher in the 90 mg treatment group than in the 45 mg group, at 64.1% and 41.6%, respectively.
- From Week 52 through Week 100, ACR responses, improvement from baseline in HAQ-DI score, and PASI response were not impacted by prior DMARD use, consistent with data through Week 52.

- At each timepoint from Week 52 through Week 100, within each treatment group, ACR responses and PASI responses were maintained in both subjects who were and were not receiving concomitant MTX.
- The mean changes from baseline in SF-36 PCS scores improved from Week 52 to Week 100, at 6.84 and 7.51 for subjects in the 45 mg and 90 mg groups, respectively, at Week 100.
- The mean changes from baseline in SF-36 MCS scores were generally maintained from Week 52 to Week 100, at 3.91 and 5.05 for subjects in the 45 mg and 90 mg groups, respectively, at Week 100.
- At Week 100, mean changes from baseline were generally maintained from Week 52 to Week 100 in all categories of the norm-based SF-36 scale scores.
- The mean improvement from baseline in disease impact on productivity was maintained or improved from Week 52 to Week 100: −2.22 and −3.01 in the 45 mg and 90 mg groups, respectively.
- The proportions of subjects who achieved ACR 20, ACR 50, and PASI 75 responses at Week 88 were higher in subjects with quantifiable steady-state trough serum ustekinumab levels compared with subjects with BQL steady-state trough serum ustekinumab levels.
- Overall, subjects who were positive for antibodies to ustekinumab tended to have slightly lower clinical efficacy compared with subjects who were negative for antibodies to ustekinumab. However, antibody positivity to ustekinumab did not preclude a clinical response.

SAFETY RESULTS

Adverse Events

- Through Week 108, the proportions of subjects who had 1 or more AEs were comparable between the combined 45 mg group and the 90 mg group: 77.1% and 72.5%, respectively. In the all ustekinumab group, 70.7% of subjects reported an AE through Week 108, which does not represent a disproportionate rate increase from Week 52, when 58.0% of subjects in the all ustekinumab groups had at least 1 AE.
- Nasopharyngitis and URTI remained the most frequently reported AEs, which was consistent with the AEs reported through Week 52.
- Consistent with data through Week 52, safety profiles were not impacted by concomitant use of MTX through Week 108.

Serious Adverse Events

- No deaths were reported through Week 108.
- Through Week 108, the proportions of subjects who had 1 or more serious adverse events (SAEs) were 12.7% and 8.3% in the combined 45 mg and 90 mg groups, respectively. In the all ustekinumab group, 9.7% of subjects reported an SAE, which does not represent a disproportionate rate increase from Week 52, when 4.8% of subjects in the all ustekinumab group had at least 1 SAE.
- No clear pattern of SAEs was observed and most were singular events, with the exception of myocardial infarction/acute myocardial infarction (MI; n=5), osteoarthritis (n=3), pneumonia-associated events (n=3), cholecystitis/cholecystitis acute (n=3), hypertension (n=2), dehydration (n=2), and depression (n=2).
- The incidence of SAEs was not impacted by concomitant use of MTX through Week 108.

Adverse Events Leading to Study Agent Discontinuation

- Through Week 108, the proportions of subjects who discontinued study agent due to an AE were low: 5.4% in the combined 45 mg group, 3.9% in the 90 mg group, and 3.8% in the all ustekinumab group. AEs leading to study discontinuation were all single events, with the exception of psoriatic arthropathy (n=2).

Infections

- Through Week 108, the proportions of subjects with infections identified as such by the investigator were 45.4% in the combined 45 mg group and 49.0% in the 90 mg group. In the all ustekinumab group, 43.3% of subjects had at least 1 infection, which does not represent a disproportionate rate increase from Week 52, when 33.4% of subjects in the all ustekinumab group had at least 1 infection.
- Through Week 108, the proportions of subjects with serious infections were low: 2.4% in the combined 45 mg group and 2.5% in the 90 mg group. In the all ustekinumab group, 1.8% of subjects had a serious infection, which does not represent a disproportionate rate increase from Week 52, when 0.8% of subjects in the all ustekinumab group had at least 1 serious infection.
- Through Week 108, the proportions of subjects with infections requiring antimicrobial treatment were 27.3% in the combined 45 mg group and 27.5% in the 90 mg group. In the all ustekinumab group, 25.3% of subjects had an infection requiring antimicrobial treatment, which does not represent a disproportionate increase from Week 52, when 16.7% of subjects in the all ustekinumab group had at least 1 infection requiring antimicrobial treatment.

Injection-site Reactions

- Through Week 108, 0.1% and 0.7% of ustekinumab 45 mg and 90 mg injections were associated with injection site reactions. All injection site reactions were reported as mild and none resulted in study agent discontinuation.
- No possible anaphylactic or possible serum sickness-like reactions to study agent were reported through Week 108.
- There was no definitive association between the development of antibodies to ustekinumab and the development of injection-site reactions.

Malignancies

- No malignancies were reported through Week 52. Four malignancies were reported after Week 52 through Week 108: 1 B-cell lymphoma (45 mg group), 1 renal cell carcinoma (placebo → 45 mg group), 1 squamous cell carcinoma (90 mg group), and 1 basal cell carcinoma (90 mg group).

Cardiovascular Events

- Seven investigator-reported MACE occurred through Week 108, 3 of them (1 cerebrovascular accident, 2 MIs) before Week 52. After Week 52, 4 additional subjects had serious MACE: 3 subjects (1 each in the 45 mg, 45 mg → 90 mg, and 90 mg groups) had MIs and 1 subject in the 45 mg group had an ischemic stroke. An increase in the rate of MACE with longer exposure to ustekinumab was not observed. All subjects with MACE had at least 2 concomitant cardiovascular risk factors in addition to PsA (eg, obesity and history of smoking, hypertension, hyperlipidemia, diabetes, or previous stroke).

Neurologic Disorders

- No events of reversible posterior leukoencephalopathy syndrome (RPLS) or demyelination were reported through Week 108.

Laboratory Test Results

- Through Week 108, the proportions of subjects with 1 or more markedly abnormal postbaseline hematology or chemistry laboratory values were low, comparable between the combined 45 mg and 90 mg groups, and did not increase disproportionately from those reported through Week 52. Concomitant use of MTX did not appear to impact hematology and chemistry values.

STUDY LIMITATIONS

The relatively short placebo-controlled period (through Week 16) limits the interpretation of long-term efficacy and safety data. The availability of early escape for subjects randomized to the 45 mg treatment group may impact the ability to assess the relative safety and efficacy of the 45 mg and 90 mg treatment groups beyond Week 16.

CONCLUSIONS

1. Through Week 100, ustekinumab doses of 45 mg and 90 mg provided substantial benefit to subjects with active PsA by reducing clinical signs and symptoms of arthritis, improving psoriatic lesions, decreasing the severity of dactylitis and enthesitis, and improving physical function and health-related quality of life. Efficacy was maintained after Week 52 through Week 100. Efficacy was not impacted by previous DMARD or concomitant MTX use.
2. Ustekinumab 45 mg and 90 mg, administered subcutaneously at Weeks 0 and 4 and then q12w in subjects with active PsA, achieved significantly greater inhibition of radiographic progression at Week 24 compared with placebo and inhibition of radiographic progression was maintained through Week 100.
3. An exposure-response relationship was observed through Week 88 for ACR and PASI responses. Subjects with BQL trough serum ustekinumab concentrations generally had lower ACR and PASI response rates compared with subjects with quantifiable trough serum concentrations. Subjects weighing >100 kg who received 90 mg doses had exposure to ustekinumab similar to that of subjects weighing ≤100 kg who received 45 mg doses. Moreover, the incremental efficacy benefit provided by the 90 mg dose was most evident for subjects weighing >100 kg.
4. Ustekinumab was generally well tolerated, with similar proportions of subjects experiencing AEs and similar types of AEs observed in the ustekinumab 45 mg and 90 mg groups through Week 108. Consistent with observations at Week 52, no disproportionate increases in event rates were seen and no additional safety concerns were identified through Week 108. Safety was not impacted by concomitant MTX use.

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