SYNOPSIS

Issue Date: 17 Jan 2013

Name of Sponsor/Company	Janssen Research & Development, Inc
Name of Finished Product	Ustekinumab
Name of Active Ingredient(s)	Ustekinumab

Protocol No.: CNTO1275PSA3002

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 Including Those Previously Treated With Biologic Anti-TNFα Agent(s)

Study Name: PSUMMIT II

EudraCT Number: 2009-012265-60

NCT No.: NCT01077362

Clinical Registry No.: CR016483

Principal Investigator: [redacted] MD

Study Center(s): 71 sites

Publication (Reference): None

Study Period: Through Week 24

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), including those previously treated with biologic anti-tumor necrosis factor alpha (anti-TNFα) agent(s), 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 is a randomized, double-blind, placebo-controlled, parallel, multicenter 3-arm study (with early escape at Week 16) of ustekinumab in subjects with PsA including those previously treated with biologic anti-TNFα agent(s). Approximately 300 subjects were planned to receive treatment with subcutaneous (SC) ustekinumab 45 mg, 90 mg, or placebo by a 1:1:1 randomization at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing, with the last dose at Week 40. Subjects randomized to placebo were to be crossed over to receive ustekinumab 45 mg at Weeks 24 and 28 followed by q12w dosing, with the last dose at Week 40. The expected duration of exposure to ustekinumab for enrolled subjects is 52 weeks. Subjects are to be followed for efficacy through Week 52 and for safety through Week 60.

Number of Subjects (planned and analyzed): Approximately 300 subjects were planned to receive treatment with ustekinumab 45 mg, ustekinumab 90 mg, or placebo (100 subjects per treatment group). A total of 312 subjects were randomly assigned: 104 to the placebo group, 103 to the ustekinumab 45 mg group, and 105 to the ustekinumab 90 mg group.

Diagnosis and Main Criteria for Inclusion: Men and women aged 18 to 99 years of age with a diagnosis of PsA for at least 6 months before the first study agent administration and had active PsA despite current or previous disease-modifying antirheumatic drug (DMARD) and/or nonsteroidal anti-inflammatory drug (NSAID) therapy. Per protocol, at least 150 but not more than 180 subjects could have been previously treated with single or multiple biologic anti-TNFα agent(s). Subjects had to manifest 5 or more swollen and 5 or more tender joints at screening and at baseline. At screening, subjects had to have C-reactive protein (CRP) ≥0.3 mg/dL, and have at least 1 of the PsA subtypes and active plaque psoriasis or a documented history of plaque psoriasis. Subjects previously treated with anti-TNFα agent(s) must have received at least 8 weeks of therapy with etanercept, adalimumab, golimumab or certolizumab pegol or at least 14 weeks of therapy with infliximab; or documented intolerance of anti-TNFα therapy for shorter periods of exposure.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab was supplied in a prefilled syringe (PFS) as a single-use, sterile solution in a BD Hypak™ 1 mL, type 1 glass syringe with a 27-gauge, 1/2-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.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo was also supplied in a PFS as a single-use, sterile solution in a BD Hypak™ 1 mL, type 1 glass syringe with a 27-gauge, 1/2-inch fixed needle. There were 2 dose volumes (ie, 1 mL nominal volume or 0.5 mL nominal volume). Each 1 mL of placebo for ustekinumab solution contained L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present.

Duration of Treatment: A total of 312 subjects were randomized to 1 of the 3 groups and received treatment with ustekinumab 45 mg, 90 mg, or placebo SC at Weeks 0 and 4 followed by q12w dosing, with the last dose at Week 40. 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 40. Expected duration of exposure to study agent is 52 weeks. Subjects will be followed for efficacy through Week 52 and for safety through Week 60. The database lock (DBL) occurred at Week 24. An additional DBL will occur at Week 60. The end of the study will occur after the last subject completes the Week 60 visit.

Criteria for Evaluation:

Pharmacokinetics: Serum ustekinumab concentrations were summarized by ustekinumab treatment group and visit through Week 24. Serum ustekinumab concentrations were also summarized by methotrexate (MTX) use at baseline, subject weight at baseline (≤100 kg vs >100 kg), and by prior anti-TNFα exposure (ie, previously experienced vs naive to biologic anti-TNFα agents). The relationship between serum ustekinumab concentrations and selected efficacy endpoints were also assessed. The results from the population PK analysis are not included in this report.

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 between antibodies to ustekinumab and serum ustekinumab concentrations and selected efficacy and safety measures were also assessed.

Efficacy: Efficacy evaluations included PsA response evaluations and psoriasis response evaluations. PsA response evaluations included joint assessments, American College of Rheumatology (ACR) responses, Disease Activity Index Score 28 using CRP (DAS28), patient and physician global assessments of disease activity, dactylitis assessment, enthesitis assessment, visual analogue scale (VAS) for pain assessment, Disability Index of the Health Assessment Questionnaire (HAQ-DI), 36-item Short Form Health Survey (SF-36), modified Psoriatic Arthritis Response Criteria (PsARC), Bath Ankylosing

Spondylitis Disease Activity Index (BASDAI), and Functional Assessment of Chronic Illness Therapy−Fatigue (FACIT-F). Psoriasis evaluations included the Psoriasis Area and Severity Index (PASI) and the Dermatology Life Quality Index (DLQI). The potential pharmacoeconomic benefit of ustekinumab treatment was also assessed. Radiographic imaging evaluations of the hands and feet will be addressed in a subsequent DBL.

Safety: Safety evaluations for all subjects were monitored through Week 24 and included measurement of vital signs (heart rate and blood pressure), physical evaluations (waist circumference and weight), and assessment of adverse events (AEs), and injection-site reactions that may have occurred at or between each evaluation visit. Tuberculosis evaluations, including QuantiFERON-TB Gold Test and Mantoux tuberculin skin test (in countries where QuantiFERON-TB Gold Testing was not licensed), were performed. Samples for routine laboratory analyses were collected.

Statistical Methods: Binary data (eg, the proportion of subjects with an ACR 20 response) were analyzed using the chi-square test or the Cochran-Mantel-Haenszel (CMH) test adjusted for baseline MTX usage (yes/no). Continuous data was analyzed using an analysis of covariance (ANCOVA) test on van der Waerden normal scores adjusted for baseline MTX usage (yes/no). Re-randomization tests were used as the primary statistical testing method to determine p-values for the analyses of the primary and the major secondary endpoints. All efficacy analyses were based on the intent-to-treat principle; thus, subjects were included in the efficacy analyses according to their assigned treatment group regardless of whether or not they received the assigned treatment. Multiplicity adjustments were made for the analyses of the primary and the major secondary endpoints. All statistical testing was performed 2-sided at an alpha level of 0.05.

RESULTS:

STUDY POPULATION

- Of the 312 subjects randomly assigned to treatment at Week 0, 104 were assigned to the placebo group, 103 to the ustekinumab 45 mg group, and 105 to the ustekinumab 90 mg group. All randomized subjects received their assigned treatment at Week 0, with the exception of 1 subject in the ustekinumab 90 mg group who withdrew consent at the baseline visit and did not receive any study agent.
  - Through Week 24, a total of 41 (13.1%) subjects discontinued across the randomized treatment groups, with a higher rate of discontinuation in the placebo group (23.1%) than in the ustekinumab 45 mg (5.8%) or 90 mg (10.5%) groups. This difference was primarily driven by the higher proportion of subjects in the placebo group who discontinued for efficacy-related reasons (ie, lack of efficacy or AEs of worsening of PsA and/or psoriasis). In all treatment groups, the majority of discontinuations occurred before Week 12.
- Subject demographic characteristics at baseline were generally comparable across treatment groups. The majority of subjects were white (98.4%) and female (52.6%); the median age was 49 years, median weight was 88.3 kg, and median body mass index (BMI) was 30.3 kg/m^2.
- Baseline clinical characteristics of PsA from the ACR core set of outcome measurements were indicative of a population of subjects with moderately to severely active PsA and were generally comparable across the treatment groups. The median numbers of swollen and tender joints were 11.0 and 22.0, respectively; median VAS of patient's assessment of pain was 6.80; median VAS of patient's global assessment of disease activity was 6.20; median VAS of physician's global assessment of disease activity was 7.10; median HAQ-DI score was 1.25; and median CRP level was 9.32 mg/L.
- Baseline disease characteristics of psoriasis measurements for subjects with ≥3% body surface area (BSA) involvement with psoriasis were generally comparable across the treatment groups and were indicative of significant psoriatic skin involvement with a substantial negative impact on health-

related quality of life (HRQoL): median percentage of BSA psoriasis skin involvement, 12%; median PASI score, 8.30; and median DLQI score, 11.00.

- Of the 312 randomized subjects, 180 (57.7%) had prior anti-TNFα exposure and 132 (42.3%) were anti-TNFα naive.
- At baseline, 157 (50.3%) subjects were receiving MTX and 155 (49.7%) subjects were not receiving MTX.
- Through Week 24, subjects who were randomly assigned to ustekinumab received a median dose of 180 mg. Subjects randomized to placebo who entered early escape received approximately 2 ustekinumab injections, while subjects randomized to ustekinumab received an average of 3 ustekinumab injections.

CLINICAL PHARMACOLOGY

Pharmacokinetics:

- Dose proportionality in serum ustekinumab concentration was observed when comparing mean serum ustekinumab concentrations between the 45 mg and 90 mg groups.
- 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 concentration of the assay (<0.16880 µg/mL) was observed in the 45 mg group compared with the 90 mg group.
- No consistent impact of MTX use on serum ustekinumab concentrations was observed between subjects who were and were not receiving MTX at baseline.
- Subjects of higher weight (>100 kg) had generally lower mean serum ustekinumab concentrations compared with subjects of lower weight (≤100 kg). Notably, mean preinjection serum ustekinumab concentrations at Week 16 were generally comparable between subjects >100 kg in the 90 mg group and subjects ≤100 kg in the combined 45 mg group.
- Mean serum ustekinumab concentrations in subjects who were previously treated with biologic anti-TNFα agents appeared to be generally lower than those in subjects who were naive to biologic anti-TNFα agents.

Immunogenicity:

- Through Week 24, the combined incidence of antibodies to ustekinumab was 6.1% (n=14) across all treatment groups.
- The incidence of antibodies to ustekinumab was generally comparable between the combined ustekinumab 45 mg group (6.0%; n=6) and the 90 mg group (7.1%; n=7).
- The incidence of antibodies to ustekinumab was lower in subjects who were receiving MTX at baseline (4.5%, n=5) compared with subjects who were not receiving MTX at baseline (7.6%, n=9).
- The incidence of antibodies to ustekinumab was higher in subjects who were previously treated with biologic anti-TNFα agents (8.5%, n=11) compared with subjects who were naive to biologic anti-TNFα agents (3.1%, n=3), although fewer subjects with prior anti TNFα exposure were taking MTX at baseline.
- Subjects who were positive for antibodies to ustekinumab had lower mean serum ustekinumab concentrations than subjects who were negative for antibodies to ustekinumab.

EFFICACY

Primary Endpoint:

- A significantly greater proportion of subjects in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups (43.8%, 43.7%, and 43.8%, respectively) achieved an ACR 20 response at Week 24 compared with subjects in the placebo group (20.2%; all $p<0.001$).

Major Secondary Endpoints:

- There was significantly greater improvement in HAQ-DI scores at Week 24 in subjects in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups (median change from baseline of −0.25, −0.13, and −0.25, respectively) compared with subjects in the placebo group (median of 0.00; all $p\leq0.002$).
- A significantly larger proportion of subjects with ≥3% BSA involvement of psoriasis at baseline in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups demonstrated PASI 75 response at Week 24 (53.4%, 51.3%, and 55.6%, respectively) compared with subjects in the placebo group (5%; all $p<0.001$).
- A significantly greater proportion of subjects in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups achieved an ACR 50 response (20.2% [p=0.002], 17.5% [p=0.018], and 22.9% [p<0.001], respectively) at Week 24 compared with subjects in the placebo group (6.7%).
- Numerically but not statistically significantly higher proportions of subjects achieved an ACR 70 response in the combined ustekinumab and ustekinumab 45 mg and 90 mg groups (7.7%, 6.8%, and 8.6%, respectively) at Week 24 compared with subjects in the placebo group (2.9%).

Other Efficacy Analyses:

- ACR 20, ACR 50, and ACR 70 responses in both ustekinumab groups were notably higher than in the placebo group beginning at Week 8. The maximum improvement based upon ACR 20, 50, 70 responses for both the 45 mg and 90 mg groups occurred at Week 20 or Week 24, 4 to 8 weeks after the Week 16 dose.
- Modified PsARC and DAS28 responses were achieved in a significantly greater proportion of subjects in the combined ustekinumab group (and in each ustekinumab dose group) than in the placebo group at both Week 12 and Week 24.
- For subjects with dactylitis at baseline, numerically but not significantly greater percentage improvements in dactylitis score were observed at Week 24 in the combined ustekinumab group and the ustekinumab 90 mg group compared with the placebo group. The percentage improvement in dactylitis score was similar between the 45 mg group and the placebo group.
- For subjects with enthesitis at baseline, significantly greater percentage improvements in enthesitis score were observed at Week 24 for the combined ustekinumab group and the ustekinumab 90 mg group compared with the placebo group ($p<0.005$ for all comparisons). Numerically but not significantly higher percentage improvement in enthesitis score was observed in the 45 mg group compared with the placebo group.
- For subjects with spondylitis with peripheral joint involvement as their primary arthritic presentation of PsA, improvement in BASDAI scores was noted at Week 24 in subjects treated with ustekinumab compared with placebo.
- ACR 20 response rates and HAQ-DI improvements were generally comparable in subjects treated with ustekinumab who were receiving MTX versus those not receiving MTX, although the treatment effect (ie, the difference in response rates between the combined ustekinumab group and placebo) was modestly greater in subjects who were not receiving MTX at baseline because of the higher

response rate or improvement in the placebo group in subjects who were receiving MTX. Significance was not reached for ACR 20 for the 90 mg group or for the change in HAQ-DI score at Week 24 for either dose group compared with placebo.

- A significantly higher proportion of subjects achieved both ACR 20 and PASI 75 at Week 24 in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (34.2%, 30.0%, and 38.3%) compared with the placebo group (2.5%; all $p<0.001$).
- At Week 24, a significantly higher proportion of subjects had a DLQI score of 0 or 1 in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups (39.0%, 35.6%, and 42.6%, respectively) compared with the placebo group (11.1%; all $p<0.001$).
- SF-36 physical component summary (PCS) score improvement was significantly greater in both ustekinumab groups as compared with the placebo group at both Week 16 ($p=0.023$ for 45 mg, and $p=0.040$ for 90 mg) and Week 24 ($p=0.005$ for 45 mg and $p=0.001$ for 90 mg).
- SF-36 mental component summary (MCS) score improvement was significantly greater in both ustekinumab 45 mg group ($p=0.037$) and 90 mg group ($p=0.003$) as compared with the placebo group at Week 16. Improvement in SF 36 MCS score was numerically greater for the both 45 mg ($p=0.153$) and 90 mg group ($p=0.086$) as compared with the placebo group at Week 24.
- A statistically significant change from baseline in FACIT-F scores was observed at Week 24 in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups compared with the placebo group (all $p<0.007$).

Health Economics Assessments:

- At both Week 16 and Week 24, the impact of PsA on work productivity was significantly greater in the combined ustekinumab group and the ustekinumab 45 mg and 90 mg groups compared with the placebo group ($p<0.001$ for all except the 45 mg group at Week 16 [$p<0.002$]).
- Overall, there were no consistently significant differences in the ustekinumab treatment groups compared with the placebo group in measures of employability or time lost from work due to PsA at Week 16 and Week 24.

Impact of Prior Anti-TNFα Exposure on Efficacy:

- Numerically higher responses for ustekinumab compared with placebo for ACR 20, ACR 50, ACR 70, and PASI 75 responses at Week 24 and greater improvement in HAQ-DI scores at Week 24 were seen in subjects with and without prior anti-TNFα exposure, although the treatment effect was higher in subjects without prior anti-TNFα exposure.
  - At Week 24, subjects with prior anti-TNFα exposure who received ustekinumab demonstrated significantly higher rates of ACR 20 response and PASI 75 response versus placebo. Significantly greater improvement in HAQ-DI at Week 24 was also seen in the ustekinumab groups compared with placebo for subjects with prior anti-TNFα exposure.

Other Subgroup Analyses:

- Numerically higher ACR 20 response was observed at Week 24 in almost all subgroups examined for both the 45 mg and 90 mg groups, although some variability in treatment effect was observed in subgroups due to smaller sample size.
  - Significantly higher ACR 20 response was observed at Week 24for both the 45 mg and 90 mg groups compared with the placebo group among subjects with prior DMARD use.

Efficacy and Pharmacokinetics:

- Subjects with higher trough serum ustekinumab concentrations tended to have higher clinical efficacy. Clinical efficacy (ACR 20, ACR 50, and PASI 75 responses) at Week 24 appeared to be generally associated with trough serum ustekinumab levels ≥0.16880 μg/mL.

Efficacy and Antibodies to Ustekinumab:

- Although the number of subjects who were positive for antibodies to ustekinumab was small, subjects who were positive for antibodies to ustekinumab tended to have lower clinical efficacy compared with subjects who were negative for antibodies to ustekinumab; however, antibody positivity did not preclude a clinical response.

SAFETY

Adverse Events:

- Through Week 16, AE rates in each of the ustekinumab groups were slightly higher than those observed in the placebo group although there was no dose response. The proportions of subjects reporting AEs were 54.8%, 63.1%, and 60.6% in the placebo and ustekinumab 45 mg and 90 mg groups, respectively.
- The SOC with the most commonly reported AEs through Week 16 was Infections and infestations (23.1%, 28.2%, and 26.0% in the placebo and ustekinumab 45 mg and 90 mg groups, respectively), predominantly nasopharyngitis and upper respiratory tract infection.
- Through Week 24, no disproportional increase from Week 16 was observed in AE rates, and the AE profile was similar to that observed through Week 16. AE rates and AE profiles were also similar between the treatment groups.
- Among subjects with prior anti-TNFα exposure, the proportions of subjects reporting AEs were comparable across treatment groups through Week 16. No disproportional increase was observed through Week 24 in AE rates among these subjects and the AE profile was similar with that observed through Week 16.
- AEs were not impacted by age, sex, baseline weight, or concomitant use of MTX, although a higher proportion of male subjects in the ustekinumab-treated groups reported AEs compared with the placebo group (primarily due to slightly higher rates of nasopharyngitis and arthralgia in these subjects).

Serious Adverse Events:

- No deaths were reported through Week 24.
- Through Week 16, serious adverse event (SAE) rates in the ustekinumab 45 mg and 90 mg groups were similar (0.0% and 1.0%) and were numerically lower than in the placebo group (4.8%). SAEs were single events in all the treatment groups without any particular pattern.
- Through Week 24, the proportion of subjects who had 1 or more SAEs remained low: 1.3% in the all ustekinumab group and 4.8% in the placebo group.
- Among subjects with prior anti-TNFα exposure, the proportion of subjects who had an SAE was low through Week 16 (3.2%, 0.0%, and 1.7% in the placebo and ustekinumab 45 mg and 90 mg groups) and remained low through Week 24 (3.2% in the placebo group and 0.8% in the all ustekinumab group).
- SAEs were not impacted by baseline weight or concomitant use of MTX.

Adverse Events Leading to Study Agent Discontinuation:

- Through Week 16, the proportions of subjects who discontinued study agent due to 1 or more AEs were higher in the placebo group compared with the ustekinumab groups: 7.7% in the placebo group and 1.9% each in the ustekinumab 45 mg and 90 mg groups.
- Through Week 24, the proportion of subjects who discontinued study agent due to 1 or more AEs remained low: 1.9% in the combined ustekinumab 45 mg group and 2.9% in the 90 mg group, and 2.1% in the all ustekinumab group and 10.6% in the placebo group.
- Among subjects with prior anti-TNFα exposure, the proportion of subjects who discontinued study agent due to an AE through Week 16 was higher in the placebo group (11.3%) than in the ustekinumab groups (0.0% and 1.7% in the 45 mg and 90 mg groups). Higher rates of discontinuation continued to be seen through Week 24 in the placebo group compared with the all ustekinumab group (16.1% vs 1.5%), mostly due to worsening arthropathy or psoriasis.

Infections:

- Through Week 16, infection rates and types of infections were generally comparable across the treatment groups: 24.0%, 29.1%, and 25.0% in the placebo and ustekinumab 45 mg and 90 mg groups, respectively. The most commonly reported infections were nasopharyngitis, upper respiratory tract infection, and sinusitis.
- Through Week 24, no disproportional increase was observed in infection rates, and the types of infections were similar to that observed through Week 16. Infection rates and types of infections were similar among the treatment groups.
- Among subjects with prior anti-TNFα exposure, infection rates through Week 16 were higher in the placebo group (32.3%) compared with the ustekinumab 45 mg and 90 mg groups (28.3% and 20.7%, respectively), but more comparable at Week 24 (33.6% and 37.1% in the all ustekinumab and placebo groups, respectively).
- Infections were not impacted by baseline weight or concomitant use of MTX.
- One serious infection was reported through Week 24 (interstitial lung disease in the placebo group).
- No opportunistic infections or cases of TB were reported.

Injection-site Reactions:

- Rates of injections with injection-site reactions through Week 24 were 0.6% for ustekinumab 45 mg injections and 1.6% for ustekinumab 90 mg injections, compared with 0.4% for placebo injections. All injection-site reactions were mild in intensity.
- No possible anaphylactic or possible serum sickness-like reactions to study agent were reported.
- None of the subjects who were positive for antibodies to ustekinumab had an injection-site reaction through Week 24. There was no apparent association between the development of antibodies to ustekinumab and the development of injection-site reactions.

Malignancies:

- One malignancy was reported through Week 24 (nonserious squamous cell carcinoma in the ustekinumab 90 mg group).

Cardiovascular Events:

- No investigator-reported major adverse cardiovascular events (MACE) were reported in any group through Week 24.

Laboratory Test Results:

- Through Week 16, markedly abnormal changes in hematology and chemistry were generally low and similar between placebo-treated and ustekinumab-treated subjects. Through Week 24, markedly abnormal changes in hematology and chemistry generally remained low. Concomitant use of MTX did not appear to affect hematology and chemistry values.
- At Week 24, shifts in fasting glucose and change from baseline in fasting glucose were similar among the placebo and ustekinumab groups.
- No clinically relevant shifts were noted for total cholesterol, HDL- or LDL-cholesterol between subjects in the ustekinumab and placebo groups.

Vital Signs and Physical Measurements:

- Heart rate, blood pressure, weight and waist circumference were similar across all treatment groups at baseline and Week 24.

STUDY LIMITATIONS: The short placebo-controlled period (through Week 16) and the early escape for subjects in the 45 mg group to the 90 mg group might have affected the ability to assess the safety and efficacy between the ustekinumab groups and the placebo group as well as between the 45 mg and 90 mg groups beyond Week 16.

CONCLUSIONS:

- Ustekinumab 45 mg or 90 mg administered at Week 0 and 4, followed by a q12w dose regimen, demonstrated consistent efficacy across various endpoints evaluating joint signs and symptoms, soft tissue disease, skin disease, and health-related quality of life in subjects with active PsA.
- Greater efficacy was observed in the ustekinumab 90 mg group for some endpoints compared with the 45 mg group.
- Efficacy was demonstrated in subjects who were and were not receiving MTX.
- Efficacy was demonstrated in subjects who had prior anti-TNFα exposure and in subjects who were anti-TNFα naive.
- Ustekinumab was generally well tolerated in the PsA population at both doses tested, without any clinically meaningful differences in safety between the 45 mg and 90 mg dose groups.
  - Ustekinumab was well tolerated regardless of concomitant MTX use.
  - Ustekinumab was well tolerated regardless of prior anti-TNFα exposure.

SYNOPSIS

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

*Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to, Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc.; or Janssen Research & Development, LLC. The term "sponsor" is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved

Date: 04 Jun 2013

Prepared by: Janssen Research & Development

Protocol No.: CNTO1275PSA3002

Title of Study: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of Ustekinumab, a Fully Human Anti-IL-12/23 p40 Monoclonal Antibody, Administered Subcutaneously, in Subjects With Active Psoriatic Arthritis Including Those Previously Treated With Biologic Anti-TNFα Agent(s)

Study Name: PSUMMIT II

EudraCT Number: 2009-012265-60

NCT No.: NCT01077362

Clinical Registry No.: CR016483

Principal Investigator: [redacted], MD - [redacted], New York

Study Center(s): 71 study sites

Publication (Reference): None

Study Period: 26 Feb 2010 (first subject consented) – 15 Nov 2012 (last patient visit for Week 60).

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) including those previously treated with anti-TNFα agent(s) 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 PsA including those previously treated with anti-tumor necrosis factor alpha (TNFα) agent(s). Approximately 300 subjects were planned to receive treatment with subcutaneous (SC) ustekinumab 45 mg, 90 mg, or placebo by a 1:1:1 randomization at Weeks 0 and 4 followed by every 12 weeks (q12w) dosing, with the last dose at Week 40. Subjects randomized to placebo were to crossover to receive ustekinumab 45 mg at Weeks 24 and 28 followed by q12w dosing, with the last dose administered at Week 40. The expected duration of exposure to ustekinumab for enrolled subjects was 52 weeks. Subjects were to be followed for efficacy through Week 52 and for safety through Week 60. Investigative study sites and subjects remained blinded to treatment assignment until the last enrolled subject completed the Week 60 evaluations, and the database was locked.

Number of Subjects (planned and analyzed): Approximately 300 subjects were planned to receive treatment with 100 subjects in each 45 mg, 90 mg, and placebo groups, respectively.

A total of 312 subjects were randomly assigned to treatment: 103, 105, and 104 subjects in the 45 mg, 90 mg, and placebo groups, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects were to be between 18 and 99 years of age at screening with the diagnosis of active PsA for at least 6 months prior to the first administration of study agent and had to have 5 or more swollen and tender joints at screening and at baseline. At screening, subjects had to have a minimum 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), have at least 1 of the PsA subsets, and manifest a disease pattern consistent with 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 [redacted] 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 No.: 09E011, 09E012, 09G041, 09G042, 10C051, 10C052, 10M031, and 10M032) were used in the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: The placebo was supplied in a prefilled syringe, a single-use, sterile solution in a [redacted] Hypak™ 1 mL, type 1 glass syringe with a 27-gauge, 1/2-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. Five lots of placebo (Batch No.: 08H021, 09E021, 09E022, 10E011, and 10E012) were used in the study.

Duration of Treatment: A total of 312 subjects were randomized to 1 of the 3 groups and received treatment with ustekinumab 45 mg, 90 mg, or placebo SC at Weeks 0 and 4 followed by q12w dosing, with the last dose administered at Week 40. Subjects randomized to placebo were eligible for crossover to receive ustekinumab 45 mg at Weeks 24, 28, and followed by q12w dosing, with the last dose at Week 40. At Week 16, subjects with <5% improvement from baseline in both tender and swollen joint counts in the 45 mg and placebo groups were eligible for early escape and began to receive ustekinumab 90 mg and 45 mg, respectively. Subjects initially randomized to 90 mg continued the same regimen. 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 40. The expected duration of exposure to study agent was 52 weeks. Subjects were followed for efficacy through Week 52 and for safety through Week 60. The database locks (DBLs) occurred at Week 24 and at Week 60. The end of the study occurred after the last subject completed the Week 60 visit.

Criteria for Evaluation:

Pharmacokinetics: Serum ustekinumab concentrations were summarized through Week 52 for subjects treated with ustekinumab. Serum ustekinumab concentrations were also summarized by methotrexate (MTX) use at baseline, by subjects' weight at baseline (≤100 kg versus >100 kg), and by prior anti-TNFα exposure (ie, previously experienced versus naïve to anti-TNFα agents). The relationships between 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: The efficacy data were summarized after Week 24 through Week 52. The efficacy evaluations included PsA response evaluations and psoriasis response evaluations. Psoriatic arthritis response evaluations included: the proportion of ACR responders, improvements in ACR core components (ie, joint assessments, Disability Index of the Health Assessment Questionnaire [HAQ-DI], change in baseline C-reactive protein [CRP] level, patient and physician global assessment of disease, patient assessment of pain), modified Psoriatic Arthritis Response Criteria (PsARC), Disease Activity Index Score 28 (DAS28) using CRP response measurements (DAS28 response, change in DAS28 score over time, DAS28 remission over time), dactylitis assessments, and enthesitis assessments. Psoriasis evaluations included Psoriasis Area and Severity Index (PASI) and dermatology life quality index (DLQI). Additional patient-reported outcomes included Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the 36-item Short Form Health Survey (SF-36), which assessed the general well-being of the subjects. Finally, the potential pharmacoeconomic benefit of ustekinumab treatment was assessed. Radiographic imaging evaluations of the hands and feet through Week 52 (including data at Week 24) are presented in a separate report.

Safety: Safety data were summarized through Week 60 for subjects treated with ustekinumab. Safety evaluations were monitored and included measurement of vital signs (heart rate and blood pressure), physical evaluations (waist circumference and weight), assessment of adverse events (AEs), and injection-site reactions that may have occurred at or between each of the evaluation visits. Tuberculosis (TB) evaluations, including the QuantiFERON®-TB Gold Test and Mantoux tuberculin skin test (in countries where QuantiFERON®-TB Gold Testing was not licensed), were performed. 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 the data. In addition, graphical summaries of the data were also used.

RESULTS:

STUDY POPULATION

Baseline demographic and disease characteristics of the study population were previously described in the CNTO1275PSA3002 24-Week CSR.

CLINICAL PHARMACOLOGY SUMMARY

Pharmacokinetics Summary

- Dose proportionality in serum ustekinumab concentration was observed when comparing mean serum ustekinumab concentrations between the 45 mg group that did not undergo early escape at Week 16 (ie, 45 mg only) and the 90 mg group through Week 52.

- Steady state was achieved at Week 28 for the 45 mg only and 90 mg groups, and trough serum ustekinumab concentrations for both groups were generally maintained at a steady state through Week 52.
- 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; <0.16880 µg/mL) was observed in the 45 mg only group compared with the 90 mg group through Week 52.
- No consistent impact of concomitant MTX use on serum ustekinumab concentrations was observed between subjects who were and were not receiving concomitant MTX.
- Subjects of higher weight (>100 kg) had generally lower mean trough serum ustekinumab concentrations compared with subjects of lower weight (≤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.
- Mean serum ustekinumab concentrations in subjects who were previously treated with anti-TNFα agents appeared to be generally lower than those in subjects who were naïve to anti-TNFα agents. However, subjects who were previously treated with anti-TNFα agents had a higher mean body weight at baseline and a higher incidence of antibodies to ustekinumab compared with subjects who were naïve to anti-TNFα agents, which may have contributed to the differences in serum concentrations.

Immunogenicity Summary

- Through Week 60, the combined incidence of antibodies to ustekinumab was 9.3% (n=26) across all ustekinumab-treated subjects.
- The incidence of antibodies to ustekinumab was generally comparable between the combined 45 mg group (9.9%, n=10) and the 90 mg group (9.1%, n=9).
- The incidence of antibodies to ustekinumab was lower in subjects who received concomitant MTX (6.4%, n=9) compared with subjects not receiving concomitant MTX (12.3%, n=17).
- The incidence of antibodies to ustekinumab was higher in subjects who were previously treated with anti-TNFα agents (12.3%, n=19) compared with subjects who were naïve to anti-TNFα agents (5.6%, n=7); with this it is noted that a lower proportion of subjects with prior anti-TNFα exposure compared to anti-TNFα naïve subjects received concomitant MTX.
- The majority (73.1%) 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 antiboides to ustekinumanb. Specifically, the incidence of antibodies to ustekinumab in subjects with BQL trough serum ustekinumab levels was higher than in subjects with quantifiable trough serum ustekinumab levels (21.7% versus 3.1%). Furthermore, the incidence of antibodies to ustekinumab was higher in subjects >100 kg when compared with subjects ≤100 kg (20.0% versus 5.0%).

EFFICACY RESULTS:

Data through Week 24, including the results of the primary efficacy analysis (the proportions of subjects who were ACR 20 responders at Week 24) and 4 of 5 major secondary endpoints, are presented in the CNTO1275PSA3002 24-Week CSR.

Efficacy Analyses After Week 24 Through Week 52:

- The fourth major secondary endpoint, change from baseline in total radiographic scores of the hands and feet at Week 24 (based upon an integrated analysis of the combined data from the CNTO1275PSA3001 and CNTO1275PSA3002 studies) is presented in a separate integrated radiographic analysis report.
- The proportions of subjects achieving ACR responses plateaued by Week 28 and were maintained through Week 52. At Week 52, the proportions of subjects who achieved an ACR 20 response were 46.8% and 48.4% respectively for the 45 mg and 90 mg groups. In the 45 mg and 90 mg groups, the proportions of subjects who achieved an ACR 50 response were 27.7% and 26.3%, respectively, and who achieved an ACR 70 response were 12.8% and 17.9%, respectively.
- The improvement from baseline in HAQ-DI in the ustekinumab 45 mg and 90 mg groups was maintained after Week 24 through Week 52. At Week 52, the median change from baseline in HAQ-DI for the 45 mg and 90 mg groups who did not undergo early escape was -0.25 and -0.25, respectively. At Week 52, the proportions of subjects in the ustekinumab 45 mg and 90 mg groups who achieved a clinically meaningful improvement (HAQ-DI ≥0.3) in HAQ-DI at Week 52 were 35.1%, and 44.2%, respectively.
- The proportion of subjects who achieved a DAS28 response was maintained after Week 24 through Week 52. At Week 52, the proportions of subjects who achieved a DAS28 good or moderate response in the 45 mg and 90 mg groups were 59.6% and 62.1%, respectively.
- Among subjects with dactylitis at baseline, the proportions of subjects with 1 or more digits with dactylitis at Week 52 were 50.0% in both the 45 mg and 90 mg groups. For subjects with dactylitis at baseline, at Week 52 the median percent improvement in dactylitis score was 95.00% for the 45 mg group and 90.91% for the 90 mg group.
- Among subjects with enthesitis at baseline, the proportions of subjects with enthesitis at Week 52 were 75.8% and 57.7% in the 45 mg group and the 90 mg group, respectively. For subjects with enthesitis at baseline, the median percent improvement in the Maastricht Ankylosing Spondylitis Enthesitis Score index at Week 52 was 36.67% and 60.00% in the 45 mg and 90 mg groups, respectively.
- The proportions of subjects with PASI responses were maintained after Week 24 through Week 52. At Week 52, the proportions of subjects with ≥3% body surface area involvement with psoriasis at baseline who achieved a PASI 75 response in the ustekinumab 45 mg and 90 mg groups were 56.5% and 64.4%, respectively.
- The change from baseline in DLQI score was generally maintained after Week 24 through Week 52. At Week 52, the median change from baseline in DLQI score was -6.00 and -7.00 in the 45 mg and 90 mg groups, respectively.
- After Week 24 and through Week 52, with each weight stratum, improvements in joint and psoriasis measurements as reflected in ACR and PASI responses were generally maintained. Subjects weighing ≤100 kg had numerically higher ACR and PASI responses than subjects weighing >100 kg independent of ustekinumab dose. At Week 52, in subjects weighing ≤100 kg, ACR 20 responses were 49.3% and 53.7% and the PASI 75 responses were 56.0% and 68.0% in the 45 mg and 90 mg groups, respectively. At Week 52, in subjects weighing >100 kg, ACR 20 responses were 40.7% and 35.7%, and the PASI 75 responses were 57.9% and 56.5% in the 45 mg and 90 mg groups, respectively.
- The proportions of subjects in ACR response, demonstrating improvement from baseline in HAQ-DI score, and the proportions of subjects with PASI response were maintained after Week 24 through Week 52 for subjects with prior disease-modifying antirheumatic drug use. These responses are generally consistent with the overall population.

- At each timepoint after Week 24 through Week 52, within each treatment group, the proportions of subjects with ACR and PASI responses were generally maintained in both subjects receiving concomitant MTX and subjects not receiving concomitant MTX. ACR and PASI responses were generally comparable regardless of concomitant use of MTX.
- After Week 24 through Week 52 the proportion of ACR and PASI responders, improvements in HAQ-DI scores and the proportion of HAQ-DI responders, as well as the percent of CRP improvement, were generally maintained in both dose groups and both subject groups, among subjects with and without prior anti-TNFα exposure, with the exception of the 45 mg dose group in subjects previously treated with anti-TNFα agent(s) in which a decrease was observed over time for the PASI responders as well as the percentage improvement in CRP and a decrease in the proportion of HAQ-DI responders at Week 52 was observed in anti-TNFα naïve subjects receiving 45 mg. The anti-TNFα naïve subjects consistently had higher rates of ACR and PASI response, greater improvement in HAQ-DI scores and a higher proportion of HAQ-DI responders, and greater median CRP improvement than those previously treated with anti-TNFα agent(s), independent of ustekinumab dose with the exception of the 45 mg dose group at Week 52 in which subjects treated with anti-TNFα agent(s) had higher proportions of HAQ-DI responders then those anti-TNFα naïve subjects.
- The mean changes from baseline in the SF-36 physical component summary (PCS) scores were 4.76 and 5.91 in the 45 mg and 90 mg groups, respectively, at Week 52. The mean changes from baseline in all 8 SF-36 mental composite summary scores were 1.84 and 3.68 in the 45 mg and 90 mg groups, respectively, at Week 52. The 90 mg group had numerically higher mean changes from baseline in the norm-based scores of all 8 SF-36 scales at Week 52 than the 45 mg group.
- The FACIT-F scores after Week 24 through Week 52 were maintained over time in all groups independent of dose.
- At Week 52, the mean change from baseline in productivity was -1.77 in the 45 mg group and -2.07 in the 90 mg group.
- The proportions of subjects who achieved ACR 20, ACR 50, and PASI 75 responses at Week 52 were higher in subjects with quantifiable steady-state trough serum ustekinumab levels when compared with subjects with BQL steady-state trough serum ustekinumab levels. Notably, the ACR 20 response rate at Week 52 generally increased with increasing steady-state trough serum ustekinumab concentrations.
- Subjects who were positive for antibodies to ustekinumab tended to have lower clinical efficacy when compared with subjects who were negative for antibodies to ustekinumab. However, antibody positivity to ustekinumab did not preclude a clinical response.

SAFETY RESULTS THROUGH WEEK 60:

Safety data through Week 60 were presented for the following treatment groups:

- The combined 45 mg group (subjects randomized to 45 mg at Week 0 who did not early escape at Week 16 and subjects randomized to 45 mg at Week 0 who qualified for early escape to 90 mg at Week 16).
- The 90 mg group (all subjects randomized to 90 mg regardless of early escape).
- The all ustekinumab group includes all subjects who received ustekinumab at any timepoint.

Adverse Events

- Through Week 60, the proportions of subjects experiencing 1 or more AEs were 78.6% among subjects in the combined 45 mg group, 77.9% among subjects originally randomized to 90 mg, and 71.8% in the all ustekinumab group. These proportions of subjects with AEs do not represent a disproportional rate increase compared with Week 24 when 70.9% of subjects in the combined 45 mg group, 69.2% of subjects in the 90 mg group, and 66.4% of subjects in the all ustekinumab group reported 1 or more AEs. Nasopharyngitis and upper respiratory tract infection (URTI) remained the most frequently reported AEs, which was consistent with the data reported through Week 24.
- Consistent with the data through Week 24, safety profiles were not impacted by concomitant use of MTX through Week 60.
- Consistent with the data through Week 24, safety profiles were not impacted by prior anti-TNFα exposure through Week 60.

Serious Adverse Events

- No deaths were reported through Week 60.
- Through Week 60, the proportions of subjects experiencing 1 or more serious adverse events (SAEs) were 5.8%, 5.8%, and 5.2% in the combined 45 mg, 90 mg, and all ustekinumab groups, respectively. No clear pattern of events was observed, and the reported SAEs were generally singular events.

Adverse Events Leading to Study Agent Discontinuation

- Through Week 60, the proportions of subjects who discontinued study agent due to an AE were 5.8% in the combined 45 mg group, 3.8% in the 90 mg group, and 3.8% in the all ustekinumab group, which did not represent a disproportional increase in rates compared with the data through Week 24 when 1.9% of subjects in the combined 45 mg group, 2.9% of subjects in the 90 mg group, and 2.1% of subjects in the all ustekinumab group discontinued study agent due to an AE. The proportions were low, and no patterns of events were identified. Some AEs leading to discontinuation were experienced by more than 1 subject (ie, psoriatic arthropathy was experienced by 3 subjects in the all ustekinumab group).

Infections

- Through Week 60, the proportions of subjects with at least 1 infection were 52.4% in the combined 45 mg group, 54.8% in the 90 mg group, and 46.7% in the all ustekinumab group, which did not represent a disproportional increase in rates compared with data through Week 24 when the proportions were 40.8%, 34.6%, and 34.5% in the combined 45 mg, 90 mg, and all ustekinumab groups, respectively.
- Through Week 60, the proportions of subjects with serious infections were low; 0% in the combined 45 mg group, 1.9% (n=2) in the 90 mg group, and 0.7% (n=2) in the all ustekinumab group.
- Through Week 60, the proportions of subjects with infections requiring antimicrobial treatment were 26.2% in the combined 45 mg group, 29.8% in the 90 mg group, and 24.0% in the all ustekinumab group, which does not represent a disproportional increase in rates compared with the data through Week 24 when 19.4% of subjects in the combined 45 mg group, 17.3% of subjects in the 90 mg group, and 16.0% of subjects in the all ustekinumab group with infections required antimicrobial treatment.

Injection-site Reactions

- Through Week 60, the proportions of injections associated with injection-site reactions were 0.2% for placebo, 0.3% for ustekinumab 45 mg, and 1.0% for ustekinumab 90 mg; the overall injection-site reaction rate was 0.6%. All injection-site reactions were reported as mild, and none resulted in study agent discontinuation.
- No possible anaphylactic or serum sickness-like reactions to study agent were reported through Week 60. There was no apparent association between development of antibodies to ustekinumab and the development of injection-site reactions.

Malignancies

- Two malignancies were reported through Week 60: 1 case of squamous cell carcinoma reported in 1 subject in the 90 mg ustekinumab group through Week 24 and 1 case of breast cancer reported in 1 subject in the placebo → 45 mg group after Week 24.

Cardiovascular Events

- There was a total of 3 major adverse cardiovascular events (MACE) reported after Week 24 through Week 60: 2 myocardial infarctions (MIs) in the 45 mg group and 1 acute MI in the 90 mg group.

Laboratory Test Results

- The proportion of subjects with 1 or more markedly abnormal hematology or chemistry laboratory values generally remained low through Week 60. Concomitant use of MTX did not appear to impact the hematology and chemistry values.

Vital Signs

- Heart rate and blood pressure were similar across all treatment groups at baseline and remained stable through Week 60.

STUDY LIMITATIONS:

The relatively short placebo-controlled period (through Week 16) limits the interpretation of long-term efficacy and safety data, although site personnel and subjects remained blinded to ustekinumab dose through the end of the study (Week 60). The availability of early escape for subjects randomized to the 45 mg treatment group with an increase in dose to 90 mg, impacts the ability to assess the relative safety and efficacy of the 45 mg and 90 mg treatment groups beyond Week 16.

CONCLUSIONS:

- Through Week 52, 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. Generally, efficacy was generally maintained after Week 24 through Week 52. Efficacy was not impacted by previous disease-modifying antirheumatic drugs or concomitant MTX use.
- The proportions of subjects achieving ACR and/or PASI, and the change from baseline in HAQ-DI score were generally maintained regardless of prior exposure to anti-TNFα agents, although responses were better in subjects who were anti-TNFα naïve subjects than in subjects who were anti-TNFα experienced.
- An exposure-response relationship was observed through Week 52. 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 dosing had similar exposure to ustekinumab as subjects weighing ≤100 kg treated with 45 mg. Moreover, the incremental efficacy benefit provided by the 90 mg dose was most evident for subjects weighing >100 kg.
- Through Week 60, ustekinumab was generally well tolerated with similar proportions of subjects experiencing AEs, and similar types of AEs were observed in the ustekinumab 45 mg and 90 mg groups. Compared with data at Week 24, there were no disproportional increases in event rates, and there were no additional safety concerns identified through Week 60. Safety was not impacted by concomitant MTX use or previous exposure to anti-TNFα agent(s).