
SYNOPSIS

Issue Date: 17 Jan 2013

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

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: [REDACTED] MD

Study Centers: 104 study sites

Publication (Reference): None

Study Period: Through Week 24

Phase of Development: Phase 3

Objectives: The primary objectives of this study are 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 are 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. Six hundred and fifteen subjects were randomized to receive treatment with ustekinumab 45 mg (45 mg), ustekinumab 90 mg (90 mg), or placebo subcutaneous (SC) injections at Weeks 0 and 4, followed by every 12 week (q12w) dosing with the last dose at Week 88. Subjects randomized to placebo were eligible for crossover to receive ustekinumab at Weeks 24 and 28, followed by q12w dosing with the last dose at Week 88. Expected duration of exposure to study agent is 100 weeks. Subjects will be followed for efficacy through Week 100 and for safety through Week 108.

Number of Subjects (planned and analyzed): A target of 600 subjects was planned to be randomly assigned to treatment with 200 subjects each in the 45 mg, 90 mg, and or placebo groups, respectively.

A total of 615 subjects was randomly assigned across treatment groups with 205, 204, and 206 subjects in the 45 mg, 90 mg, and placebo groups, respectively.

Diagnosis and Main Criteria for Inclusion: Subjects were men or women between 18 and 99 years of age 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 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) and at least 1 of the PsA subsets, and/or active plaque psoriasis, or a documented history of plaque psoriasis.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab was supplied in a pre-filled 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. Five lots of ustekinumab (Batch No.: 08F011, 08F012, 09G041, 09G042, and 10C052) were used in the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: The placebo was supplied in a PFS, 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 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 No.: 08H021, 08H022, 09E021, 09E022, 10E011, and 10E012) were used in the study.

Duration of Treatment: Approximately 615 subjects were randomized in a 1:1:1 ratio to 1 of the 3 groups and received treatment with 45 mg, 90 mg, or placebo SC at Weeks 0 and 4 followed by 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 in the 45 mg and placebo groups were eligible for early escape and begin to receive ustekinumab 90 mg and 45 mg, respectively. 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. The expected duration of exposure to study agent is 100 weeks. Subjects will be followed for efficacy through Week 100 and for safety through Week 108. The first database lock (DBL) occurred at Week 24. The 24-week DBL includes all pharmacokinetic (PK), efficacy, and safety data through Week 24 with the exception of the radiographic data for all randomized subjects. In addition, subject disposition and safety data (including laboratory data) through Week 52 for subjects randomized prior to 26 Oct 2010 who were supposed to have completed Week 52 visit by the time of the 24 week DBL (either terminated the study or completed through Week 52), and referred thereafter as “the Week 52 safety subset”, were also included. Additional database locks will occur at Week 52 and Week 108. The end of the study will occur after the last subject completes the Week 108 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 and subjects weight at baseline (≤ 100 kg versus >100 kg). The population PK modeling is not included in this report. The relationship of serum ustekinumab concentrations and selected efficacy was 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 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 PsA response criteria (PsARC) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Psoriasis evaluations included psoriasis area and severity index (PASI) and dermatology life quality index (DLQI). The potential pharmacoeconomic benefit of ustekinumab treatment was also assessed. Radiographic imaging evaluations of the hands and feet through Week 24 will be addressed in the 52-Week Clinical Study Report.

Safety: Safety evaluations for all subjects 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 between each of the evaluation visits. 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 615 subjects randomly assigned to treatment at Week 0, 206 were assigned to the placebo group, 205 were assigned to the 45 mg group, and 204 were assigned the 90 mg group. All randomized subjects received their assigned treatment at Week 0 with the exception of 1 subject in the placebo group who withdrew consent and was never treated.
 - Through Week 24, a total of 30 subjects discontinued across the randomized treatment groups with a higher rate of discontinuation in the placebo group (7.3%) than either in the 45 mg (3.9%) or the 90 mg (3.4%) groups. The most common reason for discontinuation of study agent across all study groups was due to an AE. The higher proportion of subjects discontinuing study agent in the placebo group compared with the individual ustekinumab groups was primarily due to efficacy related reasons (ie, lack of efficacy and worsening of disease).
- For the Week 52 safety subset, which included 356 subjects randomized prior to 26 Oct 2010 who completed the Week 52 visit by the time of the 24-week DBL, the subject disposition was assessed.
 - Through Week 52, 41 subjects out of 356 discontinued study agent. The proportion of subjects was comparable in the placebo (13.6%) and 45 mg (12.5%) groups, but lower in the 90 mg group (8.5%). The most common reason for discontinuation was lack of efficacy (45 mg group), withdrawal of consent (90 mg group), and due to an adverse event (placebo group).
- Demographic characteristics of subjects at baseline were generally well balanced across treatment groups:
 - the majority of subjects were men (53.7%)
 - most subjects were Caucasian (96.6%)
 - the median age was 48.0 years
 - the median weight was 86.0 kg
- Baseline clinical characteristics of PsA from the ACR core set of outcome measurements were indicative of subjects with PsA of moderate to severe activity and generally comparable across the treatment groups.
 - Median number of swollen joints (10.00)
 - Median number of tender joints (20.00)
 - Median VAS of Patient's assessment of pain (6.60 cm)
 - Median VAS of Physician's Global Assessment of disease activity (6.50 cm)
 - Median HAQ-DI score was the same in all the treatment groups (1.25)
 - Median CRP level (10.30 mg/L)

- Baseline disease characteristics of psoriasis measurements for subjects with $\geq 3\%$ 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 quality of life.
 - Median percent BSA (11.00)
 - Median PASI score (8.00)
 - Median DLQI score (10.00)
- Through Week 24, subjects in the study randomized to ustekinumab received a median dose of 180 mg. The placebo subjects who entered early escape received an average of approximately 2 ustekinumab injections while subjects randomized to the ustekinumab group received an average of approximately 3 ustekinumab injections.

CLINICAL PHARMACOLOGY SUMMARY

Pharmacokinetics Summary

- 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 $< 0.16880 \mu\text{g/mL}$ was observed in the 45 mg group compared with the 90 mg group.
- Subjects who underwent early escape had relatively lower serum ustekinumab levels compared with subjects who did not early escape, as suggested by lower mean serum ustekinumab concentrations through Week 16 and a higher proportion of subjects with trough serum ustekinumab concentrations $< 0.16880 \mu\text{g/mL}$ at Week 16. However, subjects in the 45 mg group who underwent early escape had their serum ustekinumab concentrations increased after receiving the 90 mg dose at Week 16.
- Within each treatment group, mean serum ustekinumab concentrations in subjects who received MTX at baseline was slightly higher compared with subjects who did not receive MTX at baseline.
- Subjects of higher weight ($> 100 \text{ kg}$) had lower mean serum ustekinumab concentrations compared with subjects of lower weight ($\leq 100 \text{ kg}$). Notably, mean serum ustekinumab concentrations at Weeks 4, 12, and 16 in subjects $> 100 \text{ kg}$ in the 90 mg group were generally comparable to those observed in subjects $\leq 100 \text{ kg}$ in the combined 45 mg group, and mean serum ustekinumab concentrations at Weeks 20 and 24 in subjects $> 100 \text{ kg}$ in the 90 mg group were generally comparable to those observed in subjects $\leq 100 \text{ kg}$ in the 45 mg group who did not early escape at Week 16.

Immunogenicity Summary

- Through Week 24, the combined incidence of antibodies to ustekinumab was 5.8% (n=26) across all treatment groups.
- The incidence of antibodies to ustekinumab was generally comparable between the combined 45 mg group (7.1%; n=14) and the 90 mg group (6.2%; n=12).
- The incidence of antibodies to ustekinumab was lower in subjects receiving MTX at baseline (3.3%) compared with subjects not receiving MTX at baseline (8.1%).

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- Subjects who were positive for antibodies to ustekinumab had lower mean serum ustekinumab concentrations than subjects who were negative for antibodies to ustekinumab.

EFFICACY RESULTS:

Primary Endpoint

- A significantly greater proportion of subjects in the combined ustekinumab, 45 mg, and 90 mg groups (46.0%, 42.4%, and 49.5%, respectively) achieved an ACR 20 response at Week 24 compared with subjects in the placebo group (22.8%; $p < 0.001$ for all comparisons).

Major Secondary Endpoints

- There was significantly greater improvement in HAQ-DI scores at Week 24 in subjects in the combined ustekinumab, 45 mg, and 90 mg groups (all with a median change from baseline of -0.25) compared with subjects in the placebo group (median of 0.00; $p < 0.001$ for all comparisons).
- A significantly greater proportion of subjects with $\geq 3\%$ BSA psoriasis skin involvement at baseline in the combined ustekinumab, 45 mg, and 90 mg groups demonstrated PASI 75 response at Week 24 (59.9%, 57.2%, and 62.4%, respectively) compared with subjects in the placebo group (11.0%; $p < 0.001$ for all comparisons).
- A significantly greater proportion of subjects in the combined ustekinumab, 45 mg and 90 mg groups achieved an ACR 50 response (26.4%, 24.9%, 27.9% respectively) and an ACR 70 response (13.2%, 12.2%, 14.2% respectively) at Week 24 compared with subjects in the placebo group (ACR 50: 8.7%, ACR 70: 2.4%; $p < 0.001$ for all comparisons).

Other Efficacy Analyses

- ACR 20, 50, and 70 responses in both the 45 mg and 90 mg 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. There appeared to be decreases in response rates at Week 16 in the 45 mg group for ACR 20 response and ACR 50 response which were not observed in the 90 mg group.
- PsARC and DAS28 response 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 a Week 24 ($p < 0.001$ for all comparisons).
- For subjects with dactylitis at baseline, significantly greater improvement in dactylitis score at Week 24 was observed in both the 45 mg, 90 mg, and combined ustekinumab groups as compared with the placebo group ($p < 0.001$ for all comparisons).
- For subjects with enthesitis at baseline, significantly greater improvement in enthesitis score at Week 24 was observed for both ustekinumab dose groups as compared with the placebo group ($p = 0.002$ in the 45 mg group and $p < 0.001$ in the 90 mg group).
- For subjects with the spondylitis with peripheral arthritis subset of PsA, a significantly higher proportion of subjects achieved at least 20% or at least 70% improvement in BASDAI score at Week 12 and Week 24 in both ustekinumab groups as compared with the placebo group.
 - The proportion of subjects achieving at least 50% improvement in BASDAI at Week 12 and Week 24 was numerically higher in both ustekinumab groups as compared with the placebo group.

- A significantly higher proportion of subjects achieved the ACR 20 at Week 24 in both ustekinumab groups as compared with the placebo group for both subjects receiving MTX ($p=0.011$ in the 45 mg group and $p<0.001$ in the 90 mg group) and those not receiving MTX at baseline ($p=0.004$ in the 45 mg group and $p<0.001$ in the 90 mg group).
- A significantly higher proportion of subjects achieved both ACR 20 and PASI 75 at Week 24 in both the 45 mg group (27.6%) and 90 mg group (41.6%) as compared with the placebo group ($p<0.001$ for all comparisons).
- At Week 24, there was a significantly higher proportion of subjects with a DLQI score of 0 or 1 in the combined ustekinumab group (45.2%), in the 45 mg group (37.2%), and in the 90 mg group (53.0%) compared with 8.3% in the placebo group ($p<0.001$ for all comparisons).
- A significantly greater improvement in SF-36 physical component summary (PCS) score was observed in both ustekinumab groups as compared with the placebo group at both Week 16 and Week 24 ($p<0.001$ for all comparisons).
- A significantly greater improvement in SF-36 mental component summary (MCS) score was observed in both the ustekinumab 45 mg group ($p=0.005$) and 90 mg group ($p=0.018$) as compared with the placebo group at Week 16. A significantly greater improvement in SF 36 MCS score was observed for the 90 mg group ($p<0.001$) as compared with the placebo group at Week 24.
- The proportion of subjects who achieved ACR 20, ACR 50 and PASI 75 responses at Week 24 was higher in subjects with preinjection serum ustekinumab levels ≥ 0.16880 $\mu\text{g/mL}$ when compared with subjects with preinjection serum ustekinumab levels < 0.16880 $\mu\text{g/mL}$.
- 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.
- Consistently and significantly higher proportions of subjects achieved ACR 20 at Week 24 in almost all the subgroups examined in the 90 mg group as compared with the placebo group. However, more variability was observed in the subgroups examined for the comparisons between the 45 mg group and the placebo group.
 - Statistically significant higher ACR 20 response was observed for both the 45 mg and 90 mg groups as compared with the placebo group among subjects with prior disease modifying antirheumatic drug use.
- There was no statistically significant difference in the time lost from work (days) between the ustekinumab treatment groups and placebo group at Week 16 and Week 24 for subjects < 65 years old and employed full-time at baseline.
- Overall, there were no consistent statistically significant differences in the ustekinumab treatment groups compared with the placebo group in the measure of employability due to PsA at Week 16 and Week 24.
- At both Week 16 and Week 24, the impact of PsA on work productivity was significantly greater in the combined ustekinumab group ($p<0.001$), the 45 mg group ($p=0.002$), and the 90 mg group ($p<0.001$) compared with the placebo group.

SAFETY RESULTS:

Treatment emergent AEs and laboratory analyte values were also presented and summarized through Week 16 (the placebo-controlled period), and Week 24 for all subjects and through Week 52 for the Week 52 safety subset. Vital sign measurements (heart rate and blood pressure) and physical evaluation

(waist circumference and weight) are presented and summarized through Week 24. The Week 52 safety subset included 356 subjects randomized prior to 26 Oct 2010 who completed the Week 52 visit by the time 24-week DBL occurred.

Adverse Events

- Through Week 16, AE rate, and AE profiles in each of the 2 ustekinumab groups were comparable to those observed in the placebo group. The proportion of subjects reporting AEs was 39.5%, 43.1% and 43.4% in the 45 mg, 90 mg and placebo groups, respectively. The most commonly reported system organ class of AEs was Infections and Infestations (16.6%, 20.1%, and 20.5% in the 45 mg, 90 mg and placebo groups, respectively), and the most frequently reported AEs were predominantly nasopharyngitis and upper respiratory tract infection (URTI).
- 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. Additionally, the AE rate and profile were similar between the treatment groups.
- Through Week 52, in the Week 52 safety subset, no disproportional increase from Week 24 was observed in AE rates, and the AE profile was similar to that observed through Week 24. Additionally, AE rates and AE profile were similar between the subjects initially randomized and treated with 45 mg and those with 90 mg.
- Safety profiles were not impacted by concomitant use of MTX, age, gender, and weight.

Serious Adverse Events

- No deaths were reported.
- Through Week 16, the proportion of subjects reporting one or more serious adverse events (SAEs) was similar across all 3 treatment groups (2.0%, 1.5% and 2.0% in 45 mg, 90 mg and placebo groups, respectively). SAEs were single events in all the treatment groups without any particular pattern.
- Through Week 24, the proportion of subjects experiencing 1 or more SAEs was 2.9% in the combined 45 mg and 1.5% in the 90 mg group. SAEs occurred in 2.1% of all ustekinumab-treated subjects and 2.4% of placebo-treated subjects.
- The proportion of subjects reporting one or more SAEs continued to be low among the Week 52 safety subset, 5.8% and 2.5% in the combined 45 mg and 90 mg group, respectively. No particular pattern was observed.
- SAEs were not impacted by concomitant use of MTX or weight.

Adverse Events Leading to Study Agent Discontinuation

- Through Week 16, the proportion of subjects who discontinued study agent due to 1 or more AEs were similar in the placebo group (1.5%) compared with the 45 mg (0.5%) or the 90 mg group (1.0%).
- Through Week 24, the proportion of subjects who discontinued study agent due to 1 or more AEs continued to be low (1.5% in the combined 45 mg group and 1.5% in the 90 mg group; 1.3% of all ustekinumab-treated subjects and 3.4% of placebo-treated subjects).
- The proportion of subjects who discontinued study agent due to 1 or more AEs among the Week 52 safety subset was 3.3% and 0.8% in the combined 45 mg group and 90 mg group, respectively.

Infections

- Through Week 16, infection rates and types of infections in both the 45 mg and 90 mg groups were comparable to those observed in the placebo group. The proportion of subjects reporting infections was 16.6%, 19.6% and 21.0% in the 45 mg, 90 mg, and placebo groups, respectively. The most commonly reported infections were nasopharyngitis and URTI.
- Through Week 24, no disproportional increase was observed in infection rates, and the types of infections were similar to that observed through Week 16. Additionally, infection rates and types of infections were similar between the treatment groups.
- Through Week 52, no disproportional increase was observed in infection rates, and the types of infections were similar to that observed through Week 24. Additionally, infection rates and types of infections were similar between the treatment groups.
- Infections were not impacted by concomitant use of MTX and weight.
- Serious Infections:
 - Through Week 24, no serious infections were reported.
 - Through Week 52, there were 4 serious infections: pharyngolaryngeal abscess, salpingitis, and 2 events of acute cholecystitis.

Injection-site Reactions

- Rates of injections with injection site reactions were 0.6% for the 45 mg injections and 0.8% for the 90 mg injections compared with 0.4% in the placebo injections. All injection-site reactions were mild.
- No possible anaphylactic or possible serum sickness-like reactions to study agent were reported. There was no apparent association between development of antibodies to ustekinumab and the development of injection-site reactions.

Malignancies

- No malignancies were reported.

Cardiovascular Events

- No major adverse cardiovascular event (MACE) was reported through Week 16 in any of the treatment groups.
- One subject randomized to the 45 mg group who did not enter early escape had a stroke between Weeks 16 and 24.
- In the Week 52 safety subset, 1 additional MACE (myocardial infarction reported in a placebo crossover subject) was reported approximately 6 months after the subject initiated treatment with ustekinumab.

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 and Week 52, markedly abnormal changes in hematology and chemistry generally remained low. Concomitant use of MTX did not appear to impact the 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. At Week 24, the analyses of shifts combined with the change from baseline indicated that ustekinumab did not impact fasting glucose.
- Ustekinumab-treated subjects had slightly higher increases in fasting total cholesterol (TC), low density lipoprotein, high-density lipoprotein (HDL), and triglyceride than placebo-treated subjects; however, the change in the TC/HDL ratio was similar across all 3 treatment 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 group 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.
- Dose proportionality in serum ustekinumab concentration was observed when comparing mean serum ustekinumab concentrations between the 45 mg and 90 mg groups.
- Greater efficacy was observed in the 90 mg dose group compared with the 45 mg dose group across multiple endpoints, and most notably in the primary endpoint of ACR 20 responses, and the secondary endpoints of ACR 50, ACR 70, PASI 75, enthesitis scores, and the combined ACR 20 and PASI 75 responses.
- Efficacy was demonstrated in both subjects receiving MTX and subject not receiving MTX.
- 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.
- The safety profiles are similar for subjects receiving MTX and not receiving MTX.
- The overall safety profile was consistent with that reported for ustekinumab-treated subjects with psoriasis.

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	STELARA®
<u>Name of Active Ingredient(s)</u>	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; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; 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: 2 May 2013
Prepared by: Janssen Research & Development, Inc.

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: [REDACTED] MD - [REDACTED] Scotland

Study Center(s): 104 study sites

Publication (Reference): None

Study Period: 30 November 2009 (first informed consent) to 10 May 2012 (last study-related procedure for Week 52). 12 July 2012 (database lock).

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;
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- Inhibiting the progression of structural damage.

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12 week (q12w) dosing 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. Expected duration of exposure to study agent is 100 weeks. Subjects will be followed for efficacy through Week 100 and for safety through Week 108. Investigative study sites and subjects will remain blinded to treatment assignment until the last enrolled subject completes the Week 108 evaluations and the database is locked.

Number of Subjects (planned and analyzed): A target of 600 subjects was planned to be randomly assigned to treatment with 200 subjects each in the 45 mg, 90 mg, and or placebo groups, respectively.

A total of 615 subjects was randomly assigned across treatment groups with 205, 204, and 206 subjects in the 45 mg, 90 mg, and placebo groups, respectively.

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Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab was supplied in a pre-filled syringe as a single-use, sterile solution in a ■■■ 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. Six lots of ustekinumab (Batch No.: 08F011, 08F012, 09G041, 09G042, 10C051, and 10C052) were used in the study.

Reference Therapy, Dose and Mode of Administration, Batch No.: The placebo was supplied in a pre-filled syringe, a single-use, sterile solution in a ■■■ 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. Six lots of placebo (Batch No.: 08H021, 08H022, 09E021, 09E022, 10E011, and 10E012) were used in the study.

Duration of Treatment: Six hundred and fifteen subjects were 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 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 in the 45 mg and placebo groups were eligible for early escape and began to receive ustekinumab 90 mg and 45 mg, respectively. 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 initially randomized to 90 mg remained on 90 mg throughout the study. The expected duration of exposure to study agent is 100 weeks. Subjects will be followed for efficacy through Week 100 and for safety through Week 108. The first database lock (DBL) occurred at Week 24 and the results were reported in the CNTO1275PSA3001 24-week clinical study report (CSR). This 52-week CSR presents the evaluation of the data from the 52-week DBL. The last DBL will occur at Week 108, the end of the study.

Criteria for Evaluation:

Pharmacokinetics: Serum ustekinumab concentrations were summarized for subjects treated with ustekinumab through Week 52. Serum ustekinumab concentrations were also summarized by methotrexate (MTX) use at baseline and subjects' weight at baseline (≤ 100 kg versus >100 kg). The relationship 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: The efficacy data were summarized primarily after Week 24 through Week 52. The 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), and modified PsA response criteria (PsARC). Psoriasis evaluations included psoriasis area and severity index (PASI) and dermatology life quality index (DLQI). The potential pharmacoeconomic benefit of ustekinumab treatment was also assessed. Radiographic imaging evaluations of the hands and feet through Week 52 (including data at Week 24) are presented in a separate integrated radiographic analysis report.

Safety: Safety data were summarized through Week 52 for subjects treated with ustekinumab. Safety evaluations for all subjects were monitored and included assessment of adverse events (AEs) and injection-site reactions, measurement of vital signs (heart rate and blood pressure), and physical evaluations (waist circumference and weight) that may have occurred between each of the evaluation visits. Tuberculosis (TB) 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: 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 presentations of the data were also used.

RESULTS:

STUDY POPULATION:

Baseline demographic and disease characteristics are described in the CNTO1275PSA3001 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 only and 90 mg groups through Week 52.
- Steady state was achieved at Week 28 for the 45 mg only and 90 mg groups, and trough serum ustekinumab concentrations were maintained at steady state through Week 52.
- There was no evidence of accumulation in serum ustekinumab concentrations over time.
- A higher proportion of subjects with below the lowest quantifiable sample concentration of the assay (BQL) trough serum ustekinumab concentrations was observed in the 45 mg only group compared with the 90 mg group through Week 52.
- Within each treatment group, mean trough serum ustekinumab concentrations in subjects who received concomitant MTX appeared to be slightly higher compared to subjects who did not receive concomitant MTX through Week 52.

- 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.

Immunogenicity Summary

- Through Week 52, the incidence of antibodies to ustekinumab was 7.1% (n=42) across all treatment groups.
- The incidence of antibodies to ustekinumab was generally comparable between the combined 45 mg group (8.4%; n=17) and the 90 mg group (7.0%; n=14).
- The incidence of antibodies to ustekinumab was lower in subjects receiving concomitant MTX (3.8%) compared with subjects not receiving concomitant MTX (10.2%).
- The majority (59.5%) 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 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 (22.0% versus 2.4%, respectively) and the incidence of antibodies to ustekinumab was higher in subjects >100 kg when compared with subjects ≤100 kg (11.5% versus 5.6%, respectively).

EFFICACY RESULTS:

Data through Week 24, including the results of the primary efficacy analysis (the proportion of subjects who were ACR 20 responders at Week 24) and 4 of 5 major secondary endpoints, are presented in the CNTO1275PSA3001 24-Week CSR.

Efficacy Analyses after Week 24 through Week 52:

- The fifth major secondary endpoint, change from baseline in total radiographic scores of the hands and feet at Week 24 (based upon meta-analysis of the CNTO1275PSA3001 and CNTO1275PSA3002 studies), is presented in a separate integrated radiographic analysis report.
- The proportion of subjects who achieved an ACR response was maintained after Week 24 through Week 52. At Week 52, the proportions of subjects who achieved an ACR 20 response were 55.7% and 60.3% for the 45 mg and 90 mg groups, respectively. The proportions of subjects in the 45 mg and 90 mg groups who achieved an ACR 50 response were 31.4% and 37.0%, respectively, and ACR 70 response were 18.0% and 21.2%, 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 was -0.25 and -0.38, respectively. At Week 52, the proportions of subjects in the ustekinumab 45 mg and 90 mg groups who achieved clinically meaningful improvement (HAQ-DI ≥0.3) in HAQ-DI at Week 52 were 47.4% and 51.3%, 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 response in the 45 mg and 90 mg groups were 72.7% and 74.6%, respectively.

- Among subjects with dactylitis at baseline, the proportions of subjects with 1 or more digits with dactylitis at Week 52 were 39.2% and 46.2% in the 45 mg and 90 mg groups, respectively. For subjects with dactylitis at baseline, the median percent improvement in dactylitis score was 100% for both the 45 mg and 90 mg groups at Week 52.
- Among subjects with enthesitis at baseline, the proportions of subjects with enthesitis at Week 52 were 55.6% and 54.2% in the 45 mg and 90 mg groups, respectively. At Week 52, among the subjects with enthesitis at baseline, the median percent improvement in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASSES) index was 83.3% and 74.2% in the 45 mg and 90 mg groups, respectively.
- PASI responses were maintained after Week 24 through Week 52. At Week 52, the proportions of subjects with $\geq 3\%$ BSA skin involvement with psoriasis at baseline who achieved PASI 75 response in the 45 mg and 90 mg groups were 70.1% and 68.1%, 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 -5.00 and -7.00 in the 45 mg and 90 mg groups, respectively.
- At Week 52, in subjects weighing ≤ 100 kg, ACR 20 responses were 61.6% and 62.5% in the 45 mg and 90 mg groups, respectively. In subjects weighing >100 kg, ACR 20 responses were higher in the 90 mg treatment group than in the 45 mg group (53.3% and 37.5%, respectively).
- Consistent with data through Week 24, after Week 24 through Week 52, ACR response, improvement from baseline in HAQ-DI score and PASI response were not impacted by prior disease modifying antirheumatic drug (DMARD) use.
- At each timepoint after Week 24 through Week 52, within each treatment group, ACR responses and PASI responses were maintained in both subjects receiving MTX and subjects not receiving MTX.
- The mean changes from baseline in SF-36 PCS scores were 6.25 and 6.46 for subjects in the 45 mg and 90 mg groups, respectively, at Week 52.
- The mean changes from baseline in SF-36 MCS scores were 4.09 and 4.82 for subjects 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 the SF-36 scales at Week 52 than the 45 mg group in all categories except for physical functioning and role-emotional.
- At Week 52, mean improvement from baseline in disease impact on productivity was observed in both dose groups, 1.70 in the 45 mg group and 2.80 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 50 response rate at Week 52 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 52:

Safety data were presented for the following treatment groups: the combined 45 mg group (subjects randomized to 45 mg at Week 0 that did not early escape at Week 16 and subjects randomized to 45 mg at Week 0 that qualified for early escape to 90 mg at Week 16), the 90 mg group (all subjects randomized to

90 mg regardless of early escape), and the all ustekinumab group (all subjects who received ustekinumab during the study).

Adverse Events

- Through Week 52, the proportions of subjects experiencing 1 or more AEs were 66.8% among subjects in the combined 45 mg group, 64.7% among subjects originally randomized to 90 mg, and 58.0% in the all ustekinumab group, which did not represent a disproportional rate increase compared with Week 24 when 54.1% of subjects in the combined 45 mg group, 52.5% of subjects in the 90 mg group, and 49.0% 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 AEs reported through Week 24. A higher proportion of subjects reported urinary tract infections (UTIs) in the 90 mg group than in the combined 45 mg group, which will continue to be evaluated as additional data are accrued.
- Consistent with data through Week 24, safety profiles were not impacted by concomitant use of MTX through Week 52.

Serious Adverse Events

- No deaths were reported through Week 52.
- Through Week 52, the proportions of subjects experiencing 1 or more serious adverse event (SAEs) were 5.9%, 3.4%, and 4.8% 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.
- The incidence of SAEs was not impacted by concomitant use of MTX through Week 52.

Adverse Events Leading to Study Agent Discontinuation

- Through Week 52, the proportions of subjects who discontinued study agent due to an AE were 2.4% in the combined 45 mg group, 3.4% in the 90 mg group, and 2.5% in the all ustekinumab group. The AEs leading to study discontinuation were all single events.

Infections

- Through Week 52, the proportions of subjects with infections were 37.6% in the combined 45 mg group, 41.2% in the 90 mg group, and 33.4% in the all ustekinumab group, which did not represent a disproportional rate increase compared with Week 24 when the proportions were 26.8%, 27.0%, and 24.4% in the combined 45 mg, 90 mg, and all ustekinumab groups, respectively.
- Through Week 52, the proportions of subjects with serious infections were low and 1.0% in the combined 45 mg group, 1.0% in the 90 mg group, and 0.8% in the all ustekinumab group.
- Through Week 52, the proportions of subjects with infections requiring antimicrobial treatment were 18.5% in the combined 45 mg group, 20.6% in the 90 mg group, and 16.7% in the all ustekinumab group. This rate increase is not disproportional to that through Week 24 when the proportions of subjects with at least 1 infection requiring antimicrobial treatment in the combined 45 mg, 90 mg, and all ustekinumab groups were 10.7%, 10.3%, and 9.9%, respectively.

Injection-site reactions

- Through Week 52, the proportions of injections associated with injection site reactions were 0.3% for ustekinumab 45 mg and 0.7% for ustekinumab 90 mg; the overall injection site reaction rate was 0.4%. All injection site reactions were reported as mild and none resulted in study discontinuation.

- No possible anaphylactic or possible serum sickness-like reactions to study agent were reported through Week 52. There was no apparent association between development of antibodies to ustekinumab and the development of injection site reactions.

Malignancies

- No malignancies were reported through Week 52.

Cardiovascular Events

- There were a total of 3 major adverse cardiovascular events reported: 1 stroke in the 45 mg group through Week 24 and 2 myocardial infarctions in the placebo → 45 mg group between Week 24 and Week 52.

Laboratory Test Results

- The proportions of subjects with 1 or more markedly abnormal hematology or chemistry laboratory values generally remained low through Week 52. Concomitant use of MTX did not appear to impact the 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 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 maintained after Week 24 through Week 52. The 90 mg group achieved modestly higher efficacy responses relative to the 45 mg groups across multiple endpoints. Efficacy was not impacted by previous DMARD or concomitant MTX use.
- 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 to subjects with quantifiable trough serum concentrations. Subjects weighing >100 kg who received 90 mg dosing had similar exposure to ustekinumab as subjects ≤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.
- 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 through Week 52. Compared with observations at Week 24, there were no disproportional event rate increases and there were no additional safety concerns identified through Week 52. Safety was not impacted by concomitant MTX use.

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; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; 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: 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 (\leq 100 kg). Notably, mean steady-state trough serum ustekinumab concentrations were generally comparable between subjects >100 kg in the 90 mg group and subjects \leq 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 \leq 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 $\geq 3\%$ 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 $\geq 3\%$ 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.