SYNOPSIS

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Name of Sponsor/Company	Janssen EMEA Medical Affairs
Name of Finished Product	STELARA
Name of Active Ingredient(s)	Ustekinumab

Protocol No.: CNTO1275PSO4004

Title of Study: An Exploratory Trial to Assess Naturalistic Safety and Efficacy Outcomes in Patients With Moderate to Severe Plaque Psoriasis Transitioned to Ustekinumab From Previous Methotrexate Therapy

Study Name: TRANSIT

EudraCT Number: 2008-008171-34

NCT No.: NCT01059773

Clinical Registry No.: CR016639

Principal Investigator(s): This study was conducted at 87 sites, with 87 principal investigators responsible for enrollment of subjects, study conduct, and subject safety at the study sites. There was no overall study or coordinating principal investigator.

Study Center(s): 87 sites screened subjects; sites were located across 20 countries in Europe and the Middle East.

Publication (Reference): None

Study Period: 05 October 2009 to 17 August 2011

Phase of Development: 3b/4

Objectives:

The primary objective of this study was to evaluate the comparative safety through Week 12 of 2 treatment transition strategies in patients with moderate-to-severe plaque-type psoriasis with an inadequate response to methotrexate: discontinuation of methotrexate with immediate initiation of ustekinumab versus initiation of ustekinumab with overlap and gradual dose reduction of methotrexate over 4 weeks.

The secondary objectives of the study were:

- to evaluate the safety, efficacy, and quality of life associated with ustekinumab through Week 52;
- to evaluate the effects of increasing the dose of ustekinumab from 45 mg to 90 mg at Week 28 and/or Week 40 in patients (≤100 kg) who do not achieve a Psoriasis Area and Severity Index (PASI) 75 response at Weeks 28 or 40.

Methodology:

This was a multicentre, open label, 2-arm, randomized Phase 3b/4 study in patients with moderate-to-severe plaque-type psoriasis who were transitioned to ustekinumab from previous methotrexate therapy. The overall study period was 56 weeks, including a 4-week screening period and a 52-week treatment phase. All treated patients were followed for safety and efficacy through Week 52.

The eligibility of patients to enter the study was assessed during the screening period (Week -4 to Week 0). Patients continued their current treatment schedule of methotrexate.

At Week 0, prior to the first dose of ustekinumab, patients were randomized in a 1:1 ratio to 1 of 2 treatment arms.

- **Treatment Arm 1 (UST/MTX stopped arm):** Patients were to stop methotrexate in the week prior to receiving their first ustekinumab injection and were to receive ustekinumab only throughout the study. Ustekinumab was administered by subcutaneous administration at Weeks 0, 4, 16, 28, and 40.
- **Treatment Arm 2 (UST/MTX gradually withdrawn arm):** Patients were to receive a gradually withdrawn dose of methotrexate in the first 4 weeks of the treatment phase, in addition to ustekinumab treatment administered by subcutaneous administration at Weeks 0, 4, 16, 28, and 40. The methotrexate dose reduction regime depended on the dose of methotrexate at baseline. All patients stopped methotrexate, regardless of the final dose, after 4 overlapping weeks (Weeks 0, 1, 2 and 3). The last dose of methotrexate was administered within 7 days before the Week 4 dose of ustekinumab.

Patients were stratified according to their baseline body weight (≤100 kg or >100 kg) to ensure a similar distribution of patients between the 2 treatment arms. All patients weighing ≤100 kg were to receive ustekinumab 45 mg through Week 16, while all patients weighing >100 kg were to receive ustekinumab 90 mg through Week 40. Patients ≤100 kg who did not achieve a PASI 75 response at Week 28 and/or Week 40 had their ustekinumab dose increased to 90 mg. Patients ≤100 kg who did achieve a PASI 75 response at Week 28 and/or Week 40 were continued on 45 mg. Patients >100 kg had no increase in their ustekinumab dose regardless of PASI response; however, consideration was given to discontinuing treatment in these subjects if no response was observed at Week 28.

In both treatment arms, patients had a final visit at Week 52.

Number of Subjects (planned and analyzed): The study was planned for a total of 576 patients, 288 subjects in each treatment arm. A total of 649 subjects were screened of which 490 subjects were randomized to 1 of the 2 treatment arms (244 to Treatment Arm 1 and 246 to Treatment Arm 2). A total of 489 subjects were included in the analysis of safety, efficacy, and quality of life.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were men and women aged 18 years or over with moderate-to-severe plaque psoriasis, with a PASI score ≥10, who had failed or were intolerant to methotrexate therapy. Patients entering the study must have been receiving a minimum methotrexate dose of 10 mg/week for at least 8 weeks prior to screening.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab (0.5 mL) was provided by the sponsor in prefilled syringes for subcutaneous administration (Bulk Lot Numbers [Expiry date]: 07M011 [15Jan10], 08F011 [10Jun10], 09E011 [20May11], and 09G041 [21Sep11]).

Methotrexate taken during the screening and/or treatment phase was not provided by the Sponsor; patients continued to receive the same formulation and brand of methotrexate taken prior to study entry.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: The overall study period was 56 weeks, including a 4-week screening period and a 52-week treatment phase.

Criteria for Evaluation:

Efficacy and Quality of Life Evaluations: Efficacy evaluations included PASI, Nail Psoriasis Area and Severity Index (NAPSI), and Physicians Global Assessment (PGA).

Evaluations to assess changes in quality of life included the Dermatology Life Quality Index (DLQI), Hospital Anxiety and Depression Score (HADS), EuroQol-5D dimensional questionnaire (EQ-5D), and Patient Benefit Index (PBI).

Safety Evaluations: Routine safety evaluations were performed throughout the study period, including the monitoring of treatment-emergent adverse events (TEAEs), measurement of vital signs, body weight, waist circumference, skin assessment for suspicious malignant lesions, and blood sample collection for routine laboratory analysis. In addition, an exploratory lymphocyte subset analysis was performed in a subset of patients to examine immunological cell surface markers for psoriasis.

Statistical Methods:

Statistical analyses: The primary endpoint was the proportion of patients experiencing at least 1 TEAE through Week 12 by preferred term, treatment arm, and body weight category (≤100 kg, >100 kg). Comparisons between the 2 treatment strategies were performed on a descriptive basis.

Secondary safety endpoints included reporting of TEAEs, serious TEAEs, infections, and other events of clinical interest (tuberculosis, serious cardiovascular events, malignancies, and anaphylactic/serum sickness reactions) through Week 12 and through Week 52. The number and percentage of patients with TEAEs were summarized by MedDRA system organ class and preferred term. Changes in vital signs, laboratory parameters, and other safety parameters were summarized using descriptive statistics.

Actual values and changes from baseline in PASI, PGA, NAPSI, DLQI, HADS, EQ-5D, and PBI at each time point and at endpoint (LOCF) were described using descriptive statistics and/or frequency distributions. Other analyses included the proportion of subjects achieving a PASI 50, 75, and 90 response at each time point and the time to PASI response.

Statistical Analysis Sets: The efficacy and quality of life analysis was performed on the **modified intent-to-treat (mITT) analysis set**, defined as all subjects who were randomized and received at least 1 dose of ustekinumab, regardless of their compliance with the protocol.

Safety summaries were based on the **safety analysis set**, defined as all patients from the mITT analysis set with any post-baseline safety information.

Selected efficacy, quality of life, and safety endpoints were additionally assessed using a **per protocol (PP) analysis set**, which excluded subjects with major protocol deviations.

RESULTS:

STUDY POPULATION: Of the 489 subjects in the mITT and safety analysis sets, 445 (91.0%) completed the study. Eight (1.6%) subjects discontinued the study prior to Week 12 and 44 (9.0%) discontinued prior to Week 52. The most common reasons for discontinuation through Week 52 were sponsor decision (9 subjects) and use of contraindicated medication (8 subjects).

Typical of the general population with plaque psoriasis, the majority of subjects were aged 40 or above (68.5%) and most were male (67.9%). Most (80%) had a baseline body weight ≤100kg. Baseline PASI and PGA scores spanned the moderate to severe range (median values of 15 and 3, respectively) and health-related quality of life was moderately impaired (median DLQI score of 8.0). The majority of subjects (68.5%) had received at least 1 other previous systemic therapy (in addition to methotrexate); approximately 30% had received previous biologic treatment.

Exposure to ustekinumab was consistent between the treatment arms. The majority of subjects received all 5 scheduled doses (91.4%). A total of 84 subjects ≤100 kg had their dose correctly escalated from 45 mg to 90 mg at Week 28, and 31 had their dose correctly escalated at Week 40.

PRIMARY ENDPOINT: ADVERSE EVENTS THROUGH WEEK 12

A summary of TEAEs reported through Week 12 is provided below:

Summary of Adverse Events Through Week 12

Subjects with 1 or more treatment-emergent:	UST / MTX Stopped (N=244)	UST / MTX gradually withdrawn (N=245)	Total (N=489)
Adverse events	149 (61.1%)	158 (64.5%)	307 (62.8%)
Adverse event related to ustekinumab	51 (20.9%)	56 (22.9%)	107 (21.9%)
Severe adverse events	13 (5.3%)	5 (2.0%)	18 (3.7%)

The incidence and type of TEAEs reported during the first 12 weeks of the study were comparable across treatment arms and body weight categories. The most common TEAEs reported during the first 12 weeks were headache (10.2%), nasopharyngitis (9.4%), and arthralgia (5.9%).

No individual TEAE showed a difference in incidence of ≥5% between the 2 treatment arms.

In addition, no individual TEAE showed a difference in incidence of ≥5% between the baseline body weight categories (≤100 kg and >100 kg) in the total patient group. Within the individual treatment arms, the incidence of nasopharyngitis was higher in subjects with a baseline bodyweight of >100 kg versus ≤100 kg in the UST/MTX gradually withdrawn arm (14.3% vs. 6.1%, respectively), but no difference was observed in the UST/MTX stopped arm (10.2% vs. 11.3%, respectively). For all other TEAEs the differences between bodyweight categories were <5% within each treatment arm.

The vast majority of TEAEs reported through Week 12 were mild or moderate in severity and most were considered by the investigator to be unrelated or of doubtful relationship to study drug.

EFFICACY RESULTS: Both treatment arms showed comparable and clinically meaningful improvements in PASI and PGA scores throughout the study.

- Median PASI scores decreased from approximately 15 at baseline to 1.8 at endpoint (LOCF) in both treatment arms, and approximately three quarters of all subjects achieved a PASI 75 response. The Kaplan-Meier estimate of the median time to PASI 75 response was similar between treatment arms: 86.0 days (95% confidence interval [CI], 84.0; 91.0) in the UST/MTX stopped arm and 85.0 days (95% CI, 84.0; 89.0) in the UST/MTX gradually withdrawn arm.
- Median PGA scores decreased from 3 at baseline to 1 at endpoint (LOCF) in both treatment arms. The majority of patients in both treatment arms had achieved a PGA rating of 0 'cleared' or 1 'minimal' at endpoint (66.5% of subjects in the UST/MTX stopped arm and 69.8% of subjects in the UST/MTX gradually withdrawn arm).
- Improvements in PASI and PGA were observed as early as Week 4.

Median NAPSI scores decreased from 2 at baseline to 0 at endpoint.

Evaluation of PASI and PGA scores in subjects who had their dose escalated from 45 mg to 90 mg after failing to achieve a PASI 75 response at Week 28 or Week 40 showed further improvements in these parameters following the dose increase. In patients that did not have their dose escalated during the study, PGA and PASI scores remained relatively stable from Week 28 onwards; ie, improvements in these parameters largely occurred during the first half of the study and were maintained thereafter.

In both treatment arms, the proportion of subjects achieving a PASI 75 response at Week 52 was similar (ie, 95% CIs overlapped) irrespective of the number of previously failed therapies, previous use of biological therapy (yes/no), years of anteriority of plaque psoriasis, or initial ustekinumab dose (45 mg or 90 mg).

QUALITY OF LIFE RESULTS: Both treatment arms showed comparable and clinically meaningful improvements in quality-of-life outcomes.

- Median HADS total score decreased from 9 at baseline to 6 at endpoint (LOCF) in both treatment arms.
- Median DLQI score decreased from 8 or 9 at baseline to 1 at endpoint (LOCF) in both treatment arms, and 61.7% of subjects had a DLQI score of 0 or 1. The Kaplan-Meier estimate of the median time to a DLQI score of 0 or 1 was similar in both treatment arms: 115 days (95% CI, 113.0; 120.0) in the UST/MTX stopped arm and 113 days (95% CI, 113.0; 114.0) in the UST/MTX gradually withdrawn arm.
- Median EQ-5D Health Scale score increased from 70 at baseline to 85 at endpoint (LOCF) in both treatment arms.
- Median PBI scores at endpoint (LOCF) were 3.34 in the UST/MTX stopped arm and 3.46 in the UST/MTX gradually withdrawn arm.

Improvements in DLQI were observed as early as Week 4.

Analyses of HADS, DLQI, EQ-5D, and PBI scores according to PASI 75 response status showed greater improvements in these parameters in subjects that achieved a PASI 75 response at Week 52 compared with those that did not achieve a PASI 75 response.

In subjects that had their dose escalated at Week 28 or Week 40 after failing to achieve a PASI 75 response, additional improvements in DLQI, ED-Q5 Health Scale, and PBI scores were observed

following the dose increase. In subjects that did not have their dose escalated, quality of life scores remained relatively stable from Week 28 onwards; ie, improvements in these parameters largely occurred during the first half of the study and were maintained thereafter.

SAFETY RESULTS THROUGH WEEK 52:

A summary of key safety information through Week 52 is provided below:

Summary of Adverse Events Through Week 52

	UST / MTX Stopped (N=244)	UST / MTX gradually withdrawn (N=245)	Total (N=489)
Subjects with 1 or more treatment-emergent:			
Adverse event	195 (79.9%)	208 (84.9%)	403 (82.4%)
Adverse event related to ustekinumab	73 (29.9%)	78 (31.8%)	151 (30.9%)
Severe adverse event	23 (9.4%)	16 (6.5%)	39 (8.0%)
Serious adverse event	20 (8.2%)	20 (8.2%)	40 (8.2%)
Serious adverse event related to ustekinumab	2 (0.8%)	5 (2.0%)	7 (1.4%)
Adverse event leading to discontinuation of study agent	4 (1.6%)	1 (0.4%)	5 (1.0%)
Serious adverse event leading to death	0	1 (0.4%)	1 (0.2%)
Infections			
Any infection	86 (35.2%)	104 (42.4%)	190 (38.9%)
Infections requiring treatment	40 (16.4%)	40 (16.3%)	80 (16.4%)
Serious infection	1 (0.4%)	3 (1.2%)	4 (0.8%)
Other events of Special Interest			
Tuberculosis	0	0	0
Malignancy	2 (0.8%)	2 (0.8%)	4 (0.8%)
Serious cardiovascular event	0	2 (0.8%)	2 (0.4%)
Anaphylactic/serum sickness reaction	0	0	0

Ustekinumab was well tolerated throughout this study. The most common TEAEs were nasopharyngitis, headache, and arthralgia (reported in 22%, 14%, and 11% of subjects, respectively). Other events occurring in >5% to <10% of subjects overall included hypertension, psoriasis, back pain, and pruritis.

No individual TEAE showed a difference in incidence of ≥5% between the 2 treatment arms or between baseline body weight categories (≤100 kg and >100 kg), with the exception of nasopharyngitis and back pain which had a higher incidence in subjects >100 kg versus subjects ≤100 kg.

The vast majority of TEAEs reported through Week 52 were mild or moderate in severity and most were considered by the investigator to be unrelated or of doubtful relationship to study drug.

The incidence of serious TEAEs during the first 12 weeks of the study was low and similar between the UST/MTX stopped arm (7 [2.9%] subjects) and the UST/MTX gradually withdrawn arm (6 [2.4%] subjects). Through Week 52, serious TEAEs occurred in 20 (8.2%) subjects in each treatment arm. There was 1 death in the study – cardio-respiratory arrest – which was considered by the investigator to be of doubtful relationship to ustekinumab.

The proportion of subjects with infections was comparable between treatment arms, as was the proportion of subjects with infections that were treated with oral or parental antibiotics. There was a higher incidence of infection, particularly nasopharyngitis, in subjects >100 kg compared with those ≤100 kg through the Week 52 endpoint.

No cases of psoriasis rebound were reported as TEAEs during the study. No cases of tuberculosis or anaphylactic/serum sickness were observed during the study. Two subjects had a serious cardiovascular event and 4 subjects had a malignancy.

Rates of laboratory abnormalities were low and the vast majority of abnormal findings were not considered to be clinically significant.

No clinically meaningful changes in blood pressure, pulse rate, body weight, BMI, or waist circumference were observed.

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

CONCLUSION(S): Ustekinumab treatment resulted in clinically meaningful improvements in efficacy and quality of life outcomes in subjects with moderate to severe plaque psoriasis who were transitioned to ustekinumab following an inadequate response to methotrexate.

The two transition strategies evaluated in this study (immediate cessation of methotrexate vs. gradual withdrawal of methotrexate) were equally well tolerated, as evidenced by a similar adverse event profile during the first 12 weeks.

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