SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K. K.
Name of Finished Product	To be determined
Name of Active Ingredient(s)	CNTO 1959

Status: Approved

Date: 1 October 2013

Prepared by: Janssen Pharmaceutical K. K.

Protocol No.: CNTO1959PSO1002

Title of Study: A Randomized, Double-blind, Placebo-controlled, Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of CNTO 1959 following a Single Subcutaneous Administration in Japanese Subjects With Moderate to Severe Plaque Psoriasis

Study Name: (not applicable)

NCT No.: NCT01484587

Clinical Registry No.: CR018646

Principal Investigator: Osamu Nemoto, MD - Medical Corporation Kojinkai Kita 13-jo naika·hifuka Clinic, [redacted], Japan

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Publication (Reference): None

Study Period: 23 August 2011 to 11 April 2013

Phase of Development: Phase 1

Objectives: The primary objective of this study was to assess the safety and tolerability of CNTO 1959 following a single subcutaneous (SC) dose administered to Japanese subjects with moderate to severe plaque psoriasis.

The secondary objectives of this study were to assess the pharmacokinetics (PK), immunogenicity (antibodies to CNTO 1959), and clinical response to CNTO 1959 following single SC doses administered to Japanese subjects with moderate to severe plaque psoriasis.

The exploratory objective of this study was to assess the pharmacodynamics (PD) to CNTO 1959 following single SC doses administered to Japanese subjects with moderate to severe plaque psoriasis.

Methodology: This was a Phase 1, randomized, double-blind, placebo-controlled, and ascending single-dose study of CNTO 1959 in Japanese subjects with moderate to severe plaque psoriasis. The study was to include 24 subjects: 4 cohorts (10, 30, 100, and 300 mg) of at least 6 subjects each. Ascending single doses of CNTO 1959 or placebo were administered as SC injections to 4 sequential cohorts of subjects. Subjects were randomized at a ratio of 5 active to 1 placebo in each cohort. Prior to each dose escalation, the Sponsor's Responsible Medical Officer reviewed all preliminary blinded safety data available at least 6 days after the 6th subject had been dosed in the preceding cohort. Dose escalation advanced through the 4 planned dose levels until the highest dose (300 mg) was reached.

Number of Subjects (planned and analyzed): Twenty four subjects were to be enrolled (6 subjects per cohort); 24 subjects were randomized and received study agent, 22 completed the study. All the 24 subjects were included in efficacy and safety analyses. Twenty subjects who received CNTO 1959 were included in the PK analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects aged 20 to 65 years inclusive, with a diagnosis of plaque-type psoriasis at least 6 months prior to screening, covering at least 10% of total body surface area (BSA) and with a Psoriasis Area and Severity Index (PASI) score of 12 or greater at baseline, who were candidates for systemic phototherapy or systemic treatment of psoriasis.

Test Product, Dose and Mode of Administration, Batch No.: CNTO 1959 is a human anti-IL-23 mAb developed by Centocor, Radnor, Pennsylvania, USA. It was supplied as a lyophilized white solid cake in a 2-mL glass vial and was designed for single use only. Each vial contained a nominal target of 83 mg of lyophilized CNTO 1959 for reconstitution with 0.7 mL of sterile water for injection, to yield a 100 mg/mL solution of CNTO 1959 containing L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 5.8. Subjects were given one of 4 escalating single 10, 30, 100, and 300 mg doses of CNTO 1959 as a single SC administration. However, up to 2 SC injections may have been required for the 300 mg dose level. The required volume of reconstituted CNTO 1959 for SC injections at doses of 10, 30, 100, and 300 mg was 0.1, 0.3, 1, and 3 mL, respectively. CNTO 1959, Batch Number: 100281

Reference Therapy, Dose and Mode of Administration, Batch No.: CNTO 1959 liquid placebo for SC administration was supplied as a sterile liquid containing L-histidine, L-histidine monohydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0 in a 2-mL glass vial. Placebo batch number: 1-FIN-1092.

Duration of Treatment: Each subject received a single dose of study agent. The total duration of subject participation was approximately 30 weeks, which included a screening period of up to 6 weeks before the administration of study agent.

Criteria for Evaluation:

Pharmacokinetics: PK parameters of CNTO 1959 were calculated from serum concentration over time data using noncompartmental method. PK parameters calculated included, but were not limited to, C_{max}, t_{max}, AUC_{last}, AUC_{inf}, $t_{1/2}$, CL/F, and Vd_z/F.

Pharmacodynamics: Biomarker and biopsy were evaluated separately.

Immunogenicity (antibodies to CNTO 1959): The incidence of antibodies to CNTO 1959 during the study was summarized for all subjects who received an administration of CNTO 1959 and had appropriate serum samples for antibody detection. The antibody titers of confirmed positive samples were reported.

Pharmacogenomics: Pharmacogenomic studies were evaluated separately.

Efficacy (clinical response): The PASI and PGA were used.

Safety: Safety of CNTO 1959 was determined by assessing the proportion of subjects with adverse events (AEs), including injection site reactions, and changes from baseline in vital signs, laboratory parameters, and electrocardiogram (ECG) findings.

Statistical Methods: No formal hypothesis testing was conducted. Descriptive statistics (eg, number (N) of observations, mean, standard deviation (SD), median, and minimum and maximum) for continuous parameters, frequency tabulation for discrete parameters, and appropriate graphical displays were used to summarize the data.

RESULTS:

STUDY POPULATION:

Of 32 subjects screened, 24 subjects were enrolled (6 subjects per cohort) and randomized to receive one of 4 SC doses (10, 30, 100, or 300 mg) of CNTO 1959 or placebo. Of 24 subjects (20 received CNTO 1959 and 4 received placebo), 2 subjects (one received placebo and one received 10 mg) did not complete the study; the placebo subject withdrew consent and the 10 mg CNTO 1959 subject was lost to follow-up. All 24 randomized subjects were included in the efficacy and safety analysis set. All 20 subjects who received CNTO1959 were included in the PK analysis set. Most of the subjects were male (75%, 18/24 subjects). The median age of all subjects was 46.0 years and ranged from 33 to 64 years. The median psoriasis disease duration at the time of enrollment was 14.75 years. The clinical disease characteristics at baseline included a median affected BSA of 23.0% and a median PASI score of 17.45. In addition, 20.8% (5/24 subjects) of subjects had a PGA score of Mild (2), 58.3% (14/24 subjects) had a PGA score of moderate (3), 20.8% (5/24 subjects) had a PGA score of marked (4). 12.5% (3/24 subjects) of the subjects had psoriatic arthritis.

PHARMACOKINETIC RESULTS:

Following a single SC administration of 10, 30, 100, or 300 mg CNTO 1959, mean C_{max} and AUC_{inf} values increased in an approximately dose-proportional manner (mean C_{max}: 0.457, 1.521, 6.137, and 15.076 µg/mL, respectively; mean AUC_{inf}: 14.0, 40.8, 159.9, and 427.1 µg•day/mL, respectively). Mean CL/F and Vd_z/F were dose-independent (mean CL/F: 0.696 to 1.009 L/day [10.0 to 13.9 mL/day/kg]; mean Vd_z/F: 17.276 to 19.617 L [243 to 288 mL/kg]). Mean $t_{1/2}$ values were generally consistent across all dose cohorts (15.6 to 17.6 days).

PHARMACODYNAMIC AND PHARMACOGENOMIC RESULTS:

Biomarker and biopsy results and pharmacogenomics studies will be reported separately.

IMMUNOGENICITY RESULTS:

One subject in the 10 mg dose cohort was positive for antibodies to CNTO 1959 during the study period and the incidence rate of antibodies to CNTO 1959 was 5.0% (1/20) through Day 112 (Week 16).

EFFICACY RESULTS:

Improvements in PASI scores and PGA were observed in all CNTO1959 dose groups.

PASI: The maximum clinical response (median percent improvement from baseline in PASI) was observed at Week 16 in all CNTO1959 dose groups. Median percent improvement from baseline in PASI at Week 16 in the 10, 30, 100, and 300 mg dose groups (5 subjects each) was 63.16%, 90.95%, 86.67%, and 90.65%, respectively, compared to -5.33% in the placebo group (1 subject). With the exception of the 10 mg dose group, these improvements were generally sustained over the 24-week study period. The median percent improvement from baseline in PASI in the placebo group was lower than any of the CNTO 1959 dose groups. However, 3 out of 4 subjects in the placebo group were excluded from evaluation due to the use of prohibited concomitant medications. Therefore, the median percent improvement in PASI from Week 8 to Week 12 and from Week 16 to Week 24 represented data from 2 subjects and 1 subject, respectively.

PGA: Sixteen (80.0%) of 20 subjects receiving CNTO 1959 achieved a PGA score of cleared or minimal (0-1) by Week 12. Three (60.0%), 5 (100.0%), 4 (80.0%) and 4 (80.0%) subjects in the 10, 30, 100, and 300 mg dose groups, respectively, had a PGA score of cleared or minimal (0-1) at Week 12. These scores were generally maintained through Week 24. None of the subjects receiving placebo had a PGA score of cleared or minimal (0-1) during the 24-week study period.

SAFETY RESULTS:

Eleven (55.0%) of 20 subjects receiving CNTO 1959 and 2 (50.0%) of 4 subjects receiving placebo experienced one or more AEs. There was no dose-dependent response in the incidence of AEs: 60.0% (3/5 subjects), 40.0% (2/5 subjects), 60.0% (3/5 subjects), and 60.0% (3/5 subjects) in the 10, 30, 100, and 300 mg groups, respectively.

Most AEs were considered mild in severity by the investigator. Two (10.0%) of 20 subjects receiving CNTO 1959 had moderate AEs: one subject receiving 10 mg SC CNTO 1959, had an AE of back pain, and one subject receiving 100 mg SC CNTO 1959, had an AE of meniscus lesion. No severe AEs were observed.

AEs reasonably related to study agent were reported in 3 (15.0%) of 20 subjects receiving CNTO 1959 compared to none of 4 subjects receiving placebo.

No deaths, SAEs, or AEs leading to study agent discontinuation were reported during the study.

Infections and injection site reactions were designated by the investigator. Infections were observed in 4 (20.0%) of 20 subjects receiving CNTO 1959 (3 subjects in the 10 mg group [folliculitis, sinusitis, upper respiratory tract inflammation and nasopharyngitis] and 1 subject in the 100 mg group [folliculitis and nasopharyngitis]) compared to none in the subjects receiving placebo. Injection site reactions were observed in 2 (10.0%) of 20 subjects receiving CNTO 1959 (1 subject each in the 10 and 300 mg groups [injection site erythema]) compared to none in the subjects receiving placebo.

The medical dictionary for regulatory activities (MedDRA) SOCs with the most frequently reported AEs (≥3 [15.0%] of 20 subjects receiving CNTO 1959) were Skin and Subcutaneous Tissue Disorders (5 [25.0%] compared to none in the subjects receiving placebo), Infections and Infestations (3 [15.0%] compared to none in the subjects receiving placebo) and Musculoskeletal and Connective Tissue Disorders (3 [15.0%] compared to 1 [25.0 %] of 4 subjects receiving placebo).

The most common AE (≥2 [10.0%] of 20 subjects receiving CNTO 1959) was pruritus (3 [15.0%] compared to none in the subjects receiving placebo), followed by folliculitis, nasopharyngitis, and injection site erythema (each 2 [10.0%] compared to none in the subjects receiving placebo).

No clinically significant findings related to laboratory tests, vital signs, body weight, or ECGs were observed, although a marked but transient increase in creatine kinase (CK) value was observed in 2 subjects: 1 subject in the 100 mg group experienced mild muscle spasms at Week 8 and 1 subject in the 300 mg group experienced mild myalgia at Week 2. No trends or dose related changes in AEs, vital signs, body weight, physical examinations, ECGs, or laboratory values were observed, and no safety signals were identified.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

CNTO 1959, administered as a single SC injection, was well-tolerated in Japanese subjects with moderate to severe plaque psoriasis. No trends or dose related changes in AEs, vital signs, body weight, physical examinations, ECGs, or laboratory values were observed, and no safety signals were identified.

Following a single SC administration of 10, 30, 100, or 300 mg CNTO 1959 to Japanese subjects with moderate to severe psoriasis, the systemic exposure (C_{max} and AUC_{inf}) increased in an approximately dose-proportional manner and the CL/F and Vd_z/F were dose-independent. One subject (1/20; 5.0%) in the 10 mg cohort was positive for antibodies to CNTO 1959 during the study period.

In addition, improvements in PASI and PGA in subjects with moderate to severe plaque psoriasis were observed after a single SC administration of CNTO 1959 in all dose groups. The maximum clinical response (median percent improvement from baseline in PASI) was observed at Week 16 in all CNTO 1959 dose groups. With the exception of the 10 mg dose group, this improvement was generally sustained over the 24-week study period.

The results of this study suggest that CNTO 1959 may be a useful therapeutic agent for the treatment of Japanese patients with moderate to severe plaque psoriasis.

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