SYNOPSIS

Issue Date: 11 Apr 2011

Name of Sponsor/Company	Centocor Research & Development Inc.
Name of Finished Product	CNTO 1959
Name of Active Ingredient(s)	CNTO 1959

Protocol No.: CNTO1959PSO1001

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 Intravenous or a Single Subcutaneous Administration in Healthy Subjects and in Subjects with Moderate to Severe Psoriasis

Study Name: (not applicable)

EudraCT Number: (not applicable)

NCT No.: NCT00925574

Clinical Registry No.: CR015817

Coordinating and Principal Investigator(s): Part 1: Eleanor A. Lisbon, MD, MPH – Quintiles Phase One Services, [redacted] USA. Part 2: Robert Matheson, MD, Oregon Medical Research Center, [redacted] USA

Study Center(s): Part 1: Quintiles Phase One Services, [redacted] Part 2: Comprehensive Phase One, [redacted]; Rockefeller University, [redacted]; Central Dermatology, [redacted], [redacted]; Oregon Medical Research Center, [redacted]; Therapeutics Clinical Research, [redacted]; Dermatology Research Associates, [redacted]; Parexel International, [redacted]

Study Period: For Part 1, first subject in: 16 Jun 2009 and last subject last visit: 12 Jan 2010. For Part 2, first subject in: 05 Aug 2009 and last subject last visit: 11 Oct 2010; clinical database lock: 15 Nov 2010, pharmacokinetics database lock: 07 Dec 2010.

Phase of Development: Phase 1

Objectives: The primary objective of this study was to assess the safety and tolerability of CNTO 1959 following:

- Single intravenous (IV) and subcutaneous (SC) doses administered to healthy subjects (Part 1).
- Single SC doses administered to subjects with moderate to severe psoriasis (Part 2).

The secondary objectives of this study were to assess the pharmacokinetics (PK) and immunogenicity (antibodies to CNTO 1959) following single IV and SC doses administered to healthy subjects (Part 1).

In addition, the secondary objectives of this study were to assess the PK, pharmacodynamics (PD), immunogenicity (antibodies to CNTO 1959), and clinical response to CNTO 1959 following single SC doses administered to subjects with moderate to severe psoriasis (Part 2).

Study Design: This was a Phase 1, randomized, double-blind, placebo controlled, and ascending single-dose study of CNTO 1959. In Part 1, 47 healthy subjects were to be enrolled. For Part 1 IV, 2 cohorts of 4 healthy subjects each were randomized at a ratio of 3 active to 1 placebo at dose levels of 0.03 and 0.1 mg/kg, and 4 cohorts of 8 healthy subjects each were randomized at a ratio of 6 active to 2 placebo at dose levels of 0.3, 1, 3, and 10 mg/kg. In Part 1 SC, 7 healthy subjects were randomly assigned to a single SC dose of 3 mg/kg of CNTO 1959 or placebo

in a ratio of 6:1. In Part 2, 4 cohorts of 6 subjects with psoriasis were randomized at each dose level (10, 30, 100, and 300 mg of study agent, CNTO 1959 or placebo SC) at a ratio of 5 active to 1 placebo.

Number of Subjects (planned and analyzed): Seventy-one subjects (47 healthy subjects and 24 subjects with moderate to severe psoriasis) were to be enrolled. In Part 1, 47 healthy subjects were randomized and received study agent; 45 subjects completed the study and 47 were analyzed. In Part 2, 24 subjects with moderate to severe psoriasis were randomized and received study agent; 20 subjects completed the study and 24 were analyzed.

Diagnosis and Main Criteria for Inclusion: For Part 1 of the study, subjects were healthy and 18 to 55 years old, inclusive. For Part 2, subjects, had to have a diagnosis of plaque-type psoriasis for at least 6 months prior to administration of study agent and ages 18 to 65 years, inclusive.

Test Product, Dose and Mode of Administration, Batch No.: CNTO 1959, the fully human anti-IL-23 mAb, was a lyophilized white solid cake supplied in a 2-mL glass vial and was designed for single use only. In Part 1, healthy subjects were given either an IV infusion of 0.03, 0.1, 0.3, 1, 3, or 10 mg/kg of CNTO 1959 or a single 3 mg/kg SC injection of CNTO 1959. In Part 2, subjects with psoriasis were given 4 escalating single 10, 30, 100, and 300 mg SC 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. CNTO 1959, Batch Number: D08PM7678.

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo for IV administration was sterile 0.9% Saline for Injection, USP. 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: D08PC7662.

Duration of Treatment: Each subject received a single dose of study agent. Subject participation was 16 weeks for Part 1 and 24 weeks for Part 2, in addition to a 4 week screening period.

Criteria for Evaluation:

Safety: The safety and tolerability of CNTO 1959 was monitored through Week 16 (Part 1) and Week 24 (Part 2) after study agent administration. Assessments included physical examinations, laboratory tests, vital signs, ECGs (electrocardiogram), and AE (adverse event) monitoring of all subjects who received CNTO 1959 or placebo. Baseline for all laboratory evaluations and vital signs was defined as the last evaluation done before study agent administration. ECG measurements were measured in triplicate, and the average value was used for baseline.

Pharmacokinetics: PK parameters of CNTO 1959 were calculated from serum concentration over time data using noncompartmental analyses. PK parameters calculated included C_{max}, T_{max}, AUC_{last}, AUC_{inf}, $T_{1/2}$, CL, CL/F, V_z, V_z/F, V_{ss}, MRT, and F%.

Immunogenicity: 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.

Clinical Assessments: In Part 2, the Psoriasis Area Severity Index (PASI) and Physician's Global Assessment (PGA) were used.

Statistical Methods: Only descriptive statistical methods were used to summarize the data. Continuous variables were summarized using mean, geometric mean, standard deviation (SD), median, and minimum and maximum values as appropriate. Categorical values were summarized using percentages as appropriate.

RESULTS:

In Part 1, 47 subjects enrolled, and 45 completed the study. One subject receiving 10 mg/kg IV CNTO 1959 withdrew consent, and one receiving placebo was lost to follow-up. In Part 2, 24 subjects enrolled, and 20 completed the study. Two subjects (one placebo treated and one 10 mg treated) withdrew because of a lack of efficacy. Of the other 2 placebo subjects who discontinued, one withdrew consent and one ended study participation due to a job change and a conflict with the study schedule.

In Part 1, subjects were healthy. The majority of subjects were males (95.7%). The median age of all subjects was 25.0 years. For Part 2, subjects had moderate to severe psoriasis, and 62.5% were males. The median age was 42.5 years. The median psoriasis disease duration was 17.0 years. The clinical disease characteristics at baseline included a median BSA affected by psoriasis of 17.0% and a median PASI score of 14.8. In addition, 83.3% of subjects had a PGA score of moderate (3), and 95.8% of the subjects had psoriatic arthritis.

PHARMACOKINETIC RESULTS:

In Part 1, following a single IV administration of 0.03, 0.1, 0.3, 1, 3 or 10 mg/kg CNTO 1959 to healthy subjects, mean C_{max} and AUC_{inf} values increased in an approximately dose-proportional manner (C_{max}: 0.54, 2.02, 6.54, 24.66, 58.55 and 197.46 µg/mL, respectively; AUC_{inf}: 5.22, 18.64, 59.99, 278.51, 787.92 and 2214.52 µg·day/mL, respectively). Mean values of clearance (CL) were dose independent and ranged from 3.62 to 6.03 mL/day/kg. Mean values of volume of distribution (V_z) were generally consistent across all dose cohorts and ranged from 99.38 to 123.22 mL/kg. Mean $T_{1/2}$ values following IV administration ranged from 12.3 to 19.1 days in healthy subjects. Following a single SC administration of 3 mg/kg CNTO 1959 to healthy subjects, mean C_{max} and AUC_{inf} were 9.46 µg/mL and 256.99 µg·day/mL, respectively. The median T_{max} was 5.0 days. The mean $T_{1/2}$ following SC administration was 16.8 days which is consistent with that following IV administration. The absolute SC bioavailability of CNTO 1959 (F%) was estimated to be 32.6%.

In Part 2, following a single SC administration of 10, 30, 100 or 300 mg CNTO 1959 to subjects with psoriasis, mean C_{max} and AUC_{inf} values increased in an approximately dose-proportional manner (C_{max}: 0.54, 1.14, 4.81 and 18.97 µg/mL, respectively; AUC_{inf}: 14.93, 30.26, 108.48 and 510.33 µg·day/mL, respectively). The median T_{max} values ranged from 3.2 to 6.0 days. Mean $T_{1/2}$ following SC administration was 14.7 to 16.9 days which is consistent with that in healthy subjects.

PHARMACODYNAMIC RESULTS:

Biopsy results and pharmacogenomics studies will be reported separately.

IMMUNOGENICITY RESULTS:

In Part 1, all 36 subjects who received CNTO 1959 had appropriate serum samples for the evaluation of antibodies to CNTO 1959. Following IV administration, one (3.3%) of 30 subjects who received CNTO 1959 tested positive for antibodies to CNTO 1959. This subject had slightly higher clearance (6.57 mL/day/kg) and shorter $T_{1/2}$ (11.5 days) compared to the rest of the subjects in the same cohort. None of the 6 subjects treated with CNTO 1959 by SC administration tested positive for antibodies to CNTO 1959.

In Part 2, all 20 subjects who received CNTO 1959 had appropriate serum samples for the evaluation of antibodies to CNTO 1959. Only one (5.0%) of 20 subjects who received CNTO 1959 tested positive for antibodies to CNTO 1959. The clearance and $T_{1/2}$ cannot be estimated for this subject in the 10 mg cohort due to insufficient data in the terminal phase. However, this subject showed PASI improvement over time despite testing positive for antibodies to CNTO 1959.

EFFICACY RESULTS:

In Part 2, efficacy was measured by Psoriasis Area and Severity Index (PASI) and Physician's Global Assessment (PGA) which were conducted from the screening period through Week 24. Improvements in PASI scores were observed in all dose groups. The maximum clinical response was observed between Weeks 8 and 16 in all dose groups. Evidence of a dose-response relationship was observed for the 10 mg, 30 mg and 300 mg dose groups in which a ≥ 75%, improvement from baseline (eg, PASI 75) response was maintained through Week 24. PGA scores were generally consistent with results of the PASI analysis.

SAFETY RESULTS:

The safety results from this study show that CNTO 1959 or placebo administered either via IV infusion or SC injection in healthy subjects or by SC injection in subjects with moderate to severe psoriasis was generally safe and well tolerated. There was no dose-dependent response in the incidence of AEs and all AEs were considered to be mild to moderate in intensity by the investigator. One subject with psoriasis experienced a serious AE of traumatic brain injury secondary to motor vehicle accident, which was considered unrelated to study agent by the investigator. In Part 1, the most common AEs were headache (9 [25.0%] of 36 subjects on CNTO 1959 and 3 [27.3%] of 11 subjects on placebo) and upper respiratory infection (5 [13.9%] of 36 subjects on CNTO 1959 and 1 [9.1%] of 11 subjects on placebo). In Part 2, the most common AEs were upper respiratory tract infection and vomiting (each in 2 [10.0%] of 20 subjects on CNTO 1959) which were not observed in subjects who received placebo. No trends or dose related changes in vital signs, physical examinations, ECGs, or laboratory values were observed. No subjects terminated study participation due to AEs.

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

CONCLUSIONS:

CNTO 1959, administered as an IV infusion or SC injection, was well-tolerated in healthy subjects and in subjects with moderate to severe psoriasis. No trends or dose related changes in AEs, vital signs, physical examinations, ECGs, or laboratory values were observed.

Overall, CNTO 1959 showed linear pharmacokinetics at dose levels ranging from 0.03 mg/kg to 10 mg/kg following IV administration and from 10 mg to 300 mg following SC administration. The CNTO 1959 pharmacokinetics were generally comparable between healthy subjects and subjects with moderate to severe psoriasis. The incidence of antibodies to CNTO 1959 was low.

CNTO 1959 was well tolerated in both healthy subjects and subjects with moderate to severe psoriasis and no safety signals were identified. In addition, improvements in PASI and PGA in subjects with moderate to severe psoriasis were observed after a single SC administration of CNTO 1959 in all dose groups. The maximum clinical response was observed between Weeks 8 and 16 in all CNTO 1959 dose groups. With the exception of the 100 mg dosing group, this improvement was generally sustained over the 24 week study period and suggests a correlation of clinical response with the dose of CNTO 1959. The results of this study suggest that CNTO 1959 may be a useful therapeutic agent for the treatment of moderate to severe psoriasis and warrants further testing in a Phase 2 dose ranging study in a larger population.

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