SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development
Name of Finished Product	Not Applicable
Name of Active Ingredient	CNTO 3649

Protocol No.: CNTO3649DIB1001

Title of Study: A Phase 1, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Ascending Intravenous and Subcutaneous Single-Dose Study in Healthy Subjects and Ascending Subcutaneous Multiple-Dose Study in Subjects with Type 2 Diabetes Mellitus to Evaluate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Immune Response of CNTO 3649.

Principal Investigator: Maria Gutierrez, MD.

Publication (Reference): None.

Study Period: 17 Feb 2009 to 6 Apr 2010

Phase of Development: 1

Objectives

Primary Objective: To evaluate the safety and tolerability of ascending doses of CNTO 3649 when administered as a single IV infusion in healthy subjects (Part 1a), a single SC injection in healthy subjects (Part 1b), and multiple SC injections in subjects with type 2 diabetes mellitus (T2DM, [Part 2]).

Secondary Objectives

To investigate the pharmacokinetics (PK), pharmacodynamics (PD), and immune response (IR) of ascending doses of CNTO 3649 when administered as a single IV infusion in healthy subjects (Part 1a), a single SC injection in healthy subjects (Part 1b), and multiple SC injections in subjects with T2DM (Part 2).

Methods:

This phase 1, first in human, multicenter, randomized, double-blind, placebo-controlled, ascending IV and SC single-dose study in healthy subjects and ascending SC multiple-dose study in subjects with T2DM was to be conducted in 2 parts.

Part 1a (single IV dose in healthy subjects): Part 1a was to be performed in approximately 48 healthy subjects in 6 cohorts (Cohorts 1, 2, 3, 4, 5, 6) of 8 subjects each, such that approximately 6 subjects complete the study at each dose level. Six escalating single dose levels were planned: 1, 3, 10, 30, 100, and 300 μg/kg of CNTO 3649 or placebo were to be administered as a single 2-hour IV infusion. Subjects were to be randomized at each dose level at a ratio of 6 active to 2 placebo. In each cohort, subjects were to receive a single dose of study agent with a follow-up of 4 weeks after dose administration.

Part 1b (single SC dose in healthy subjects): Part 1b of the study was to be performed in approximately 32 healthy subjects in 4 cohorts (Cohorts 7, 8, 9, and 10) of 8 subjects each, such that approximately 6 subjects complete the study at each dose level. Four escalating single dose levels were planned: 10, 30, 100, and 300 μg/kg of CNTO 3649 or placebo were to be administered as an SC injection. Subjects were to be randomized at each dose level at a ratio of 6 active to 2 placebo. In each cohort, subjects were to receive a single dose of study agent with a follow-up of 4 weeks after dosing.

Part 2 (multiple SC doses in subjects with T2DM): Part 2 of the study was to be performed in approximately 36 subjects with T2DM in 3 cohorts (Cohorts 11, 12, 13) of 12 subjects each, such that approximately 6 subjects complete the study at each dose level. Three escalating dose levels were planned: 30, 100, and 300 μg/kg multiple doses of CNTO 3649 or placebo administered as an SC injection. Subjects were to be randomized at each dose level at a ratio of 9 active to 3 placebo. In each cohort, subjects were to receive 4 doses of study agent, administered once weekly for 4 consecutive weeks, with a follow-up of 4 weeks after the last dose.

Number of Subjects (planned and analyzed): Approximately 116 subjects (80 healthy subjects and 36 subjects with T2DM) were planned to be enrolled in the study. A total of 133 subjects were treated and evaluated for safety: 94 healthy subjects in Part 1 and 39 subjects with T2DM in Part 2.

Diagnosis and Main Criteria for Inclusion:

Part 1: Healthy male and female subjects of 18 to 55 years of age, inclusive with a body mass index (BMI) between 18.5 and 30 kg/m^2 (body weight in a range of 50 to 100 kg, inclusive).

Part 2: Male and female subjects of 18 to 65 years of age, inclusive and diagnosed with T2DM at least 12 months prior to screening. Subjects with T2DM were to be diagnosed with the disease and stable on diet and exercise or with a stable oral antidiabetic medication/dose regimen for at least 3 months prior to screening. Subjects with a BMI between 20 and 40 kg/m^2 were to be included.

Test Product, Dose and Mode of Administration, Batch No.: CNTO 3649 was supplied as a single use, sterile, preservative-free, lyophilized white solid cake in a Type 1 glass vial closed with a grey rubber stopper and aluminum seal, and covered with a plastic flip-off cap. CNTO 3649 was reconstituted (and diluted for lower dose levels) and administered by IV infusion using an in-line filter or by SC injection of filtered liquid. The batch number for CNTO 3649 19 mg/mL was D08PG7673.

Reference Therapy, Dose and Mode of Administration, Batch No.: CNTO 3649 liquid placebo was supplied as a sterile liquid in an 8R Type 1 glass vial closed with a grey rubber stopper and aluminum seal, and covered with a plastic flip-off cap. The reference drug ie, placebo was administered by IV infusion using an in-line filter or by SC injection of filtered liquid. The batch number for placebo was D08PE7668.

Duration of Treatment:

Part 1a and 1b: subjects were to receive a single dose of study agent with a follow-up of 4 weeks after dose administration.

Part 2: subjects were to receive 4 doses of study agent, administered once weekly for 4 consecutive weeks, with a follow-up of 4 weeks after the last dose.

Criteria for Evaluation

Safety Analyses: Safety and tolerability were to be assessed by summarizing the incidence and type of AEs and SAEs, vital signs, electrocardiogram (ECG) measurements, laboratory values, and changes in laboratory parameters. Safety analyses were to be carried out by study part and treatment group for all treated subjects.

Pharmacokinetics Analyses: The serum concentration was to be summarized for all subjects over time by the assigned CNTO 3649 dose level. Pharmacokinetic parameters including maximum observed concentration (Cmax), time to reach the maximum observed concentration (tmax), area under the concentration versus time curve from time 0 to infinity with extrapolation of the terminal phase (AUC), AUC to the tlast (time corresponding to the last concentration [Clast]) above the limit of quantification (AUC[0-tlast]), AUC from time 0 to the dosing interval (τ)(AUC[0-τ]), t1/2, total clearance of drug after intravenous administration (CL), volume of distribution during terminal phase after IV administration (Vz), volume of distribution at steady state (Vss), and absolute bioavailability (F) were to be estimated for individuals and summarized by the assigned CNTO 3649 dose level. Dose proportionality was visually inspected across the dose range.

Pharmacodynamic Analyses: Pharmacodynamic results are not yet available.

Immune Response Analyses: The formation of antibodies to CNTO 3649 was to be evaluated on blood drawn from all subjects. The proportion of subjects with positive antibodies to CNTO 3649 was to be summarized. Analyses for the detection of antibodies to CNTO 3649 included determination of specific reactivity of antibodies with the fragment crystallizable (Fc) and glucagon-like peptide-1 (GLP-1) domains and determination of neutralizing ability. Other analyses were to be performed to further characterize the antibodies.

Statistical Methods: Continuous variables were to be summarized using the number of observations, mean, standard deviation, minimum, median, and maximum values as appropriate. Categorical values were to be summarized using the number of observations and percentages as appropriate. No formal hypothesis testing was to be conducted and no formal sample size determination was to be made for this study. Only descriptive statistical methods were to be used to summarize the data.

RESULTS:

PHARMACOKINETIC RESULTS:

After a single IV infusion of CNTO 3649, the mean Cmax increased with increasing dose although not in a dose-proportional manner. The mean t1/2 ranged from 5.31 to 81.02 hours, mean systemic CL ranged from 2.17 mL/h/kg to 5.43 mL/h/kg and mean Vz ranged from 41.61 mL/kg to 303.37 mL/kg after a single IV infusion across all dose groups. Overall, the CL, and Vz for CNTO 3649 appeared to be independent of dose after IV infusion of doses ranging from 10 μg/kg to 100 μg/kg.

CNTO 3649 was absorbed into the systemic circulation with a median tmax of 48 hours after a single SC administration of doses ranging from 10 μg/kg to 300 μg/kg. After a single SC administration, CNTO 3649 was eliminated from circulation with a mean t1/2 ranging from 90.76 to 135.12 hours across all treatment groups. The estimated bioavailability after SC administration of CNTO 3649 was 1.07 indicating excellent systemic bioavailability.

Following multiple weekly SC administrations of CNTO 3649, the median tmax after the last dose of was 48 hours across all treatment groups. After the last SC dose of CNTO 3649 the mean t1/2 values ranged from 115.58 to 149.02 hours across all dose groups. The mean accumulation index (R) ranged from 1.93 to 2.40 across all treatment groups suggesting that moderate drug accumulation occurred after multiple weekly SC administration of CNTO 3649.

IMMUNOGENICITY RESULTS:

Two out of 62 treated subjects (4.16%) in Part 1a given a single IV infusion were classified as positive for antibodies to CNTO 3649 through Day 29. No treated subjects in Part 1b or Part 2 were classified as positive for antibodies to CNTO 3649.

SAFETY RESULTS:

There were no clinically significant effects of CNTO 3649 on vital signs, laboratory values, electrocardiograms, or physical exams at single doses of up to 60 μg/kg IV and 300 μg/kg SC, and multiple doses up to 300 μg/kg SC. Single doses of 100 μg/kg IV were associated with AEs that lead to 60 μg/kg IV being determined as the maximum tolerated IV dose.

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