SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.
Name of Finished Product	siltuximab
Name of Active Ingredient(s)	CNTO 328 (siltuximab)

Status: Approved
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Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: JPN-C0328-MM-101

Title of Study: A Phase 1 Study of CNTO 328 (siltuximab) in Combination with Bortezomib and Dexamethasone for Subjects with Relapsed or Refractory Multiple Myeloma

NCT No.: NCT01309412

Clinical Registry No.: CR017737

Study Center(s): The study was conducted at 5 study sites in Japan.

Publication (Reference): None

Study Period: 28 February 2011 to 06 December 2012

Phase of Development: Phase 1

Objectives:

The primary objective of the study was to assess the safety and the tolerability of siltuximab up to 11.0 mg/kg in combination with bortezomib and dexamethasone for subjects with relapsed or refractory multiple myeloma.

The secondary objectives were to describe the pharmacokinetics of siltuximab, to explore preliminary efficacy (antitumor effect), and to assess the antibodies to siltuximab (immunogenicity).

Methodology:

This study was a nonrandomized, open-label, multicenter study of siltuximab in subjects with relapsed or refractory multiple myeloma receiving siltuximab in combination with bortezomib and dexamethasone. The objectives were to evaluate safety, pharmacokinetics, efficacy, and immunogenicity.

This study was a dose escalation study of siltuximab; the two doses studied 5.5 mg/kg (Dose Level 1) and 11.0 mg/kg (Dose Level 2), administered every 3 weeks. The recommended dose was to be determined based on the incidence of dose-limiting toxicity (DLT) observed in subjects with relapsed or refractory multiple myeloma at each dose level of siltuximab when given in combination with bortezomib and dexamethasone. Treatment with siltuximab was started at Dose Level 1, and treatment at Dose Level 2 was not started until the safety evaluation at the end of the observation period of Cycle 1 for all subjects receiving Dose Level 1 was complete.

Number of Subjects (planned and analyzed):

The maximum number of planned subjects was 15 (Dose Level 1: 3-6 subjects, Dose Level 2: 6-9 subjects).

Of 10 consented subjects, 9 subjects (Dose Level 1: 3 subjects, Dose Level 2: 6 subjects) received at least 1 dose of siltuximab.

Diagnosis and Main Criteria for Inclusion:

Adult subjects 20 years of age or over, with relapsed or refractory multiple myeloma were enrolled. Subjects, who have previously received 1-3 regimens for multiple myeloma, proven to have symptomatic or nonsecretory multiple myeloma according the International Myeloma Working Group (IMWG) diagnostic criteria.

Test Product, Dose and Mode of Administration, Batch No.:

Siltuximab was supplied as a sterile, lyophilized formulation for reconstitution and IV infusion (Batch No: 9ID7701, BBS0N01).

Duration of Treatment:

A 3-week period was defined as 1 cycle (21 days) and the cycle was repeated until progression.

Criteria for Evaluation:

Efficacy Evaluations

Preliminary efficacy evaluation was to be performed in terms of antitumor effect, according to criteria for assessment of antitumor effect similar to the European Group for Blood and Marrow Transplantation (EBMT) criteria.

Pharmacokinetic Evaluations

Serum siltuximab concentration and the pharmacokinetic endpoints included, but were not limited to, the following: $AUC_{0\text{-}21days}$, C_{max}, AUC_{∞}, $t_{1/2}$, CL and Vd_z.

Immunogenicity Evaluations

Antibodies to siltuximab were to be measured.

Safety Evaluations

Safety endpoints included adverse events, laboratory tests (hematology, blood chemistry, lipid panel, urinalysis and blood coagulation), pregnancy test, electrocardiogram (ECG), chest X-ray, vital signs (body temperature, pulse rate, and blood pressure), and body weight.

Statistical Methods:

Efficacy analysis

For the evaluation of anti-myeloma effect using EBMT criteria, frequency was summarized by dose level for all subjects. Descriptive statistics were used to summarize change over time with serum and urine myeloma protein, the number of lytic bone lesion, serum calcium corrected for albumin, proportion of plasma cell in bone marrow, and reduction and growth percentage of two-way sum of productions for soft tissue tumor (plasmacytoma). These analyses were performed by dose level for all subjects.

Pharmacokinetic analysis

Descriptive statistics were calculated for serum siltuximab concentration and pharmacokinetic parameters by dose level.

Immunogenicity analysis

The incidence of antibodies to siltuximab was summarized for all subjects who have appropriate serum samples for detection of antibodies.

Safety analysis

For the adverse events aggravated or onset after study agent administration, frequency was summarized by dose level for all subjects. Descriptive statistics were used for continuous variables. Frequency was summarized for discrete variables. Change over time with laboratory parameters, urinalysis, ECG, vital signs, body weight, and chest X-ray were summarized.

RESULTS:

STUDY POPULATION:

- Of 10 consented subjects, 9 subjects (Dose Level 1: 3 subjects, Dose Level 2: 6 subjects) received at least 1 dose of siltuximab.
- All subjects permanently discontinued study treatment. Five (55.6%) subjects discontinued treatment due to an adverse event, 1 (11.1%) subject discontinued treatment due to other reason (subject's decision), and 3 (33.3%) subjects discontinued treatment due to the sponsor's decision to terminate the study.

EFFICACY RESULTS:

- In Dose Level 1, 1 (33.3%) subject had CR and 2 (66.7%) subjects had partial response (PR). In Dose Level 2, 1 (16.7%) subject had CR, 2 (33.3%) subjects had PR, and 3 (50.0%) subjects had no change (NC).
- A total of 9 subjects (3 in Dose Level 1 and 6 in Dose Level 2) had at least 1 serum M-protein response. One (33.3%) subject in Dose Level 1 and 3 (50.0%) subjects in Dose Level 2 had ≥90% reduction.
- A total of 3 subjects (all in Dose Level 2) had at least 1 urine M-protein response. 3 (50.0%) subjects had ≥90% reduction in Dose Level 2.
- Corrected serum calcium values were 9.30 mg/dL or lower in Dose Level 1, and 9.52 mg/dL or lower in Dose Level 2.
- One subject (Subject 11, Dose Level 2 group) had a reduction of percentage of two-way sum of productions for soft tissue tumor.

PHARMACOKINETIC RESULTS:

After the first administration of siltuximub at doses of 5.5 and 11.0 mg/kg in combination with bortezomib and dexamethasone, mean Cmax of serum siltuximab was 118.2 and 194.3 μg/mL and mean $AUC_{0\text{-}21\ days}$ was 886.0 and 1548.1 μg・day/mL, respectively. C_{max} and AUC of serum siltuximab increased in an approximately dose-proportional manner. Mean $t_{1/2}$, CL, and Vd_z values were similar in the dose range of 5.5 and 11.0 mg/kg.

SAFETY RESULTS:

- All 9 (100%) subjects received siltuximab in combination with bortezomib and dexamethasone experienced 1 or more AEs during the study and for all subjects, the events were considered to be reasonably related to siltuximab.
- All subjects experienced 1 or more TEAEs Grade 3 or higher.

- Four (44.4%) subjects experienced 1 or more treatment-emergent SAEs (1 subject in Dose Level 1 and 3 subjects in Dose Level 2).
- The incidence of AEs leading to siltuximab discontinuation was 33.3% and 66.7% for Dose Level 1 and Dose Level 2, respectively.
- No infusion related reactions were observed at either Dose Level in this study.
- No DLT was observed.

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