SYNOPSIS

Issue Date: 25 Feb 2012

Name of Sponsor/Company	Janssen Research & Development
Name of Finished Product	Siltuximab
Name of Active Ingredient	Siltuximab (CNTO 328)

Protocol No.: C0328T03

Title of Study: A Phase 1 Study of Multiple Intravenous Administrations of a Chimeric Antibody Against Interleukin-6 (CNTO 328) in Subjects with B-Cell Non-Hodgkin's Lymphoma, Multiple Myeloma, or Castleman's Disease

NCT No.: NCT00412321

Clinical Registry No.: CR008566

Coordinating Investigator(s): Razelle Kurzrock, MD
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Study Centers: 9 study centers in the United States

Publication (Reference):

Ahmed B, Tschen JA, Cohen PR, et al. Cutaneous Castleman's disease responds to anti-interleukin-6 treatment. *Mol Cancer Ther*. 2007;6(9):2386-2390.

van Rhee F, Fayad L, Voorhees P, et al. Siltuximab, a novel anti-interleukin-6 monoclonal antibody, for Castleman's disease. *J Clin Oncol*. 2010;28(23):3701-3708.

Study Period:
First subject consented 09 Jun 2005
Last subject last visit 29 Apr 2011

Phase of Development: Phase 1

Objectives: The primary objective was to assess the safety and pharmacokinetics of multiple dosing regimens of siltuximab (CNTO 328) administered as an IV infusion in subjects with B-cell non-Hodgkin's lymphoma (including chronic lymphocytic leukemia [CLL]/small lymphocytic lymphoma [SLL] and Waldenstrom's macroglobulinemia [WM]), multiple myeloma, or Castleman's disease.

The secondary objectives were to assess the pharmacodynamics, immune response, and clinical effects of multiple dosing regimens of siltuximab administered as an IV infusion in subjects with B-cell non-Hodgkin's lymphoma (including CLL/SLL and WM), multiple myeloma, or Castleman's disease.

Methodology: This was an open-label, nonrandomized, dose-finding Phase 1 study with siltuximab in subjects with B-cell non-Hodgkin's lymphoma (including CLL/SLL and WM), multiple myeloma, or Castleman's disease (a lymphoproliferative disorder).

Initially, up to 5 dose cohorts were to be evaluated in sequential order (ie, in order of increasing total dose exposure), and initially 6 subjects were to be enrolled in each of the following dose cohorts and were to receive 1 course of siltuximab. A course was defined as the number of scheduled administrations allotted for each dose cohort as outlined below:

- Dose Cohort 1: 3 mg/kg every 2 weeks x 4 administrations (Days 1, 15, 29, 43)
- Dose Cohort 2: 6 mg/kg every 2 weeks x 4 administrations (Days 1, 15, 29, 43)
- Dose Cohort 3: 12 mg/kg every 3 weeks x 3 administrations (Days 1, 22, 43)
- Dose Cohort 4: 6 mg/kg weekly x 7 administrations (Days 1, 8, 15, 22, 29, 36, 43)
- Dose Cohort 5: 12 mg/kg every 2 weeks x 4 administrations (Days 1, 15, 29, 43)

A safety review was to be conducted by the Data Monitoring Committee (DMC) prior to initiating enrollment of subjects in a subsequent dose cohort.

An interim review of safety and pharmacokinetic data from Cohorts 1-5 was conducted. One dose regimen was further explored as Cohort 6, with up to 12 additional subjects to evaluate the safety and pharmacokinetics of administering siltuximab as a 1-hour infusion. Initially, 6 subjects were to be enrolled. After the sixth subject had completed all study-related evaluations scheduled on Day 2, a safety review was to be conducted by the DMC prior to enrollment of the remaining subjects in Cohort 6.

- Dose Cohort 6: 12 mg/kg every 3 weeks x 3 administrations (Days 1, 22, 43)

In Cohorts 1-6, disease response to siltuximab treatment was to be evaluated 2 weeks after the last scheduled administration of siltuximab (Day 57). Subjects responding to siltuximab treatment at that timepoint (ie, having stable disease [SD] or better) may have received a course(s) of siltuximab treatment during extended administration.

- Dose Cohort 7a: 9 mg/kg siltuximab every 3 weeks

Twelve subjects with Castleman's disease were to be enrolled to evaluate the safety and pharmacokinetics of siltuximab being administered as a 1-hour infusion. Siltuximab was to be administered until 1 of the following occurred: documented disease progression, unacceptable or unmanageable treatment-related toxicity, withdrawal of consent, or the investigator felt it was in the best interest of the subject to discontinue treatment. After Amendment 6 (19 Nov 2008), all new subjects were to be treated with a 12 mg/kg dose every 3 weeks, and all current subjects were permitted to escalate to a 12 mg/kg dose every 3 weeks if the clinical response to date was felt to be suboptimal. Subjects in Cohort 7a who experienced intolerable toxicity after escalating to or receiving 12 mg/kg every 3 weeks were to have the option of reverting to a dose of 9 mg/kg every 3 weeks if the investigator felt it was clinically indicated.

- Dose Cohort 7b: 12 mg/kg siltuximab every 3 weeks

Up to 8 subjects with Castleman's disease were to be enrolled in this translational research cohort to collect clinical specimens for gene/protein expression profiling of IL-6 signatures in lymph nodes and peripheral whole blood. Note: Whenever Cohort 7 is referred to in this study, it refers to Cohorts 7a and 7b.

Subjects were to be contacted every 6 months after the last study agent administration to assess disease status and survival until the end of the study. The data cutoff for the primary analysis was to be 1 year after the last evaluable subject had enrolled in the study.

Number of Subjects (planned and analyzed): This study planned to enroll from 6 to 70 subjects depending on the need to expand dose cohorts for dose-limiting toxicity (DLT) evaluation and whether additional subjects were enrolled for further safety and pharmacokinetic evaluation.

Of the 72 subjects enrolled in the study, 5 subjects were never treated. Sixty-seven subjects received treatment in the study:

- Cohort 1 (3 mg/kg every 2 weeks) 6 subjects
- Cohort 2 (6 mg/kg every 2 weeks) 7 subjects
- Cohort 3 (12 mg/kg every 3 weeks) 10 subjects
- Cohort 4 (6 mg/kg weekly) 6 subjects

- Cohort 5 (12 mg/kg every 2 weeks) 6 subjects
- Cohort 6 (12 mg/kg every 3 weeks) 12 subjects
- Cohort 7a (9 mg/kg every 3 weeks) 12 subjects
- Cohort 7b (12 mg/kg every 3 weeks) 8 subjects

Diagnosis and Main Criteria for Inclusion: In Cohorts 1-6, the study population included subjects with B-cell non-Hodgkin's lymphoma (including CLL/SLL and WM), multiple myeloma, or Castleman's disease. Enrollment in Cohort 7 was to begin after all subjects in Cohort 6 had been enrolled and was limited to subjects with Castleman's disease to further explore the safety and pharmacokinetics of siltuximab in this population. Subjects must have had disease that had progressed on or after standard therapy or for which there was no effective standard therapy, or which was not suitable for standard therapy in the opinion of the treating physician. At screening, subjects with B-cell non-Hodgkin's lymphoma (including CLL/SLL) or multiple myeloma must also have had detectable serum C-reactive protein (CRP) levels as well as measurable disease (as appropriate for the target disease). Subjects with WM must have had measurable disease but were not required to have detectable CRP. Subjects with Castleman's disease must have had unresectable localized or multicentric disease and were not required to have detectable CRP. Initially, 6 subjects were to be enrolled in Cohorts 1-5. Of these 6 subjects, at least 3 subjects with a screening CRP level of < 10 mg/L and 3 subjects with ≥ 10 mg/L were to be enrolled to further evaluate the AE profile. Subjects with Castleman's disease and WM without detectable CRP were to be assigned to the < 10 mg/L group. Subjects enrolled in Cohorts 6 and 7 were not to be stratified by screening CRP level.

Test Product, Dose and Mode of Administration, Batch No.: Siltuximab was supplied as 100 mg vials containing 5 mL liquid at a concentration of 20 mg/mL. The study agent was to be administered intravenously at the specified doses and dosing schedule, with an infusion time of 2 hours for Cohorts 1-5 and 1 hour for Cohorts 6 and 7. Subjects received study agent from cell line C175H (lot numbers D04PJ7380, D04PJ7380ZA, D04PL7405, D05PA7410, D06PJ7520, D06PM7543, D07PD7575, D07PF7585, D07PK7615, D07PM7636, D09PE7688, and D10PB7698).

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

Duration of Treatment: Cohorts 1-6: 42 days. Subjects responding to treatment with SD or better may have been eligible to receive extended administration.

Cohort 7: Siltuximab was to be administered until 1 of the following occurred: documented disease progression, unacceptable or unmanageable treatment-related toxicity, withdrawal of consent, or the investigator felt it was in the best interest of the subject to discontinue treatment.

Criteria for Evaluation:

Pharmacokinetics assessments:
The pharmacokinetic parameters were to include:
- Partial area under the serum concentration time curve (partial AUC)
- Maximum observed concentration (Cmax)

If sufficient samples were available, other pharmacokinetic parameters such as half-life (t1/2), clearance (CL), and volume of distribution (Vz), were to be evaluated.

Pharmacodynamic and Pharmacogenomic Assessments:
Pharmacodynamic analyses of biological markers, including but not limited to CRP, IL-6, soluble IL-6 receptor (glycoprotein [GP]80), soluble GP130, tumor necrosis factor α (TNFα), IL-8, IL-10, soluble IL-2 receptor (sIL-2R), interferon γ (IFNγ), serum amyloid A (SAA), N-telopeptide (NTx), C-telopeptide (CTx), hepcidin-25, vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) were

to be performed for serum samples, and for Cohorts 1-6 plasma samples for VEGF and FGF were to be collected at the timepoints specified in the study protocol.

An assessment of serum IL-6 bioactivity was to be performed if an appropriate assay was available. In addition, accessible tumor or bone marrow was to be biopsied for quantification of IL-6, IL-6 receptor, and siltuximab localization, if the biopsy was performed as per routine clinical management.

For Cohort 7b, lymph node biopsies of subjects with Castleman's disease were to be evaluated for gene expression profiling, IL-6 signaling pathways markers, cancer gene mutations, and global microRNA expression. Whole blood was to be collected for determination of baseline and siltuximab-induced gene expression changes, changes in B-cell and T-cell phosphoproteins associated with IL-6 neutralization, IL-6/IL-6 receptor (IL-6R) polymorphism, and to evaluate whether whole blood could serve as a surrogate for lymph node biopsies in future studies. Serum was to be collected for analysis of potential pharmacodynamic markers such as IL-6, CRP, and hepcidin.

Immune Response:
Antibodies to siltuximab were assessed.

Clinical Assessments:

Protocol-specified clinical assessments were to include:

- Disease response, according to standard criteria for B-cell non-Hodgkin's lymphoma (including CLL/SLL and WM), multiple myeloma, or for Castleman's disease; and staging (at baseline) for B-cell non-Hodgkin's lymphoma (including CLL/SLL) and multiple myeloma
- Clinical benefit
- Karnofsky performance status evaluation
- Weight
- Reduction of fever
- For Cohorts 1-6, Brief Pain Inventory ([BPI] short form Question 3)
- Survival
- Results of additional studies performed as part of standard of care to assess the current disease status may have also been collected

Safety Assessments:

The safety of siltuximab was evaluated by the DMC using the following assessments:

- Incidence of DLT
- Allergic reactions/hypersensitivity and cytokine release syndrome/acute infusion reactions
- All reported AEs
- Changes from baseline vital signs, neurologic exams, and safety-related parameters were evaluated for clinical significance
- New, clinically important ECG findings

DLT was defined as a Grade 3 or higher toxicity (excluding hematologic toxicity), or Grade 2 or higher allergic reaction/hypersensitivity, attributed to siltuximab as judged by the investigator and as defined by the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), Version 3.0 and observed prior to the second study agent administration.

Statistical Methods: This study planned to enroll from 6 to 70 subjects depending on the need to expand dose cohorts for DLT evaluation and whether additional subjects were enrolled for further safety and pharmacokinetic evaluation. This size was chosen to allow for collection of sufficient data in each dose cohort.

Descriptive statistics (eg, number of observations, means, standard deviations, medians, and ranges) was used to summarize data. Subject listings were also to be provided if necessary. No formal hypothesis testing was performed.

No formal interim analysis was conducted; however an interim review consisted of a periodic review of safety, pharmacokinetic, pharmacodynamic, and clinical assessment data by the DMC. At the end of the dose-finding exploration (Cohorts 1-5), a preliminary analysis of the pharmacokinetic, pharmacodynamic biomarker (ie, CRP), safety, and clinical outcomes data was conducted.

RESULTS:

STUDY POPULATION:

Of the 72 subjects enrolled in the study, 5 subjects were never treated. Sixty-seven subjects, including 37 subjects with Castleman's disease, were treated at 9 study centers in the US. There were 29 subjects treated long-term (≥ 12 months) in the study.

All 67 treated subjects discontinued study treatment, including 20 subjects (29.9%) who continued treatment with siltuximab in other studies; 13 subjects (19.4%) discontinued because of disease progression, 7 subjects (10.4%) discontinued because of AEs, and none of the subjects discontinued study agent because of death. Of the 67 treated subjects in the study, 8 subjects (11.9%) from Cohorts 1-6 completed Day 43 of study agent administration (1 course of siltuximab as specified in the protocol) but did not receive extended administration.

For the 67 treated subjects, the median age was 54.0 years (range 18 to 82 years). A similar percentage of male subjects (34 subjects; 50.7%) and female subjects (33 subjects; 49.3%) were enrolled in the study. The majority (53 subjects; 79.1%) were Caucasian, 10 subjects (14.9%) were Black, and 4 subjects (6.0%) subjects were Asian. The median weight was 78.0 kg (range 40.1 to 169.8 kg). The median Karnofsky performance status was 80.0 (range 60 to 100).

For the 37 treated subjects with Castleman's disease, the median age was 48.0 years (range 18 to 76 years). A similar percentage of male subjects (19 subjects; 51.4%) and female subjects (18 subjects; 48.6%) were enrolled in the study. The majority (27 subjects; 73.0%) were Caucasian, 6 subjects (16.2%) were Black, and 4 subjects (10.8%) subjects were Asian. The median weight was 78.0 kg (range 40.1 to 169.8 kg). The median Karnofsky performance status was 80.0 (range 60 to 100).

On 12 Dec 2005 the sponsor suspended siltuximab administration because of clinical supply issues. This was followed by a clinical hold on siltuximab administration imposed by the FDA on 27 Dec 2005. During the clinical hold, treatment with siltuximab was interrupted for 7 subjects; for these subjects, the duration they were not treated during the clinical hold ranged from 75 days (2.5 months) to 161 days (5.3 months).

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

- Following the first dose, serum concentrations of siltuximab declined in a bi-exponential manner with a mean terminal phase half-life ranging from 17.73 to 20.64 days
- Following the first dose and repeated doses, approximate dose-proportional increases in Cmax and AUC 0-t were observed
- The accumulation following repeated doses is consistent with the terminal phase half-life following the first dose, suggesting no time-dependent changes in pharmacokinetics
- Following the first dose, intersubject pharmacokinetic variability in terms of CV% for the 12 mg/kg dose level ranged from 27.3% to 33.3% for Cmax and 7.9% to 39.2% for AUC0-t

- No apparent differences in pharmacokinetic profiles were observed when comparing subjects with non-Hodgkin's lymphoma, multiple myeloma, or Castleman's disease
- None of the 31 subjects with appropriate samples were positive for antibodies to siltuximab at any time during the study.

PHARMACODYNAMIC AND PHARMACOGENOMIC RESULTS:

- CRP suppression was observed in all disease types tested across all dose cohorts, with greater decreases in higher dose cohorts
- Baseline systemic IL-6 levels do not appear to be predictive of clinical response in the limited number of subjects evaluated for each disease type
- Hepcidin decreased posttreatment in a majority of subjects, with a general trend toward hemoglobin improvement
- Differential gene expression or IL-6 activity strength was not evident in the very limited number of samples (only Cohort 7b) available for testing
- A majority of subjects with Castleman's disease tested for single-nucleotide polymorphisms (SNPs) in Cohort 7b (7 of 8) who showed expression of the minor allele of 2 IL-6R SNPs, also showed higher levels of serum sIL-6R

EFFICACY RESULTS:

- Of the 37 treated subjects with Castleman's disease, 32 subjects (86.5%) had improvement in 1 or more components of clinical benefit assessments, 28 subjects (75.7%) had improvement in 2 or more components of clinical benefit assessments, and 21 subjects (56.8%) had improvement in 3 or more components of clinical benefit assessments.
- Of the 37 treated subjects with Castleman's disease, 1 subject (2.7%) had a best response of complete response (CR), 11 subjects (29.7%) had a best response of partial response (PR), 3 subjects (8.1%) had unconfirmed PR, and 20 subjects (54.1%) had SD. The 1 CR and 8 of 11 PRs were in subjects treated with the highest dose of siltuximab (12 mg/kg).
- All 24 subjects with Castleman's disease treated long-term (≥ 12 months) in the study had sustained clinical benefit responses, and half (n = 12) also had an objective radiologic response, including 1 CR and 11 PRs based on central radiology review. Nine of the 12 responders were treated with the highest dose of siltuximab (12 mg/kg).
- Of the 14 subjects with non-Hodgkin's lymphoma evaluable for disease response (ie, those who had at least 1 postbaseline disease evaluation), 2 subjects (1 subject in Cohort 2 [6 mg/kg every 2 weeks] and 1 subject in Cohort 6 [12 mg/kg every 3 weeks]) had a confirmed PR. Of the 13 treated subjects with multiple myeloma, 2 subjects (1 subject in Cohort 4 [6 mg/kg weekly] and 1 subject in Cohort 6 [12 mg/kg every 3 weeks]) had a confirmed CR.
- Five subjects with multiple myeloma or non-Hodgkin's lymphoma treated long-term (≥ 12 months) in the study also had clinical benefit, including 2 CRs and 1 prolonged SD in 3 subjects with multiple myeloma and a durable PR (> 4 months) in 2 subjects with non-Hodgkin's lymphoma.

SAFETY RESULTS:

- No DLTs were observed in Cohorts 1-6 of the study, in which DLTs were evaluated
- The safety profile (AEs, Grade 3 or higher AEs, reasonably related AEs, SAEs, Grade 3 or higher SAEs, or AEs resulting in discontinuation of study agent) was similar at all dose levels
- Of the 67 treated subjects, 66 subjects (98.5%) had AEs, 40 subjects (59.7%) had AEs of toxicity grade 3 or higher, 19 subjects (28.4%) had SAEs, 8 subjects (11.9%) permanently discontinued study agent because of an AE, and 2 subjects (3.0%) died because of an AE (disease progression in a subject with non-Hodgkin's lymphoma considered not related to siltuximab, and renal impairment in a subject with multiple myeloma considered unlikely related to siltuximab)
- The highest frequency of treatment-emergent adverse events (TEAEs) of toxicity grade 3 or higher (≥ 10% frequency) was reported in the system-organ class blood and lymphatic system disorders (21 subjects; 31.3%); gastrointestinal disorders and infections and infestations (12 subjects each; 17.9%); metabolism and nutrition disorders (9 subjects; 13.4%); respiratory, thoracic, and mediastinal disorders (8 subjects; 11.9%); and nervous system disorders (7 subjects; 10.4%). The most frequent Grade 3 or higher TEAEs (≥ 5%) by preferred term were neutropenia (14 subjects; 20.9%), hypertension (6 subjects; 9.0%), thrombocytopenia (5 subjects; 7.5%), and cellulitis (4 subjects; 6.0%). Only 1 subject each discontinued study agent because of neutropenia and thrombocytopenia. Hypertension was manageable by antihypertensive medications, and no subject discontinued study agent because of hypertension. No subjects had dose delays or discontinued study agent because of cellulitis.
- Of the 67 treated subjects, 19 (28.4%) had Grade 3 or higher reasonably related TEAEs. The most frequent reasonably related Grade 3 or higher TEAEs (≥ 4.5%) were neutropenia (11 subjects; 16.4%) and thrombocytopenia (3 subjects; 4.5%).
- The highest frequency of treatment-emergent SAEs (≥ 5%) was reported in the system-organ class infections and infestations (9 subjects; 13.4%); gastrointestinal disorders and respiratory, thoracic, and mediastinal disorders (7 subjects; 10.4%); and blood and lymphatic system disorders and cardiac disorders (4 subjects each; 6.0%). The only SAEs by preferred term reported in > 1 subject were cellulitis and pleural effusion (3 subjects each; 4.5%); and bacteremia, device related infection, sepsis, abdominal pain, and pulmonary embolism, (2 subjects each; 3.0%).
- Of the 67 treated subjects, 4 subjects experienced infusion related reactions (Grade 3 hypertension, Grade 2 rash, Grade 1 pruritus, and Grade 1 dizziness and flushing). The infusion related reactions were reversible, and subjects were able to continue treatment with siltuximab with or without prophylactic treatment without recurrence of these events.
- Of the 37 treated subjects with Castleman's disease, all 37 had AEs, 20 subjects (54.1%) had AEs of toxicity grade 3 or higher, 10 subjects (27.0%) had SAEs, 3 subjects (8.1%) permanently discontinued study agent due to an AE, and none died because of an AE
- All 29 subjects treated long-term (≥ 12 months) in the study reported TEAEs, 18 subjects (62.1%) had AEs of toxicity grade 3 or higher, and 9 subjects (31.0%) had SAEs. None of the subjects treated long-term (≥ 12 months) in the study permanently discontinued study agent because of an AE, and no deaths were reported.
- Laboratory data indicate a trend toward increases in hemoglobin and triglycerides and decreases in neutrophils, platelets, and WBC with time, but no clear association with dose level was observed

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

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