SYNOPSIS

Issue Date: 19 May 2011

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

Protocol No.: C0328T05

Title of Study: A Phase 2 Multicenter Study of CNTO 328 (Anti IL-6 Monoclonal Antibody) in Subjects with Relapsed or Refractory Multiple Myeloma

EudraCT Number: 2006-001897-26

Coordinating Investigator:

Peter M. Voorhees, MD
The University of North Carolina at Chapel Hill, Div. of Hematology/Oncology
Chapel Hill, NC, USA

Publication (Reference): There are no final publications based on the clinical results of this study.

Study Period: The first subject signed informed consent on 22 Sep 2006. The first and last siltuximab infusions were administered on 06 Oct 2006 and 28 Jul 2009, respectively. The last study-related procedure was conducted on 26 Apr 2010. All subjects discontinued study treatment prior to the clinical database lock.

Phase of Development: Phase 2

Objectives: The primary objectives of this study were to assess the safety and efficacy of CNTO 328 administered as an IV infusion in subjects with relapsed or refractory multiple myeloma.

The secondary objectives were to assess the pharmacokinetics, pharmacodynamics, and immune response of CNTO 328 administered as an IV infusion in subjects with relapsed or refractory multiple myeloma.

Methods: This was an international, open-label, multicenter, nonrandomized, Phase 2 study of the safety and efficacy of siltuximab in subjects with relapsed or refractory multiple myeloma. The study was designed with 2 alternative treatment plans: In Treatment Plan A, subjects received siltuximab monotherapy starting from Cycle 1; dexamethasone was added at the first sign of disease progression on siltuximab monotherapy, or if no response (partial response [PR] or complete response [CR]) was observed after 2 full cycles of siltuximab. In Treatment Plan B, subjects received the combination of siltuximab and dexamethasone from the start of treatment. The goal of the study was to evaluate the efficacy and safety of siltuximab before and after the addition of dexamethasone.

The first 14 eligible subjects were to follow Treatment Plan A. A data evaluation was to be conducted by the DMC after 14 eligible subjects were treated and all ongoing subjects had up to 2 cycles of treatment and 2 postbaseline disease assessments. If at least 1 response (CR or PR) was observed in the first 14 eligible subjects, all subsequent subjects were to follow Treatment Plan A. However, if no responses (CR or PR) were observed with siltuximab monotherapy, all subsequent subjects were to follow Treatment Plan B. The safety and efficacy of the study was to be monitored by the DMC, and by the sponsor on an ongoing basis throughout the study.

Number of Subjects (planned and analyzed): The planned total sample size was approximately 90 subjects; 53 subjects were treated in the study.

Diagnosis and Main Criteria for Inclusion: Subjects were considered eligible if they had a confirmed diagnosis of relapsed or refractory multiple myeloma; measurable secretory disease at study entry; received at least 2 prior lines of therapy with documentation of either no response to previous treatment or progression after completing the last treatment; and prior exposure to VELCADE® (bortezomib).

Test Product, Dose, and Mode of Administration, Batch No.: All subjects received 6 mg/kg siltuximab (CNTO 328) intravenously once every 2 weeks; 2 siltuximab infusions were administered during each 28-day treatment cycle. Siltuximab was supplied from 5 separate lots; D05PA7410, D05PM7467, D06PJ7520, D07PD7575, and V07PG7075. Dexamethasone was administered in combination with siltuximab (CNTO 328) in this study. The dexamethasone (40 mg dose) tablets were administered orally from commercially available supplies. Therefore, batch numbers are not available.

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

Duration of Treatment: The planned duration of treatment for each subject was up to 12 cycles of therapy; however, additional treatment was allowed, with approval from the sponsor, for subjects benefiting with a response of stable disease (SD) (ie, no change) or better.

Criteria for Evaluation: Key efficacy, pharmacology, and safety evaluations are listed below:

Efficacy Evaluations: The primary endpoint was overall response rate for siltuximab if Treatment Plan B was not used. Otherwise, the primary endpoint was the overall response rate of siltuximab plus dexamethasone (Treatment Plan B). A 95% confidence interval of the response rate was to be provided.

The major secondary endpoints were time-to-progression (TTP) for siltuximab and TTP for siltuximab plus dexamethasone combination, and duration of response for each treatment regimen. Other efficacy parameters included progression-free survival (PFS) and overall survival.

Efficacy was evaluated using the following disease assessments: M-protein in serum and urine by immunofixation, serum and 24-hour urine protein (urinary light chain) electrophoresis, serum beta2 microglobulin, blood chemistry (serum calcium corrected for albumin and total protein), complete bone skeletal survey (and radionucleotide bone scan, if performed), bone marrow biopsy/aspirate, evaluation of visual and palpable lesions, and radiologic imaging of plasmacytomas, quantitative immunoglobulins.

Response to treatment was to be assessed by the investigator based on European Group for Blood and Marrow Transplantation (EBMT) criteria. The determination of progressive disease and response was to be largely determined by M-protein changes reported by the central laboratory or by specific measurements of plasmacytomas provided by the investigators. The investigator made the primary determination of response and progression; the sponsor later verified these assessments based on central laboratory results.

Relapse from CR or progressive disease was to be confirmed by at least 1 repeat investigation (serum and 24-hour urine protein [urinary light chain] electrophoresis; serum and urine immunofixation). Skeletal X-rays were not required for confirmation of response; however, if performed, they were to be used in the assessment of progressive disease.

Pharmacology Evaluations: Population pharmacokinetic analysis of siltuximab serum concentration-time data will be performed using nonlinear mixed effects modeling, which provides pharmacokinetic parameter estimates including total clearance of drug after IV administration (CL). The population pharmacokinetic analysis will combine data from this study and other clinical studies conducted with siltuximab. The results of this analysis will be presented in a separate report, when sufficient data are available.

The pharmacodynamic effects of siltuximab were to be evaluated through C-reactive protein (CRP) and IL-6, and other biomarkers, such as, IL-10, C-telopeptide (CTx), and N-telopeptide (NTx). Bone marrow samples were to be evaluated for IL-6, mitogen-activated protein kinase (pMAPK), signal transducer and

activators of transcription (pSTAT-3), and IL-6 receptor expression, and other biomarkers, such as, myeloid cell leukemia-1 (Mcl-1) and Syndecan-1.

Safety Evaluations: The safety endpoints were the incidence of all AEs, Grade 3 or higher AEs, SAEs, deaths, and clinically significant changes in vital signs, safety-related laboratory parameters, and ECGs. Safety evaluations included; physical exam, weight, vital signs, routine clinical laboratory assessments (hematology, coagulation, blood chemistry, lipid panel, amylase and lipase, urinalysis), serum pregnancy test, 12-lead ECGs, and Eastern Cooperative Oncology Group (ECOG) performance status. Adverse events that may have occurred between site visits and any changes to concomitant medications were to be reported. Adverse events were evaluated according to the National Cancer Institute's (NCI) Common Terminology Criteria for AEs (CTCAE), Version 3.0. Serum samples for the determination of the presence of antibodies to siltixumab were also to be collected.

Statistical Methods: No formal hypothesis testing was planned. Descriptive statistics were to be used to summarize data. For continuous parameters, number of observations, mean, standard deviation, median, and range were to be used. For discrete parameters, frequency was to be summarized. For time-to-event parameters, Kaplan-Meier estimates were to be provided. The study was designed to evaluate each treatment plan individually. In addition, data from subjects treated in Treatment Plan B were combined with data from subjects treated with the combination of siltuximab and dexamethasone in Treatment Plan A to provide the most comprehensive assessment of efficacy and safety for the combination.

Subjects who had a confirmed diagnosis of multiple myeloma, measurable secretory disease based on EBMT criteria (serum M protein ≥ 1 g/dL or urine monoclonal [light chain] protein [> 200 mg/24 hours]), received at least 1 siltuximab administration, and had at least 1 postbaseline disease assessment were evaluable for disease response.

All subjects who receive at least 1 administration of siltuximab were evaluable for safety. Data were summarized for all subjects from the start of treatment to the last administration of siltuximab for each treatment group – siltuximab monotherapy and siltuximab with dexamethasone. The incidence rate of antibodies to siltuximab was also evaluated.

RESULTS: Fifty-three subjects were treated in the study; 30 (57%) male subjects and 23 (43%) female subjects. The median age for all treated subjects was 65 years (range, 43 to 89), with 27 (51%) subjects ≥ 65 years of age. The majority (93%) of subjects had ECOG performance status of 0 or 1.

All 53 subjects had secretory-myeloma, primarily IgG (64%) and IgA (23%) myelomas; 5 subjects (9%) had light chain disease. According to the International Staging System based on beta2-microglobulin and albumin, 35% of subjects had Stage I disease, 37% had Stage II disease, and 29% had Stage III disease at baseline. The median time since multiple myeloma diagnosis to study treatment was 4 years (range, 0.7 to 13.2). The median number of prior lines of therapy was 4 (range, 2 to 9) with almost half (45%) of the subject receiving ≥ 5 prior lines of therapy.

The median number of treatment cycles for the 53 treated subjects was 4 (range, 1 to 24). The median duration of siltuximab treatment was 3 months (91 days) and the maximum was 2.2 years (807 days). The median cumulative siltuximab dose was 3120 mg (range, 480 to 21360). Forty-nine subjects received at least 1 dose of dexamethasone in combination with siltuximab; the median dexamethasone cumulative dose was 1520 mg (range, 320 to 3200). The median duration of dexamethasone treatment was 3.3 months (91 days) and the maximum was approximately 2.1 years (751 days). All 14 subjects in Treatment Plan A received siltuximab monotherapy in during Cycle 1. Dexamethasone was added to the treatment regimen for 4 (40%) subjects during Cycle 2 and 6 (60%) subjects during Cycle 3.

Of the 53 subjects treated with siltuximab, 37 (70%) discontinued siltuximab treatment due to disease progression, 12 (23%) subjects discontinued due to an AE, and 4 (8%) subjects discontinued for other reasons. The median duration of study follow-up was 13.9 months (range, 0.5 to 37.7).

EFFICACY RESULTS: The DMC reviewed safety and efficacy data after the 14 eligible subjects in Treatment Plan A were treated and all ongoing subjects had up to 2 cycles and 2 postbaseline assessment. The decision to proceed with Treatment Plan B was based on the absence of response with siltuximab monotherapy. Therefore, all subsequent subjects were to be enrolled into Treatment Plan B, according to the protocol. The positive response (5/9 evaluable subjects) observed with the combination treatment was a basis for expanding the population size to 90. Subjects in Treatment Plan B received siltuximab plus dexamethasone concurrently, starting from Day 1 of Cycle 1.

Fifty-one treated subjects met the criteria to be considered evaluable for response. Endpoints are presented individually for subjects treated with siltuximab plus dexamethasone in Treatment Plan A and Treatment Plan B. In addition, data are presented for all subjects treated with the combination of siltuximab plus dexamethasone.

- The efficacy of the siltuximab-dexamethasone combination was analyzed in a heavily pre-treated population. Median number of prior lines of therapy was 4 (range, 2 to 9); all subjects had prior therapy with proteasome inhibitors and corticosteroids, 91% received alkylating agents; 89% received immunomodulatory agents; 68% received anthracyclines; and 66% received prior stem cell transplant. Furthermore, 29% of subjects in Treatment Plan A and 81% of subjects in Treatment Plan B were refractory to their last regimen containing dexamethasone.
- Thirty-eight of the 39 subjects in Treatment Plan B were evaluable for disease response. Three (8%) subjects had a PR, and 3 (8%) subjects had a MR.
- There was no response (CR or PR) to the siltuximab monotherapy for the 14 subjects in Treatment Plan A; 8 (62%) subjects had SD and 5 (39%) subjects had progressive disease. Ten (71%) subjects had dexamethasone added to the regimen after 2 cycles as per the protocol, 5 (36%) of whom subsequently achieved a PR; no additional MRs were observed.
- Forty-seven of the 49 subjects who received the siltuximab and dexamethasone combination (Treatment Plan A and Treatment Plan B combined) were evaluable for disease response: 8 (17%) subjects had PR, 3 (6%) subjects had MR, 27 (57%) subjects had SD, and 8 (17%) subjects had progressive disease. Of the 11 subjects with at least MR, 5 subjects were refractory to the last regimen containing dexamethasone and 7 had less than MR on a prior regimen containing dexamethasone.
- The median duration of response (CR+PR) was 5.9 months (181 days) (95% CI: 148, 301 days) for Treatment Plan B, the same as for all subjects receiving combination treatment (5.9 months; 95% CI: 147, 365 days). The median duration of response for subjects receiving combination treatment in Treatment Plan A was 12 months (95% CI: 92, 506 days). Three subjects had a long-lasting response for 9 months or more.
- The median PFS was 3.7 months (114 days) (95% CI: 82, 135 days) for Treatment Plan B, the same as for all subjects receiving combination treatment (3.7 months; 95% CI: 84, 148 days). The median PFS for subjects in Treatment Plan A was 4.9 months (148 days) (95% CI: 43, 386 days).
- The median overall survival was 20.4 months (621 days) (95% CI: 347, 960 days) for all treated subjects (range, 14 to 1147 days). Of the 49 subjects who received combination treatment, 27 subjects were alive at 1 year and 8 subjects were alive at 2 years.

PHARMACOKINETIC and IMMUNOGENICITY RESULTS: The Cmax serum concentrations of siltuximab increased up to Cycle 3 reflecting an accumulation of siltuximab, consistent with the previously reported half-life value. Steady-state was not achieved in this study following 3 repeated doses of siltuximab administered at 6 mg/kg every 2 weeks. Dexamethasone treatment does not appear to affect siltuximab pharmacokinetics. Immunogenicity samples were collected up to 9 months following the last dose of siltuximab; none of the 36 subjects with appropriate samples were positive for antibodies to siltuximab.

PHARMACODYNAMIC and PHARMACOGENOMIC RESULTS: The combination of siltuximab and dexamethasone decreased CRP levels starting at Cycle 1 Day 15. The reduced levels of CRP were sustained

until Cycle 12 and the end of treatment. Preliminary evidence of differential levels of 3 serum proteins, brain-derived neurotrophic factor (BDNF), alpha-2-macroglobulin (A2M), and platelet-derived growth factor beta polypeptide (PDGFBB), was observed in subjects with MR and PR compared to subjects with progressive disease. Though the sample size for pharmacogenomic analysis was very limited (n = 9), exploratory gene expression analysis using bone marrow samples indicated that the IL-6 pathway gene classifier derived from published data correctly predicted 1 of the 2 responders and 6 of the 7 nonresponders. These observations are preliminary and needs to be further confirmed in future studies.

SAFETY RESULTS: The discussion of treatment-emergent AEs is based on all subjects receiving the combination of siltuximab and dexamethasone (Treatment Plan A and Treatment Plan B combined). All 49 subjects treated with the combination of siltuximab and dexamethasone experienced at least 1 or more treatment-emergent AE during the study. The majority (74%) of subjects had 1 or more Grade ≥ 3 AEs and 41% of subjects had 1 or more SAE.

Summary of treatment-emergent AEs; treated subjects

	Treatment Plan A			
	Before Dexamethasone Added (CNTO 328)	After Dexamethasone Added (CNTO 328 + Dexamethasone)[a]	Treatment Plan B (CNTO 328 + Dexamethasone)	Combination Treatment (CNTO 328 + Dexamethasone)[a,b]
Subjects treated	14	10	39	49
Subjects with any AEs	14 (100.0%)	10 (100.0%)	39 (100.0%)	49 (100.0%)
Subjects with any AEs of toxicity grade 3 or higher	8 (57.1%)	7 (70.0%)	29 (74.4%)	36 (73.5%)
Subjects with any AEs reasonably related to CNTO 328	8 (57.1%)	7 (70.0%)	37 (94.9%)	44 (89.8%)
Subjects with any AEs reasonably related to dexamethasone	1 (7.1%)	8 (80.0%)	37 (94.9%)	45 (91.8%)
Subjects with any serious AEs	3 (21.4%)	2 (20.0%)	18 (46.2%)	20 (40.8%)
Subjects with any serious AEs reasonably related to CNTO 328	0 (0.0%)	0 (0.0%)	13 (33.3%)	13 (26.5%)
Subjects with any serious AEs reasonably related to dexamethasone	0 (0.0%)	1 (10.0%)	10 (25.6%)	11 (22.4%)
Subjects who permanently discontinued CNTO 328 due to AEs	2 (14.3%)	3 (30.0%)	9 (23.1%)	12 (24.5%)
Subjects who permanently discontinued dexamethasone due to AEs	0 (0.0%)	3 (30.0%)	9 (23.1%)	12 (24.5%)
Subjects who had temporary CNTO 328 dose interruption	4 (28.6%)	4 (40.0%)	16 (41.0%)	20 (40.8%)
Subjects who had temporary dexamethasone dose interruption or modification	0 (0.0%)	4 (40.0%)	19 (48.7%)	23 (46.9%)
Subjects who died due to an AE[c]	2 (14.3%)	1 (10.0%)	2 (5.1%)	3 (6.1%)

[a] Includes AEs that occurred after dexamethasone was added to treatment regimen.
[b] Includes Plan A subjects who received CNTO 328 plus dexamethasone treatment and all subjects in Plan B.
[c] Includes subjects who died due to disease progression.

RE315:[S_AE_168_A], 27MAY2010 11:30

Fifty-three subjects were treated in the study and of these, 49 received the combination of siltuximab and dexamethasone; 10 subjects in Treatment Plan A and 39 subjects in Treatment Plan B.

The most frequently occurring AEs by body system reported by ≥ 50% of subjects receiving combination treatment were Gastrointestinal Disorders (71%), General Disorders and Administration Site Conditions (71%), Blood and Lymphatic System Disorders (67%), Metabolism and Nutrition Disorders (67%), Infections and Infestations (57%), Nervous System Disorders (55%), Musculoskeletal and Connective Tissue Disorders (51%), and Respiratory, Thoracic and Mediastinal Disorders (51%).

The most frequently occurring AEs in the Gastrointestinal Disorders System Organ Class (SOC) were diarrhea (29%), nausea (22%), and constipation (20%). In the General Disorders and Administration Site Conditions SOC, fatigue (43%) and peripheral edema (29%) were the most frequently occurring AEs. Adverse events in both these SOC were generally lower in grade with only 4% and 14% of subjects, respectively, experiencing Grade ≥ 3 AEs and 6% and 8% of subjects, respectively, having AEs in these SOCs that were considered to be serious.

The most frequently occurring AEs in the Blood and Lymphatic Systems Disorders SOC were thrombocytopenia (49%), anemia (35%), neutropenia (29%), and leukopenia (22%). In the Infections and Infestations SOC, upper respiratory tract infections (14%) and oral candidiasis (10%) were the most frequently occurring AEs. The incidence of Grade ≥ 3AEs for the Blood and Lymphatic Systems Disorders and Infections and Infestations SOCs were 47% and 18% of subjects, respectively. Serious AEs were reported by 16% and 12% of subjects, respectively.

Adverse events by preferred term with a ≥ 15% incidence not in the aforementioned SOCs included abnormal hepatic function (31%), dyspnea (27%), dizziness (25%), insomnia (22%), weight increase (20%), myalgia (16%), and enzyme abnormality (16%). Despite the use of high-dose dexamethasone, no thromboembolic events were observed in this study.

Grade ≥ 3 AEs by preferred term reported by ≥ 5% of subject receiving combination treatment were thrombocytopenia (27%), neutropenia (18%), anemia (16%), fatigue (8%), abnormal hepatic function (8%), and pneumonia (6%). Serious adverse events by preferred term reported by 2 or more subjects were pneumonia (8%), thrombocytopenia (6%), septic shock, anemia, hemolytic anemia, and multiple myeloma (4% for each event).

Five subjects died during the treatment period; 3 subjects died less than 30 days after the last dose of study agent and all 3 deaths were due to progressive disease. Two subjects died due to infection; 1 subject died due to nosocomial infection 27 days after receiving siltuximab alone. The investigator considered the death not related to siltuximab treatment; and 1 subject died 31 days after the last dose of study agents as a result of the SAE of septic shock, 13 and 41 days after the last siltuximab and dexamethasone treatment, respectively. The event was considered by the investigator to have a possible relationship to study agents.

The incidence of treatment discontinuations due to AEs for subjects receiving combination treatment was 25%, most commonly for hemolytic anemia, abnormal hepatic function, and depression (2 subjects; 4% for each event). The incidence of AEs leading to siltuximab dose withholding and AEs leading to a temporary dose interruption or dose modification of dexamethasone was 41% and 47%, respectively. Siltuximab doses were most commonly withheld for thrombocytopenia (10%), abnormal hepatic function (6%), anemia, neutropenia, pneumonia, and upper respiratory tract infection (4% for each event). Dexamethasone dose interruptions or modifications were most frequently due to thrombocytopenia (10%), neutropenia, pneumonia, upper respiratory tract infection, muscular weakness, insomnia, abnormal hepatic function, and syncope, each event reported by 4% of subjects. Overall, of the 518 total doses of siltuximab administered, 32 doses were delayed.

Two (4%) subjects treated with the combination of siltuximab and dexamethasone had low grade (Grade 1 or 2) infusion-related reactions of tachycardia, chills, and allergic pruritus as assessed by the investigator.

Hematologic toxicities were the most frequent laboratory abnormalities reported. Shift from baseline to the maximum postbaseline toxicity grade showed Grade ≥ 3 neutropenia, thrombocytopenia, and anemia to be the most frequently occurring severe hematological toxicities. Chemistry abnormalities were low grade and infrequent.

The mean hemoglobin was relatively stable with combination treatment. Although transient decreases were observed in the mean WBC and neutrophil count, overall these parameters were generally Grade 1 or better throughout the treatment cycles. Fluctuations were observed in the mean platelet count; however, overall, the mean platelet count was generally above the lower limit of normal.

STUDY LIMITATIONS: The study was amended to increased enrollment (target of 90 subjects) to allow estimation of the response rate with increased precision. However, enrollment into the study was slow due to changes in the standard of care since the start of study. Therefore, the sponsor discontinued enrollment and all 53 treated subjects completed the study as planned. Furthermore, full enrollment was no longer deemed necessary because the primary objectives of the study were met. The 53 treated subjects provided sufficient data to evaluate the efficacy and safety of the combination of siltuximab and dexamethasone.

CONCLUSION:

- The efficacy of the siltuximab-dexamethasone combination was analyzed in a heavily pre-treated population including that were refractory to their last regimen containing dexamethasone.
- The primary endpoint was the overall response rate (CR+PR) of siltuximab plus dexamethasone (Treatment Plan B). The per protocol response rate was 8% for Treatment Plan B. The response rate was 17% in all subjects receiving combination treatment (Treatment Plan A and Treatment Plan B).
- Response rate (CR+PR+MR) for all evaluable subjects who received combination treatment in the study was 23%.
- Responses were durable with a median duration of PR of 5.9 months (range, 92 to 506 days). Six of 8 subjects with a PR were still alive at the time of data analysis.
- All subjects with a response of PR were treated with at least 3 prior lines of therapy for myeloma and most of the subjects had disease that was refractory to the last line of treatment. Of the 11 subjects who obtained at least a MR on siltuximab-dexamethasone combination, 5 were refractory to the last dexamethasone regimen and 7 had less than MR on a prior dexamethasone regimen.
- The median TTP was 4.4 months (95% CI: 86, 169 days) for subjects receiving combination treatment.
- Median overall survival was 20.4 months (range, 14 to 1147) for all treated subjects.
- Siltuximab and dexamethasone have an acceptable safety profile when given in combination to subjects with relapsed or refractory multiple myeloma. Infections and reversible hematological adverse events and infections were the most frequent adverse events. Infusion reactions were infrequent and mild.
- Dexamethasone treatment does not appear to affect siltuximab pharmacokinetics.
- None of the 36 subjects with appropriate samples were positive for antibodies to siltuximab.
- Treatment with siltuximab in combination with dexamethasone caused suppression of CRP, a pharmacodynamic marker of IL-6 inhibition, which was sustained until the end of treatment.
- Preliminary evidence of differential levels of serum analytes (BDNF, A2M, PDGFB) between PR and MR versus progressive disease was observed.

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.