SYNOPSIS

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

Protocol No.: CNTO328STM2001

Title of Study: A Phase 1/2, Multiple-dose, Dose-escalation Study to Assess the Safety, Efficacy, and Pharmacokinetics of Intravenous CNTO 328, an Anti-Interleukin 6 (IL-6) Monoclonal Antibody, in Subjects with Solid Tumors

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Clinical Registry No.: CR015580

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Study Center(s): 3 sites in France, 2 sites in Spain, 3 sites in Belgium, 3 sites in the United Kingdom (UK), and 2 sites in the United States (US)

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

Study Period: The first subject initiated treatment on 03 Mar 2009 and was enrolled into Phase 1.The date of the first study related procedure/observation recorded as part of the database was 19 Feb 2009. The date of the last observation recorded as part of the database and the end of the study was 11 Apr 2011.

Phase of Development: Phase 1/2

Objectives: The primary objective of the Phase 1 portion of this study was to determine a recommended dose for Phase 2 (RP2D) of siltuximab monotherapy. The primary objective of the Phase 2 portion of this study was to estimate the clinical benefit rate (CR+PR+SD of duration >6 weeks) of siltuximab monotherapy in subjects with ovarian cancer and subjects with *KRAS* mutant tumors.

The secondary objectives of the Phase 1 portion of this study were to assess: the safety profile, including the adverse event (AE) profile and dose limiting toxicities (DLTs), the pharmacokinetic profile, immunogenicity, pharmacodynamic effects associated with the IL-6 pathway and mechanisms of anemia, and the clinical effects of siltuximab.

The secondary objectives of the Phase 2 portion of the study were to assess: the safety profile of siltuximab, pharmacodynamic effects associated with the IL-6 pathway, mechanisms of anemia, and correlation with *KRAS* mutations, pharmacokinetics, immunogenicity, and patient-reported outcomes (PRO) for subjects with ovarian cancer.

Methodology: This was a 2-part, Phase 1/2, open-label, multiple-dose, dose-escalation study to assess the safety, efficacy, and pharmacokinetics of IV siltuximab in subjects with malignant solid tumors. Phase 1 (Cohort 1 [pharmacokinetics only], dose escalating Cohorts 2 through 4, and dose expansion Cohort 5) was conducted at 4 sites (2 in the US and 2 in the EU). Phase 2 (Ovarian Cancer and *KRAS* Mutant Tumors Cohorts) was conducted in 13 sites (3 sites in France, 2 sites in Spain, 3 sites in Belgium, 3 sites

in the UK, and 2 sites in the US). The recommended dose regimen used in the Expansion Cohort 5 was used in Phase 2, provided preliminary evidence of efficacy was observed.

Number of Subjects (planned and analyzed): Approximately 90 subjects were planned to be included in this study. Eighty-four subjects were treated with siltuximab and were evaluable for assessments.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were to be ≥18 years old and have malignant solid tumors that have progressed on or after standard therapy, or for which there is no effective therapy. In Phase 1, Cohorts 1-4 (pharmacokinetics and dose-escalation) were to enroll all solid tumor types. Expansion Cohort 5 (20 subjects) was to enroll from a limited number of solid tumor types, which had been selected as having an unmet clinical need and a rationale for targeting IL-6, including epithelial ovarian cancer and tumors with known *KRAS* mutations or pancreatic cancer, or non-small cell lung cancer (NSCLC), colorectal cancer (CRC), or head and neck (H&N) cancer that were refractory or resistant to anti-EGFR therapy (referred to as the *KRAS* Mutant Tumors Cohort). Assuming preliminary efficacy, as per protocol definitions, was demonstrated in the Phase 1 portion of the study, Phase 2 was to enroll subjects with ovarian cancer and subjects with tumors harboring known *KRAS* mutations or pancreatic cancer, or subjects with CRC, NSCLC, or H&N cancer that were refractory or resistant to anti-EGFR treatments.

Test Product, Dose and Mode of Administration, Batch No.: The study agent infusion (approximately 250 mL over 1 hour) was given using an administration set with a 0.22 µM filter (supplied) or an alternative set identified in the Pharmacy Manual instructions that was provided by the Sponsor. All study administrations were calculated based on the subject's weight at Day 1. Siltuximab was dosed relative to actual body weight, regardless of ascites or edema**.** Siltuximab was supplied for this study from production lots D07PK7614 and D08PJ7676.

Duration of Treatment: Screening for all cohorts was up to 4 weeks. The treatment period for Cohort 1 through Cohort 4 consisted of a 28-day (4 week) duration between Administration 1 and 2, Administrations 2 through 4 were every 2 weeks in Cohorts 1 and 2 and every 3 weeks in Cohorts 3 and 4. Extended doses were to be 2 weeks apart in Cohort 1 and Cohort 2 and 3 weeks apart in Cohort 3 and Cohort 4. Cohort 5 and Phase 2 Cohorts consisted of 12 administrations every 3 weeks, up to 36 weeks. Extended dosing was to be every 3 weeks. Follow-up was to occur for 12 weeks. The Post-treatment Follow-up was to occur every 3 months for up to 1 year after the last study agent administration.

Criteria for Evaluation: Subjects evaluable for safety (or Treated subjects): All subjects who received at least 1 administration of study agent were to be evaluable for safety. All subjects who have safety follow-up data up to 3 weeks after the first administration and go off study for any reason other than a DLT were to be evaluable. This population was to be used for all analyses unless stated otherwise.

Response Population: Response evaluable subjects were defined as subjects who received at least 1 administration of siltuximab and have at least 1 post-baseline disease evaluation. Confirmation of tumor response using RECIST criteria should be used, wherever possible.

Hemoglobin (Hb) Response Population: Hemoglobin response evaluable subjects were subjects who received at least 1 siltuximab administration and have a baseline Hb that is below the lower limit of normal (within 2 weeks prior to starting treatment) and at least 1 post-baseline Hb evaluation.

Pharmacokinetic Evaluations: Blood samples were to be collected from all subjects for the measurement of serum siltuximab concentration for pharmacokinetic analyses. The pharmacokinetic endpoints were to include, but were not limited to, the following: AUC_{inf}, $AUC_{(t1-t2)}$, C_{max}, $t_{1/2}$, CL, $C_{min,ss}$, and V_{ss}.

Immunogenicity Evaluations: Immunogenicity was evaluated by detecting antibodies to siltuximab in serum samples prepared from blood samples. Detection of antibodies to siltuximab was performed using a bridging immunoassay in which siltuximab-derived reagents were used to capture and detect antibodies.

Pharmacodynamic Evaluations: Pharmacodynamic assessments were to include CRP, IL-6 and other markers associated with the target (soluble IL-6R [GP80], soluble GP130) and inflammatory cytokines (IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α), and relevant factors associated with angiogenesis (IL-8, platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), intercellular adhesion molecule (ICAM)-1, E-Selectin, and tissue inhibitor of metalloproteinase (TIMP)-1, Coll-IV, and TIE-2. In addition, markers associated with anemia and iron metabolism (eg, hepcidin) were also to be evaluated in pre and post treatment serum samples. Further, soluble IL-6 receptor (GP80), soluble GP130, inflammatory cytokines (IL-1β, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, TNF-α), and angiogenesis markers such as, IL-8, PDGF, HGF, FGF, and VEGF may have been assessed in ascites of ovarian cancer subjects (depending on the availability of ascites samples for the Dose Expansion Cohort 5 and Phase 2 Ovarian Cancer Cohort).

Efficacy Evaluations: Preliminary clinical efficacy was to be evaluated based on pre-defined major and minor response criteria. Major response criteria included tumor shrinkage (PR or CR, defined by RECIST, where applicable). Minor response criteria included (any one of the following): tumor stabilization (SD) confirmed on >6 week interval, tumor marker response (CA-125 or other), increase in Hb of at least 10 g/L over baseline in anemic subjects, and clinical improvement as judged by the investigator in the absence of disease progression. The primary efficacy endpoint of clinical benefit was defined as the proportion of subjects that achieve a CR, PR, or SD of duration >6 weeks.

Safety Evaluations: The safety evaluations included an assessment of all reported AEs, incidence of dose-limiting toxicity, Grade 3 or higher AEs, serious adverse events (SAEs), allergic reactions/hypersensitivity and cytokine release syndrome/acute infusion reactions, incidence of clinically important changes from baseline vital signs, laboratory parameters, clinically important findings in electrocardiograms (ECGs), dose limiting toxicities (DLTs), and deaths. DLTs were defined as clinically relevant Grade 3 or higher AEs regardless of relationship with study treatment occurring within 21 days after the first dose.

Statistical Methods: Descriptive statistics (eg, number of observations, means, standard deviations, medians, and ranges) were used to summarize data. No formal hypothesis testing was performed. No formal interim analysis was planned. There was to be an interim analysis for futility prior to initiation of the Phase 2 cohorts for subjects with ovarian cancer and *KRAS* mutant tumors.

Sample size: The sample sizes for the first 4 cohorts (pharmacokinetic and dose escalation cohorts) were not based on hypothesis testing. For each specific tumor type in the dose expansion cohort (Cohort 5), assuming a 5% null hypothesis response rate and an alternative hypothesis rate of 10%, 15%, or 20%, and for a fixed one-sided level of significance of 10%, the power to reject the null hypothesis would be for sample sizes 10, 12, and 15. A sample size of 10 for each specific tumor type was selected. Thus, the Expansion Cohort 5 was to enroll up to 20 evaluable subjects. For each specific tumor type in the Phase 2 Ovarian Cancer and *KRAS* Mutant Tumors Cohorts, assuming a 5% null hypothesis response rate and an alternative hypothesis rate of 10%, 15%, or 20%, and for a fixed one-sided level of significance of 10%, the power to reject the null hypothesis would be for samples of size 20 (size of Ovarian Cancer and *KRAS* Mutant Tumors Cohorts) and 30 (obtained by combining specific tumor types from Expansion Cohort 5 and Phase 2 cohorts.

RESULTS: STUDY POPULATION: Eighty-four subjects were enrolled and received at least 1 siltuximab administration. The median age was 60 years (range 32 to 81) and over half of the subjects were female (55 subjects; 65.5%). The majority of subjects in the study were Caucasian (76 subjects;

90.5%); 5 subjects (6 %) were Black or African American and 1 subject (1.2%) was Asian. The most commonly reported tumor types were colorectal cancer (35 subjects; 41.7%), ovarian cancer (29 subjects; 34.5%), and pancreatic cancer (9 subjects; 10.7%). The median duration since diagnosis was 3.15 years. The median duration since diagnosis in the Ovarian Cancer Cohort and the *KRAS* Mutant Tumors Cohort were 5.30 years and 3.04 years respectively. Eighteen subjects in the *KRAS* Mutant Tumors Cohort were tested for *KRAS* mutations. Thirteen of the 18 tested *KRAS* mutation positive and 4 of 18 subjects were *KRAS* mutation negative. Five subjects in the *KRAS* Mutant Tumors Cohort did not have sufficient tissue available for testing. All subjects received prior systemic therapies; approximately half (48.8%) of the subjects received 5 or more lines of therapies prior to study entry. All subjects enrolled had metastatic disease. Sixty (71.4%) subjects had liver metastases, 48 (57.1%) subjects had lung metastases, 36 (42.9%) subjects had metastases in both liver and lungs, and 54 (64.3%) subjects had metastases in more than 3 organ systems at study entry. The table presents the 84 subjects by cohort:

Cohort	Dose (mg/kg)	No. of Subjects
1	2.8	1
2	5.5	6
3	11	6
4	15	7
5	15	24
Ovarian Cancer	15	17
KRAS Mutant Tumors	15	23

Of the 84 treated subjects, 9 (10.7%) subjects completed treatment and 75 (89.3%) subjects discontinued. The reasons for treatment discontinuation were disease progression (68 subjects; 81.0%), AE (5 subjects; 6.0%), and physician decision and death (1 subject each, 1.2%).

There were 11 protocol deviations reported. Two subjects did not meet selection criteria, however received treatment. Nine subjects received either the wrong treatment or an incorrect dose, based on not meeting retreatment criteria for liver function tests (LFTs). Treated subjects with increased ALT, AST, or bilirubin levels had underlying liver metastases. No safety issues were raised due to these protocol deviations. Per protocol, subjects with prostate cancer were permitted use of low-dose corticosteroids. However, 13 subjects with equivalent low doses of corticosteroids with cancers other than prostate cancer were accepted and assessed as minor deviations during the medical review.

The median number of siltuximab administrations was 3.0 (range 1 to 45). The median duration of exposure to siltuximab was 42.0 days (range 1 to 638 days) and the median cumulative dose was 38.26 mg/kg (range 2.8 to 255.5 mg/kg).

EFFICACY RESULTS: The primary efficacy endpoint of clinical benefit rate observed in the 7 cohorts ranged from 0.0% to 28.6%. Five out of 84 subjects reached SD for ≥6 weeks, 4 of the 5 subjects were treated at the higher dose level of 15 mg/kg, once every 3 weeks. Nine subjects showed clinical improvement, as judged by the investigator. No objective response (either by RECIST or by investigator assessment) was observed in any of the cohorts. The decision to open the Phase 2 cohorts was made based Hb response observed in Cohort 5. Cohorts 1 through 4 had 5/8 Hb responders, Cohort 5 had 12/17 Hb responders, the Ovarian Cancer Cohort had 7/9 Hb responders, and the *KRAS* Mutant Tumors Cohort had 9 /13 Hb responders.

The median PFS for Phase 1 ranged from 17 days to 131 days. For the Phase 2 Ovarian Cancer and *KRAS* Mutant Tumors Cohorts, the median PFS were 57 days and 59 days, respectively. TTP ranged from 17 days to 131 days for Phase 1 and were 56 days and 59 days in the Phase 2 Ovarian Cancer and *KRAS*

Mutant Tumors Cohorts, respectively. Median OS ranged from 37 days to 268 days for Phase 1 and 335 days to 127 days for the Phase 2 Ovarian Cancer and *KRAS* Mutant Tumors Cohorts, respectively.

PHARMACOKINETIC, PHARMACODYNAMIC, and PHARMACOGENOMIC RESULTS: For subjects in Cohorts 1 and 4, serum concentrations of siltuximab declined in a bi-exponential manner with a mean terminal $t_{1/2}$ ranging from 12.7 days to 19.2 days following the first dose. The mean clearance of siltuximab ranged from 2.97 mL/kg/day to 6.64 mL/kg/day. For the 15 mg/kg and 11 mg/kg dose cohorts, the mean clearance of siltuximab ranged from 2.97 mL/kg/day to 3.54 mL/kg/day. Inter-subject pharmacokinetic variability in terms of CV% following the first dose of 11 mg/kg and 15 mg/kg ranged from 12.3% to 16.7% for C_{max} and ranged from 11.7% to 30.4% for AUC_{∞}.

For subjects in the Expansion Cohort 5, and the Ovarian Cancer and *KRAS* Mutant Tumors Cohorts where siltuximab was administered at a dose of 15 mg/kg every 3 weeks, serum concentrations of siltuximab declined in a bi-exponential manner with a mean terminal $t_{1/2}$ ranging from 15.4 days to 20.0 days following the first dose. The C_{max} and AUC_{∞} were similar among Expansion Cohort 5, and the Ovarian Cancer and *KRAS* Mutant Tumors Cohorts and similar to Cohort 4 of the escalation phase. The mean clearance was similar in each of the cohorts and ranged from 2.92 mL/kg/day to 4.05 mL/kg/day. Inter-subject pharmacokinetic variability in terms of CV% for the cohorts ranged from 19.3% to 26.6% for C_{max} and ranged from 25.5% to 35.6% for AUC_{∞}.

Sustained CRP suppression was observed in all subjects post treatment with CHO-derived siltuximab. Median CRP levels decreased from baseline by 82.09% (Cohort 1; 2.8 mg/kg) to 93.70% in the Phase 1 Cohorts and 91.60% to 93.30% in the Phase 2 cohorts. The median percent decrease in Cohort 3 (11 mg/kg) was 92.96% at Dose 1 Day 8, decreasing up to 98.04% by Dose 1 Day 15, and remained suppressed at the later timepoints including extended treatment and the last timepoint tested (ie, Week 4, post last dose). Similar CRP suppression was observed in subjects dosed with 15 mg/kg every 3 weeks also; with 87.84% to 93.70% median decrease by Dose 1 Day 8. Baseline IL-6 levels were not predictive of the best overall response by RECIST. Decreased hepcidin was observed after siltuximab treatment, with a general trend towards Hb improvement. No evidence of increased systemic inflammation after treatment was observed, as indicated by relatively stable levels of the inflammation associated cytokines tested. Strong and consistent IL-6 network strength-related gene expression changes in pre- and post-treatment samples were not observed.

SAFETY RESULTS: Eighty-four subjects were treated in the study and of these 82 (97.6%) subjects experienced at least 1 or more treatment-emergent AEs and in 37 (44.0%) subjects the events were considered to be reasonably related to siltuximab. More than half of the subjects (59.5%) had 1 or more Grade 3 or higher AE and in 8 (9.5%) subjects the Grade 3 or higher AEs were reported as drug-related. In total, 35 (41.7%) subjects had 1 or more SAEs; only 2 (2.4%) subjects had SAEs reported as drug-related. The most frequently occurring Grade 3 or higher AEs by preferred term reported by ≥5% of treated subjects were hepatic function abnormal (15.5%), fatigue (10.7%), hyperbilirubinaemia and dyspnoea (7.1% for each event). The most frequently occurring SAEs by preferred term reported by ≥5% of treated subjects were generally physical health deterioration (7.1%) and dyspnoea (6.0%). The most frequently reported drug-related Grade 3 or higher AE by preferred term reported by ≥2% of treated subjects was neutropenia (3.6%). Disease progression was the underlying cause of death for 17 subjects who died on study and 1 subject died due to a reasonably related AE of intestinal perforation. Only 6 administrations were given with a dose delay due to AEs. Sixteen (19.0%) subjects experienced 1 or more AEs that led to discontinuation of siltuximab, only 1 subject discontinued treatment due to a drug-related AE. The remaining discontinuations were due to disease progression.

There was an apparent increase in incidence of AEs with increasing dose. However, the sample sizes for the first 4 cohorts were not based on hypothesis testing; therefore there are limitations to data interpretation due to the small sample size. There are no apparent differences in the safety profiles

between 11 mg/kg and 15 mg/kg. No DLTs were observed in the highest dose cohorts. Grade 3 or higher laboratory abnormalities were infrequent and were found for following laboratory evaluations: neutropenia, leukopenia, lymphopenia, bilirubin, and potassium. No grade 4 neutropenia or thrombopenia was reported.

One single DLT of bowel perforation observed in a subject in Cohort 2 (5.5 mg/kg). This subject entered the study with colorectal cancer metastasized to the liver, lung, peritoneum, and adrenal glands. Although the bowel perforation was assessed as probably not related to siltuximab, this could not be definitely excluded at that time. Confounding factors included prior bevacizumab exposure and prior abdominal surgery and abdominal metastases. Cohort 2 was expanded with 3 additional subjects. One additional subject in Cohort 5 developed a bowel perforation. Confounding factors included prior bevacizumab exposure and prior abdominal surgery and abdominal metastases. The protocol was amended to include a longer washout period for prior bevacizumab.

In 17 out of 84 subjects treated with at least 1 dose of siltuximab, 19 out of 303 study agent administrations were given with a dose delay. Six delays were due to AEs and 13 delays for administrative or non-medical reasons. Three low-grade infusion-related reactions were reported in 2 subjects (2.4%). There was no evidence of temperature increase after the infusion, the subjects recovered, and no dose delays occurred. Subject 3403-00625 experienced AEs of chest pain (Grade 1), nausea (Grade 2), and vomiting (Grade 2) and these were reported as infusion related reactions by the investigator. Subject 4403-00710 experienced AEs of infusion site reactions (infusion site pruritus [Grade 1] and infusion site paraesthesia [Grade 1]) as reported by the investigator. These 2 subjects did not have samples for antibodies or serum concentration drawn; therefore any determination for immune response could not be assessed.

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

CONCLUSION(S): In this Phase 1/2 study of CHO-derived siltuximab in subjects with advanced solid tumors (all subjects had metastatic disease), a single DLT was observed in the 5.5 mg/kg cohort, no further DLTs were observed and the maximal tolerated dose was not reached with dosing up to 15 mg/kg. There were no apparent dose related toxicities and no apparent differences in the safety profiles between 11 mg/kg and 15 mg/kg. Though more than half of the subjects (59.5%) had 1 or more Grade 3 or higher AEs, only in 8 (9.5%) subjects these Grade 3 or higher AEs were reported as drug-related. The most frequently reported drug-related Grade 3 or higher AE by preferred term reported by ≥2% of treated subjects was neutropenia (3.6%). Although almost all subjects reported AEs, the majority was within context of and expected for subjects with advanced and heavily pretreated metastatic disease and is consistent with the most commonly included tumor types (eg, ovarian and CRC).

Clinical efficacy was limited, with no objective responses (either by RECIST or investigator assessment) observed in any of the cohorts. In total, 5 out of 84 subjects reached SD for ≥6 weeks; 4 of the 5 subjects were treated at the highest dose level of 15 mg/kg every 3 weeks. The clinical benefit rate observed in all 7 cohorts ranged from 0% to 28.6%. Median OS ranged from 37 days to 268 days for Phase 1, and was 335 days for the Phase 2 Ovarian Cancer cohort and 127 days in the *KRAS* Mutant Tumors cohort.

Sustained CRP suppression was observed after treatment with CHO-derived siltuximab and reduction >90% was observed in the 11 mg/kg and 15 mg/kg dose cohorts. In a cross-study comparison, the pharmacokinetic profile in cancer subjects of CHO-derived siltuximab appears to be similar to the pharmacokinetic profile of Sp2/0 derived siltuximab. A decrease of hepcidin, a marker associated with iron regulation, was observed after siltuximab treatment, with a general trend towards Hb improvement. No evidence of increased systemic inflammation after treatment was observed, as indicated by relatively stable levels of the inflammation associated cytokines tested.

Based on the safety profile (including DLT evaluation and the AE profile), pharmacokinetic profile, and pharmacodynamic assessments (eg, CRP), doses of CHO-derived siltuximab of 11 mg/kg and 15 mg/kg every 3 weeks can be used in future clinical studies.

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