SYNOPSIS

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

Protocol No.: CNTO328SMM1001

Title of Study: A Study of Siltuximab (Anti-IL-6 Monoclonal Antibody) Effects on the QT Interval in Subjects with Monoclonal Gammopathy of Undetermined Significance, Smoldering Multiple Myeloma, or Indolent Multiple Myeloma

EudraCT Number: 2010-018998-37

NCT No.: NCT01219010

Clinical Registry No.: CR017452

Coordinating Investigator:
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Study Centers: Countries and the number of sites within each country where the study was conducted: Belgium (2); Russia (3); United States (US) (3).

Publication (Reference): Not applicable

Study Period:
First subject consented 25 Oct 2010
Last subject visit for the primary analysis 22 May 2012
Data cutoff date 22 May 2012

Phase of Development: Phase 1

Objectives: The primary objective was to determine if siltuximab would have an effect on the QT interval in subjects with monoclonal gammopathy of undetermined significance (MGUS), smoldering multiple myeloma (SMM), or indolent multiple myeloma (IMM).

The secondary objectives were to evaluate the safety, preliminary activity (monoclonal protein [M-protein] response), pharmacokinetics, pharmacodynamics, pharmacokinetic/pharmacodynamic relationships, and immunogenicity of siltuximab in subjects with MGUS, SMM, or IMM.

Methodology: This was a Phase 1, open-label, single-arm, multicenter study of 25 evaluable subjects with MGUS, SMM, or IMM to evaluate the effect of siltuximab on the QT interval.

During the Treatment Period, subjects were to receive siltuximab at a dose of 15 mg/kg every 3 weeks for 4 cycles. At the end of the Treatment Period, subjects who achieved a response (defined as a $\geq$ 50% reduction in M-protein) were eligible to receive extended treatment with siltuximab at a dose of 15 mg/kg every 4 weeks for a maximum of 2 years. Subjects who did not complete electrocardiogram (ECG) assessments at each prespecified timepoint (must have had at least duplicate ECG measurements at each timepoint in Cycle 1 and Cycle 4) or did not receive 4 full doses of siltuximab in the Treatment Period

were to be replaced until 25 subjects were considered evaluable. Subjects in the Extended Treatment Period were not to be replaced.

The sponsor's Medical Monitor and the principal investigators who had enrolled subjects were to assess subject safety on an ongoing basis throughout the study.

ECGs were to be performed with the subject in the same comfortable supine resting position for at least 10 minutes before and after the ECG tracings. The 12-lead ECGs were to be done in triplicate (three 10-second digital EGCs within 5 minutes) using ECG machines provided by the central ECG laboratory. The actual test time should have been consistent for each timepoint for both the screening and on-study ECGs, to minimize variability in the results obtained. Similarly, siltuximab infusions were to be administered at approximately the same time of day in Cycles 1 and 4. All digital ECG tracings were sent to a third-party central ECG laboratory for measurement of intervals, diagnostics of abnormalities, and review of ECG waveform morphology. For the triplicate ECGs collected at each time point, the mean of 3 measurements for each ECG parameter were considered for all listings and statistical analyses.

Number of Subjects (planned and analyzed):
Planned: 25 evaluable subjects.

Analyzed: Of the 49 subjects screened, 33 subjects were eligible for the study. Thirty of the 33 eligible subjects were treated at 8 study centers in Belgium (2 sites), Russia (3 sites) and the US (3 sites), and 27 of these subjects were evaluable for ECG analysis.

Diagnosis and Main Criteria for Inclusion: The study population was to consist of subjects 18 years or older with a diagnosis of MGUS, SMM, or IMM who had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 and a normal baseline ECG. Subjects with symptomatic multiple myeloma or significant cardiac disease, prior exposure to approved or investigational myeloma treatments, or prior exposure to agents targeting interleukin-6 (IL-6) or the IL-6 receptor were to be excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.: Siltuximab is a chimeric (murine-human) IgG_1 kappa monoclonal antibody (mAb) against IL-6. Siltuximab was supplied as a sterile, lyophilized product for intravenous (IV) infusion in single-use vials. Siltuximab concentration was 20 mg/mL upon reconstitution with 5.2 mL sterile water for injection. The formulation consisted of siltuximab with sucrose, histidine, polysorbate 80 at pH 5.2. The study agent was to be administered intravenously at the specified doses and dosing schedule, with an infusion time of 1 hour. Subjects received study agent from the Chinese hamster ovary (CHO)-derived cell line, C1612A (lot numbers 8KS3L00 and ASH0E02).

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

Study Duration:
Screening Period: Up to 3 weeks

Treatment Period: Subjects were to be treated for 4 cycles unless disease progression, unacceptable toxicity, or withdrawal of consent occurred. They were to have an End of Treatment Visit within 4 weeks (± 1 week) after the last siltuximab administration.

Extended Treatment Period: At the end of the Treatment Period, subjects who achieved a response (defined as a ≥ 50% reduction in M-protein) were eligible to receive extended treatment. For subjects completing 1 year of extended treatment, the sponsor must have approved further treatment based on disease evaluation. No subject was to receive more than 2 years of extended treatment. Subjects were to discontinue extended treatment upon disease progression, unacceptable toxicity, withdrawal of consent, or

if the sponsor ends the study, whichever occurred first. They were to have an End of Extended Treatment Visit within 4 weeks (± 1 week) after the last siltuximab administration.

Follow-up Visit: All subjects were to have a follow-up visit 12 weeks after the last siltuximab administration for disease evaluation, and to obtain samples for immunogenicity, serum concentrations of siltuximab, and C-reactive protein (CRP) evaluation.

End of study: The study was to end when all treated subjects had completed their 12-Week follow-up visits.

Criteria for Evaluation:

Safety Evaluations
The primary endpoint was the change in QTc interval (at each measured timepoint) from baseline, where baseline is the QTc measurement before administration of siltuximab on Cycle 1 Day 1.

Other safety endpoints were:

- Incidence of adverse events (AEs) and AEs ≥ Grade 3
- Incidence of serious adverse events (SAEs)
- Incidence of infusion related reactions
- Incidence of clinically significant abnormal laboratory parameters

Efficacy Evaluations
Efficacy endpoints included:

- M-protein response (≥ 50% reduction in M-protein from baseline)
- Minor M-protein response (≥ 25% and < 50% reduction from baseline)

Pharmacokinetic Evaluations
Samples for determining siltuximab serum concentrations were to be obtained from all subjects. Pharmacokinetic parameter endpoints included:

- Minimum observed serum concentration (Cmin)
- Maximum observed serum concentration (Cmax)

Antibodies to Siltuximab
The incidence of antibodies to siltuximab was to be summarized for all subjects who received an administration of siltuximab and had appropriate serum samples for detection of antibodies.

Pharmacodynamic Evaluations
The pharmacodynamic endpoint was change in CRP.

Pharmacokinetic/Pharmacodynamic Evaluations
Pharmacokinetic/pharmacodynamic modeling of the relationship between serum concentrations of siltuximab and change from baseline in QTc interval was performed.

Statistical Methods: Assuming that the intrasubject standard deviation for change from baseline in QTc (ΔQTc) is 20 milliseconds and that the true difference in means is 5 milliseconds, a sample size of 25 evaluable subjects (completers) had 80% power to show that the upper limit of the two-sided 90% confidence interval (1-sided upper 95% confidence interval) for the difference in mean QTc at each timepoint and baseline (preinfusion assessment on Cycle 1 Day 1) was less than 20 milliseconds.

Descriptive statistics were used to summarize data. For continuous parameters, the number of observations, mean, standard deviation, median, and range were used. For discrete parameters, frequency was summarized. When sample sizes were small, sample listings were provided instead.

A mixed-effects analysis of variance (ANOVA) model was fit with QTc as the dependent variable, scheduled timepoint of measurement as the fixed effect, and subject as a random effect. Using the means and intrasubject variance obtained from this model, 2-sided 90% confidence intervals were calculated for the difference in the mean QTc from baseline at each scheduled timepoint. An effect on QTc was ruled out if the upper bound of the 90% confidence interval for the difference in means between the postbaseline QTc (at each timepoint) and preinfusion Cycle 1 Day 1 QTc was less than 20 milliseconds.

A data cutoff, including an analysis of siltuximab serum concentrations, occurred as specified in the protocol; 4 weeks after the last subject received the Cycle 4 siltuximab administration. A safety update, including immune response, is planned to occur 12 weeks after the last siltuximab administration (ie, the last 12-Week follow-up visit).

RESULTS:

STUDY POPULATION:

Of the 30 treated subjects, 28 subjects (93.3%) completed the Treatment Period and 2 subjects (6.7%) discontinued study treatment during the Treatment Period, both due to an AE. Two subjects (6.7%) entered the Extended Treatment Period.

The median age was 59.5 years (range 24 to 79 years). Twice as many female subjects (20 subjects; 66.7%) were enrolled in the study compared with male subjects (10 subjects; 33.3%). All subjects were White, with only 1 subject (3.3%) of Hispanic or Latino ethnicity.

The median number of siltuximab cycles was 4 cycles (range 1 to 17 cycles). Of the 30 treated subjects, 26 subjects (86.7%) received 4 cycles of treatment per protocol, 2 subjects (6.7%) who entered the Extended Treatment Period per protocol received > 4 cycles of treatment, and 2 subjects (6.7%) received < 4 cycles of treatment. Median duration of treatment was 64.0 days (range 1 to 436 days).

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

- The mean Cmax following the first dose (Cycle 1, Day 1) was 343.63 μg/mL and the mean Cmax following the fourth dose (Cycle 4, Day 1) was 460.00 μg/mL.
- The intersubject variability for Cmax expressed as the coefficient of variation was 31.6% for the first dose and 33.7% for the fourth dose.
- The pharmacokinetic profile of siltuximab in subjects with MGUS, SMM, or IMM appears to be similar to that in subjects with solid tumors observed in other studies.
- Sustained decreases in CRP levels were observed posttreatment, reflecting in vivo neutralization of IL-6 activity.

ECG RESULTS:

The QT evaluable population consisted of 27 subjects who completed ECG assessments at each prespecified timepoint in Cycle 1 and Cycle 4 and received 4 full doses of siltuximab in the Treatment Period.

ECG results indicated that:

- The difference in means between the postbaseline QTcF and QTcB (at each timepoint in Cycle 1 and Cycle 4) and preinfusion Cycle 1 Day 1 QTc was less than 20 milliseconds.
- The upper bound of the 90% confidence interval for the difference in means between the postbaseline QTc (at each timepoint in Cycle 1 and Cycle 4) and preinfusion Cycle 1 Day 1 QTc was less than 20 milliseconds; therefore an effect of siltuximab on either QTcF or QTcB can be ruled out.
- None of the 27 QT evaluable subjects showed a > 30 msec change from baseline in either QTcF or QTcB during treatment with siltuximab.
- There were no meaningful changes at any timepoint tested in mean QTcF or QTcB, or in mean change from baseline in QTcF or QTcB.
- The mean PR, QRS, and heart rate remained stable during treatment with siltuximab.
- No clinically significant ECG abnormalities related to siltuximab treatment were observed.
- Pharmacokinetic/pharmacodynamic modeling showed no statistically significant relationships between paired siltuximab serum concentrations and change from baseline in QTcF or QTcB.

SAFETY RESULTS:

- Of the 30 treated subjects, 20 subjects (66.7%) had AEs, 8 subjects (26.7%) had AEs grade 3 or higher (including neutropenia in 3 subjects), 3 subjects (10%) had SAEs, 2 subjects (6.7%) had AEs leading to discontinuation of siltuximab, and no subject had an AE leading to death.
- The most frequently occurring treatment-emergent adverse events (TEAEs) by preferred term were fatigue and nausea (6 subjects each; 20.0%); thrombocytopenia and headache (4 subjects each; 13.3%); and upper respiratory tract infection, leukopenia, neutropenia, paresthesia, dyspnea, and abnormal hepatic function (3 subjects each; 10.0%).
- Three subjects (10%) had SAEs: Grade 3 cellulitis and Grade 3 peripheral edema, Grade 1 peripheral neuropathy, and Grade 2 atrial fibrillation.
- Of the 30 treated subjects, 2 subjects experienced infusion related reactions (1 subject experienced Grade 1 and Grade 2 hypersensitivity reactions, and 1 subject experienced Grade 2 nausea). The infusion related reactions were reversible, and the subjects were able to continue treatment with siltuximab.
- No clinically significant changes in systolic or diastolic blood pressure, body temperature, or body weight were observed during treatment with siltuximab.

EFFICACY RESULTS:

- Of the 30 treated subjects, 3 subjects (10%) had an M-protein response (≥ 50% reduction from baseline) and 9 subjects (30%) had a minor M-protein response (≥ 25% and < 50% reduction from baseline).
- Duration of response for the 3 responders ranged from 71+ to 365+ days, and duration of response for the 9 minor responders ranged from 1+ to 135+ days.
- There was no clinically relevant deterioration in ECOG Performance Status during treatment with siltuximab.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

The results of this study indicate that siltuximab, given at the highest dose level used in clinical studies (15 mg/kg every 3 weeks), did not prolong the QT interval. No clinically significant ECG abnormalities related to siltuximab treatment were observed. Furthermore, siltuximab had an acceptable safety profile in subjects with MGUS, SMM, or IMM. M-protein responses were seen by local laboratory assessment within the first 4 cycles.

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