SYNOPSIS

Name of sponsor/Company	Janssen Research & Development*
Name of Finished Product	Siltuximab
Name of Active Ingredient(s)	CNTO328 (siltuximab)

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Status: Approved

Date: 16 July 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO328MDS2001

Title of Study: A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter Study Comparing Siltuximab Plus Best Supportive Care to Placebo Plus Best Supportive Care in Anemic Subjects with International Prognostic Scoring System Low- or Intermediate-1-Risk Myelodysplastic Syndrome.

EudraCT Number: 2011-000261-12

NCT No.: NCT01513317

Clinical Registry No.: CR100752

Coordinating Investigator: Guillermo Garcia-Manero, MD, MD Anderson Cancer Center - University of Texas, 1515 Holcombe Blvd 0428, Houston, TX 77030, USA

Study Centers: Australia (3), Belgium (4), the Netherlands (2), Spain (7), Sweden (1), Russia (3), and USA (5).

Publication (Reference): None

Study Period: 18 October 2011 to 13 September 2012

Phase of Development: 2

Objectives:

Primary Objective

The primary objective was to assess the clinical efficacy of siltuximab, demonstrated by a reduction in red blood cell (RBC) transfusions to treat the anemia of myelodysplastic syndrome (MDS).

Secondary Objectives

The key secondary objectives were:

- To demonstrate symptomatic improvement of subjects treated with siltuximab compared with the placebo group
- To assess the change in hemoglobin among MDS subjects treated with siltuximab compared with the placebo group

- To compare disease progression (proportion of bone marrow blasts and cytogenetic change) for subjects treated with siltuximab compared with the placebo group
- To assess the safety profile of siltuximab and RBC transfusions among subjects with Low- or intermediate-1 (INT-1)-risk MDS
- To assess the pharmacodynamics, pharmacokinetics, and antibodies to siltuximab (immunogenicity) in MDS subjects
- To investigate a biomarker profile that predicts response to siltuximab in this MDS population.

Hypothesis

A higher proportion of siltuximab-treated subjects would achieve a reduction in RBC transfusions to treat the anemia of MDS, compared with the placebo group.

Methodology: This was a randomized, double-blind, placebo-controlled, multicenter study in subjects with Low- or INT-1-risk MDS who had received a documented RBC transfusion of at least 2 units of RBC for the treatment of the anemia of MDS in the 8 weeks before the date the informed consent form was signed. Approximately 75 subjects were to be randomized in a 2:1 ratio to receive siltuximab + best supportive care (BSC) or placebo + BSC and were stratified for IPSS risk category and history of RBC transfusion for anemia of MDS.

In the treatment period, the study drug was administered in a double-blinded fashion for 12 weeks or until the time of treatment discontinuation, if prior to Week 13. Subjects who completed 12 weeks of treatment could have qualified to enter the second phase of the treatment period and receive open-label siltuximab. Treatment was to continue until death, unacceptable toxicity, withdrawal of consent, or the clinical cutoff (defined as 24 weeks after the last subject was randomized), whichever occurred first. All subjects who discontinued study treatment and who did not withdraw consent from study participation were to have an end of treatment visit (4 weeks after the last study agent administration), and visits at 8 and 12 weeks after the last study agent administration.

The study was monitored by an Independent Data Monitoring Committee (IDMC). The primary purpose of the IDMC was to ensure the safety of the subjects in this study by monitoring safety data. The IDMC reviewed the unblinded safety data after the first 25 and 40 subjects had been treated for 12 weeks and conducted a futility analysis on the efficacy data after the first 40 subjects had been treated for 12 weeks.

Number of Subjects:

Seventy-six subjects were randomized to the study (50 subjects for the siltuximab group and 26 subjects for placebo group).

Diagnosis and Main Criteria for Inclusion: Subjects had to be 18 years or older with a confirmed diagnosis of MDS, according to the World Health Organization (WHO) or French-American British (FAB) pathologic classification, with an International Prognostic Scoring System (IPSS) score 0, 0.5, or 1.0, indicating Low- or INT-1-risk disease. Subjects had to have documented RBC transfusion of at least 2 units of RBC for the treatment of the anemia of MDS in the 8 weeks before the date the informed consent form was signed. Red blood cell transfusions that occurred during the Screening period were not counted towards the number of RBC units considered for study eligibility.

Subjects who had received prior treatment with other agents targeting Interleukin-6 (IL-6) or its receptor, had chronic myelomonocytic leukemia, or had anemia caused by conditions other than MDS were excluded from the study.

Test Product, Dose and Mode of Administration, Batch No.: Siltuximab was supplied as a sterile, lyophilized formulation for reconstitution and intravenous (IV) infusion. The drug product after reconstitution of the lyophile contained siltuximab, histidine, sucrose, and polysorbate-80. Siltuximab was supplied in 2 lots (lot numbers ABS4F00 and BIS1500). Siltuximab (15 mg/kg) was administered as a 1-hour infusion every 4 weeks + BSC.

Reference Therapy, Dose and Mode of Administration, Batch No.: The placebo supplied for this study was supplied as a sterile, lyophilized formulation for reconstitution and IV infusion. The lyophilized placebo after reconstitution contained histidine, sucrose, and polysorbate-80. The lot number for placebo was ABX13016.

Criteria for Evaluation:

Efficacy: Efficacy evaluations included assessments of RBC transfusion, hemoglobin, bone marrow examination, and symptoms.

The primary endpoint was reduction in RBC transfusions to treat the anemia of MDS, defined as a ≥50% relative decrease and a ≥2 unit absolute decrease in RBC transfusions in the 8 weeks before the unblinding (scheduled to occur after 12 weeks of treatment), compared with RBC transfusions in the 8 weeks before the date the informed consent form was signed. The major secondary endpoints included: anemia symptom improvement, number of RBC units transfused to treat the anemia of MDS during the 8-week period before the unblinding, proportion of subjects who did not require a RBC transfusion to treat the anemia of MDS, proportion of subjects achieving hemoglobin improvement (≥1.5 g/dL increase in hemoglobin from baseline) unrelated to RBC transfusion, change in percentage of bone marrow blasts compared with baseline. Treatment failure was defined as a <50% relative decrease or a <2 unit absolute decrease in RBC transfusions to treat the anemia of MDS in the 8 weeks before the unblinding compared with RBC transfusions in the 8 weeks before the date the informed consent form was signed.

Safety: Adverse events (AE) and serious adverse events (SAE) were reported by the subject for the duration of the study. An assessment of severity grade was made using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (Grade 1-4). All SAEs occurring during clinical studies were to be reported to the appropriate sponsor contact person by investigational staff within 24 hours of their knowledge of the event.

All initial reports of pregnancy were to be reported to the sponsor by the investigational staff within 24 hours of their knowledge of the event.

Clinical laboratory analyses included serum chemistry, hematology, lipid panel, iron panel, and coagulation panel. Vital signs (temperature, pulse/heart rate, and blood pressure) were measured prior to study agent administration on Day 1 of each cycle, at the end of infusion on Cycle 1 Day 1, and as clinically indicated. A complete physical examination was required at Cycle 1, Week 13, and then every 24 weeks for subjects who remained on treatment, and the End of Treatment Visit. Weight was to be recorded during the Screening Period, Day 1 of each cycle, and at the End of Treatment Visit.

Pharmacokinetics and Immunogenicity: Venous blood samples were to be collected from all subjects for PK assessments before and immediately after study agent administration on Day 1 of Cycles 1, 4, 6, and 12, at the End of Treatment Visit, and Posttreatment Period Weeks 8 and 12. The PK parameters of siltuximab included minimum observed serum concentration (C_{min}) and maximum observed serum concentration (C_{max}). The detection and characterization of antibodies to siltuximab (immunogenicity) was performed using a validated assay method. Additionally, samples were also to be collected for subjects who experienced an AE suspected to be related to immunogenicity (eg, infusion reactions or hypersensitivity).

Biomarkers: Assessments were to include, but were not limited to, quantification of serum levels of markers such as C-reactive protein (CRP), IL-6, tumor necrosis factor α (TNF-α), bone morphogenetic protein-6 (BMP-6), hepcidin, leptin, and erythropoietin (EPO) at relevant pre and posttreatment time points.

Statistical Methods: Assuming the proportion of subjects who achieved a ≥50% relative decrease and a ≥2 unit absolute decrease in RBC transfusions to treat the anemia of MDS in the 8 weeks before the unblinding (scheduled to occur after 12 weeks of treatment) was 30% for the siltuximab group and 4% for the placebo group, and using a 2:1 randomization, with a sample size of 75 (50 for siltuximab and 25 for placebo), a binomial test based on the normal approximation to the binomial distribution with a 0.05 2-sided significance level had 80% power to detect the difference between the siltuximab group and the placebo group.

The analysis sets included were: intent-to-treat population, per-protocol population, pharmacokinetic evaluable population, antibodies to siltuximab evaluable population, and safety population.

All statistical tests were 2-sided. Testing of the hypothesis was conducted at a 0.05 level. There were no multiple comparison adjustments for any of the secondary analyses. No imputation for missing value was applied for the efficacy endpoints, unless specified otherwise.

All safety analyses were based on safety population.

RESULTS:

STUDY POPULATION: Seventy-six subjects were randomized to the study; 50 subjects to the siltuximab group and 26 subjects to the placebo group. All 76 subjects discontinued study treatment. The primary reason for study discontinuation was treatment failure at Week 13. Twenty-six subjects (34.2%) discontinued due to termination of the study by the sponsor. There were very few discontinuations due to AEs in either treatment group: 3 subjects (6.0%) in the siltuximab group and 2 subjects (7.7%) in the placebo group.

Both treatment groups were balanced in baseline demographic characteristics. The mean platelet count was higher in the siltuximab group (227.6 109/L; standard deviation [SD]: 167.61) compared with the placebo group (179.9 109/L, SD: 132.51

The most commonly used prior MDS therapies (>35% of subjects) were antianemic preparations (69.7%), antineoplastic agents (39.5%), and all other therapeutic products (36.8%). Use of these therapies was similar between the treatment groups. Six subjects (23.1%) in the placebo group and 12 subjects (24.0%) in the siltuximab group had at least 1 major protocol deviation.

The majority of subjects (60 subjects [78.9%]) received 3 cycles of treatment. The median duration of study treatment administration was 12 weeks while the median dose intensity was 15.0 mg/kg/4-week for both treatment groups. The median dose received by the siltuximab group was 3133.5 mg.

EFFICACY RESULTS: The study did not meet the prespecified hypothesis that a higher proportion of siltuximab-treated subjects would achieve a reduction in RBC transfusions to treat the anemia of MDS compared with the placebo group. Six subjects (12%) in the siltuximab group and 1 subject (3.8%) in the placebo group reported reductions in RBC transfusions. This difference was not statistically significant (p=0.271).

At the time of the planned futility analysis, data from the first 40 subjects were analyzed (27 subjects in the siltuximab group and 13 subjects in the placebo group). Only 3 subjects (11.1%) in the siltuximab group reported reductions in RBC transfusions. This observed improvement in 11.1% siltuximab subjects was below the prespecified cut-off criteria of 15% for the efficacy analysis to determine futility, and therefore, upon the recommendation of the IDMC and with concurrence of the Sponsor Committee, the study was terminated early.

There were no clinically relevant changes in the mean hemoglobin concentrations from baseline through Week 13 in either treatment group during the double-blinded treatment phase, or from the end of treatment during the post-treatment period. Five subjects (4 subjects [8.0%]) in the siltuximab group and 1 subject [3.8%] in the placebo group) reported hemoglobin improvement ≥1.5 g/dL unrelated to RBC transfusion at Week 13. The median number of units of RBC transfusions required to treat the anemia of MDS during the 8 weeks before Week 13 unblinding were similar in the 2 treatment groups in subjects who completed Week 13 unblinding. None of the 13 placebo subjects who received open-label siltuximab during the study (median [range] duration of treatment: 13.14 [4.3; 20.1] weeks), reported a reduction in RBC transfusions to treat the anemia of MDS.

SAFETY RESULTS: IDMC reported no safety concerns at any of the scheduled reviews.

The incidence of TEAEs and SAEs was balanced in the 2 treatment groups. Most of the AEs reported in the siltuximab group were mild to moderate in severity

Forty subjects (80.0%) in the siltuximab group and 19 subjects (73.1%) in the placebo group reported 1 or more TEAEs during the double-blinded phase. A slightly higher proportion of subjects reported AEs in the Infections and Infestations system organ class (SOC) in the siltuximab group (30.0%) than in the placebo group (23.1%).

During the double-blinded phase of the study, the most frequently reported AEs were in the Gastrointestinal Disorders SOC. The incidence of thrombocytopenia and neutropenia was low throughout the study and comparable between the 2 treatment groups. One subject from the siltuximab group had Grade 4 thrombocytopenia, which was considered to be very likely related to the study drug, while 1 subject had Grade 4 neutropenia which was considered to be possibly related to the study drug. Two subjects from the placebo group reported neutropenia (1 subject each with Grades 3 and 4 severities).

The incidence of treatment discontinuations due to AE was very low in both groups. A total of 3 subjects from the siltuximab group and 2 subjects from the placebo group reported TEAEs leading to treatment discontinuation. Two subjects enrolled in a site in Russia died during the study (1 in each treatment group). Both subjects had MDS transformation to acute myeloid leukemia (AML). An independent review of the baseline bone marrow biopsies was conducted to confirm eligibility for both subjects, which revealed that the subject treated with siltuximab had erythroleukemia at study entry.

A similar proportion of subjects from both treatment groups reported treatment-emergent SAEs during the double-blinded phase: 10 subjects (20.0%) in the siltuximab group and 7 subjects (26.9%) in the placebo group. A relatively higher proportion of subjects on siltuximab reported SAEs in the Infections and Infestations SOC (7 subjects [14.0%]) as compared with placebo (1 subject [3.8%]). A total of 4 subjects (8.0%) on siltuximab and 1 subject (3.8%) on placebo experienced infusion related reactions, which were mild to moderate in severity (Grade 1 to 3).

There was no particular trend in the change from baseline in the WBC and neutrophil counts between the 2 treatment groups. Mean platelet count decreased in the siltuximab group; however, the mean platelet count remained within the normal range throughout the treatment.

None of the subjects in either treatment group had any abnormal chemistry parameters of Grade 4. Two subjects (3.8% each) in the placebo group had Grade 3 values for alanine aminotransferase (ALT) and aspartate aminotransferase (AST), while Grade 3 values for ALT, bilirubin, and triglycerides were reported in one subject each in the siltuximab group. There was an unexpected increase in serum ferritin in the siltuximab since siltuximab was expected to decrease serum ferritin levels.

There were no trends observed in any vital sign evaluated during any cycle.

PHARMACOKINETIC, IMMUNOGENICITY RESULTS: The mean C_{max} following the first dose (Cycle 1, Day 1) was 261.37 µg/mL and following the fourth dose (Cycle 4, Day 1) was 338.03 µg/mL. The intersubject variability for C_{max} expressed as the coefficient of variation was 26.1% for the first dose. The mean C_{min} prior to the Cycle 4 dose was 82.61 µg/mL.

None of the 48 subjects with evaluable samples in the siltuximab-treated group were positive for antibodies to siltuximab at any of the time points assessed.

BIOMARKERS: Strong, sustained CRP suppression was observed in the siltuximab group and not in the placebo group, indicative of in vivo neutralization of IL-6. A median decrease in CRP from baseline of 86.67% was observed in the siltuximab group compared with a 2.38% decrease in the placebo group at Cycle 2 Day 1. Posttreatment reduction in serum levels of iron-regulatory peptide hormone hepcidin was observed in the siltuximab group (median decrease of 45.83% at Cycle 2 Day 1) and not in the placebo group (median increase of 5.77% at the same time point). There was a large inter-subject variation in CRP and IL-6 observed at baseline, and none of the analytes tested showed any apparent trends predictive of clinical efficacy response.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSIONS:

The IDMC recommended stopping this study early due to lack of efficacy and the Sponsor concurred.

Efficacy:

- Six subjects (12%) in the siltuximab group and 1 subject (3.8%) in the placebo group met the protocol defined definition for reductions in RBC transfusions. This difference was not clinically relevant or statistically significant. No characteristics could be identified that were predictive of response

Safety:

The study treatments were generally well tolerated.

- The frequency of TEAEs, SAEs and TEAEs of Grade ≥3 were similar between the 2 treatment groups. The frequency of TEAEs in the infections and infestations SOC were slightly higher in the siltuximab group than the placebo group, while the frequency of TEAEs in the cardiac disorders SOC were slightly higher in the placebo group than the siltuximab group.
- Dose delays and discontinuations due to AEs were infrequent.

Pharmacokinetics and Immunogenicity:

- The pharmacokinetic profile of siltuximab in MDS appears to be similar to patients with solid tumors and other hematological malignances.
- None of the subjects with evaluable samples in the siltuximab-treated group were positive for antibodies to siltuximab.

Biomarkers:

- A strong, rapid and sustained suppression of CRP was observed in the siltuximab group and not in the placebo group.

Overall Conclusions:

- In conclusion, the study did not meet the prespecified hypothesis that a higher proportion of siltuximab-treated subjects would achieve a reduction in RBC transfusions to treat the anemia of MDS, compared with the placebo group, in transfusion dependent Low and INT-1 risk subjects.

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