SYNOPSIS

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Name of Sponsor/Company	Cougar Biotechnology, Inc.
Name of Finished Product	abiraterone acetate
Name of Active Ingredient(s)	abiraterone acetate, JNJ-212082

Protocol No.: COU-AA-006

Title of Study: A QT/QTc and multi-dose PK Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer

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Study Period: Study start: 06 Jun 2009 (first subject enrolled); last subject enrolled: 29 Oct 2009; Data cutoff: Cycle 2 Day 2; Study database lock: 16 Jul 2010.

Phase of Development: Phase 1b

Objectives: The primary objective of this study was to evaluate effects of abiraterone acetate plus prednisone on cardiac QT/QTc interval by using pharmacokinetic and time-matched ECGs in subjects with metastatic CRPC. The secondary objective of this study was to evaluate the pharmacokinetics of abiraterone acetate and abiraterone after multiple doses of abiraterone acetate.

Methodology: This was a multi-center, open-label, single arm study of abiraterone acetate and prednisone conducted at 4 investigative sites in approximately 34 subjects with metastatic CRPC who failed gonadotrophin releasing hormone (GnRH) therapy and have a PSA $\geq$ 2 ng/mL, who were medically or surgically castrated, and received no more than 1 course of chemotherapy. All subjects were to have received abiraterone acetate 1000 mg daily (QD) as 4 × 250-mg tablets, and undergo time-matched 12-lead ECG and pharmacokinetic sample collection, and also were to have received prednisone 5 mg orally twice a day (BID). Subjects were to receive study treatment (abiraterone acetate plus prednisone) until disease progression. During the follow-up period, survival follow-up were to be collected by a telephonic interview or chart review every 3 months for up to 60 months or until a subject dies, is lost to follow-up, withdraws informed consent, or until abiraterone acetate was commercially available or clinical development was discontinued.

Number of Subjects (planned and analyzed): Total number of subjects planned: 34; number of subjects screened: 43; 33 evaluable subjects were enrolled, treated, and analyzed for QTc, safety, and pharmacokinetics.

Diagnosis and Main Criteria for Inclusion: Medically or surgically castrated male subjects with documented metastatic CRPC who have failed GnRH hormone therapy and have a PSA $\geq$ 2 ng/mL or who have received not more than 1 course of prior chemotherapy, were enrolled in this Phase 1b study.

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate 1000 mg (administered as 4 x 250 mg tablets) was administered orally once daily at least 1 hour before a meal or 2 hours after a meal, plus prednisone 5 mg was administered orally twice daily. Batch numbers for abiraterone acetate: 9405.021, 9405.022, 9405.023.

Duration of Treatment: Treatment was to continue until disease progression or unacceptable toxicity. If subjects had not progressed and were benefiting from the study treatment, they may continue beyond Cycle

12. Survival follow-up was to continue for up to 60 months or until a subject dies, is lost to follow-up, withdraws informed consent, or until abiraterone acetate was commercially available or clinical development was discontinued.

Criteria for Evaluation: The primary endpoint was the mean maximal change in QTc from baseline. The secondary endpoints included: Correlation between measurements of abiraterone acetate pharmacokinetic parameters and time-matched ECG QT interval measurement, proportion of subjects with change from baseline QTc > 30 msecs at any time after first study drug administration, and proportion of subjects with change from baseline QTc > 60 msecs at any time after first study drug administration.

Statistical Methods: All subjects who received study treatment and with sufficient data available for pharmacokinetic parameter estimations are included in pharmacokinetic analysis. All subjects who received study treatment, had the ECG assessment at predose and at least 1 postdose assessment are included in ECG analysis. All subjects who received any part of an abiraterone acetate dose were included in the safety analysis set.

Sample size determination: Based on preliminary results the mean maximal QTcF change from baseline in subjects treated with abiraterone acetate is approximately 7 msecs with a SD of 8.5 msec. Using a two-sided test at the 5% level of significance, a sample size of approximately 34 subjects provides 90% power to detect a QTcF change from baseline > 5 msec.

Pharmacokinetic and ECG Analyses: ECG parameters were evaluated in conjunction with the Pharmacokinetic-Pharmacodynamic findings. To explore any concentration effect relationship, plasma concentrations of drug were plotted against the QTcF for Day 1, Cycles 1 and 2. The data from Cycle 1 Day -1 was plotted as the zero concentration value. Linear mixed models were applied to explore the relationship between plasma concentrations and change in QTcF.

Efficacy Analyses: All efficacy endpoints will be descriptively summarized using the methods above in the Final CSR. These will include: the proportion of subjects with PSA response after 12 weeks, Time to PSA progression, objective radiographic response and overall survival. Efficacy data for this Cycle 2 Day 2 CSR are incomplete and will be summarized in the final report for the study.

Safety Analyses: The safety parameters evaluated through Cycle 2 Day 2 were adverse events, clinical laboratory values, vital sign measurements, physical examination, chest x-rays, and ECOG performance status. The population evaluable for safety included all treated subjects who received any part of an abiraterone acetate dose. Safety data were summarized by incidences (number or percent of subject experiencing an adverse event).

RESULTS:

STUDY POPULATION: Forty-three subjects with metastatic CRPC were screened and 33 subjects were enrolled and treated in this study starting on 06 Jun 2009 though the Cycle 2 Day 2. Subjects were enrolled at 3 sites in the United States (US) and 1 site in Canada. For the total population included in this study, the median age was 65 years. The large majority of subjects enrolled in this study with a baseline ECOG performance status of 0 (26 [79%]), with 7 (21%) subjects starting therapy with an ECOG performance status of 1.

Based on the Sponsor's assessment, 4 subjects (18%; including 4 subjects with inclusion or exclusion criteria violations) had 6 major protocol deviations that included laboratory assessments not completed, a screening ECOG not completed, a site failure to report a serious adverse event within allowed timeframe. One subject did not receive the required LHRHa therapy at the time of enrollment nor was concurrently receiving LHRHa treatment while on study and continued use of prohibited DES therapy while on study.

A high percentage of subjects in this study (32 [97%] subjects) had a drug compliance level of 95 to 100% up to the time of data cutoff at Cycle 2 Day 2. The median abiraterone acetate treatment duration was 4.3 weeks. All 33 subjects enrolled into the study had completed up to Cycle 2 Day 2 at time of data cutoff. All subjects would continue on study treatment until disease progression.

PHARMACOLOGY RESULTS:

Pharmacokinetics: After a single dose of abiraterone acetate systemic exposure, as assessed by C_{max} and AUC_{24h} was 182 ng/mL and at 675 ng*h/mL, respectively.

Systemic exposure values were comparable after multiple dosing on Cycle 1 Day 8 and Cycle 2 Day 1. Mean C_{max} values of 207 ng/mL and 226 ng/mL were observed on Cycle 1 Day 8 and Cycle 2 Day 1, respectively. Mean AUC_{24h} values were estimated at 965 ng*h/mL and 993 ng*h/mL on Cycle 1 Day 8 and Cycle 2 Day 1, respectively. Accumulation after multiple dosing was modest as the mean accumulation ratio (AR) values for C_{max} and AUC_{24h} were 1.8 and 2.0, respectively, on Cycle 1 Day 8. The ARs remained consistent since AR was similar on Cycle 1 Day 8 and Cycle 2 Day 1, 2.0 and 2.2, respectively.

Pharmacodynamics (ECG): The subject population consisted of 33 males with metastatic CRPC ranging from 42 to 85 years old. A total of 3,068 evaluable ECGs were reviewed in this study, out of 3,168 expected ECG extractions. Post-treatment ECGs (Day 1 of Cycles 1 and 2) were time-matched to their corresponding baseline extractions (Cycle 1 Day -1). In addition to the QT and QTcF measurements, ECGs were analyzed for other general abnormalities that might be regarded as clinically significant. In particular, the HR, QRS duration, and the PR interval were analyzed.

The upper bound of the two sided 90% CI for the baseline-adjusted mean change in QTcF duration across all postdose time points were below 10 msecs, the suggested threshold of regulatory concern for non-antiarrhythmic drugs in the ICH-E14 guideline. Data showed that instances of QTcF readings > 450 msecs remained the same during the initial dose, and decreased during steady state. Two subjects have an increase from baseline in QTcF of greater than 30 msecs but less than 60 seconds post-dose

No clinically important changes were seen in the QTcF. As expected, some of the subjects entered the study with higher than normal QTcF values (normal is considered to be 450 msecs or less). Additionally, none of the subjects experienced an overall value greater than 480 msecs. Of the subject population, only two subjects (6.1% of the population) experienced one instance each of a QTcF increase of greater than 30 msecs but less than 60 msecs post-dose. Both instances were not considered clinically significant with 35.7 msecs increase for Subject 299-307, and 34.0 msecs increase for Subject 299-308. None of the subjects experienced an increase in QTcF of greater than 60 msecs.

Changes in HR were examined in this study, as this could reflect toxicity due to autonomic factors such as exaggerated sympathetic response. However, the mean HR changes were minimal and not clinically significant. The PR intervals were examined for prolongation, which could reflect toxicities related to alteration of atrioventricular conduction, as could be seen in varying degrees of atrioventricular block. However, no systematic changes were seen in the PR interval. The QRS durations of subjects were also analyzed for prolongation, which could reflect toxicities manifested as prolongation of intraventricular conduction. The largest mean change in QRS duration was less than 2 msecs. The changes in QRS duration were minimal and considered not clinically meaningful.

Change in baseline QTc versus time profiles indicate that there was no notable increase or decrease in mean QTc values at any measured timepoints. Upon visual inspection, there was a minor difference in mean QTc profile when comparing Cycle 1 and Cycle 2. However, there was no notable trend or significant difference across cycles, considering the wide variability around each mean QTc value.

Pharmacokinetic-Pharmacodynamic Results: The individual change from baseline in QTcF interval and corresponding abiraterone plasma concentrations exhibited no apparent relationship. A linear mixed effects model was fit to the data with change from baseline in QTcF as dependent variable and abiraterone concentration as a predictor and subject as a random effect. The statistical analysis results indicate no significant correlations between the change in QTcF from baseline and plasma concentration (estimated slope was 0.0031 with the associated 90% CI [-0.0040, 0.0102], that includes 0). Similar observation was made upon further examination of individual peak concentrations (C_{max}) and the corresponding change

from baseline in QTcF at individual T_{max} by applying a similar model. No trend was observed between changes from baseline QTc at Cmax across both Cycles.

SAFETY RESULTS: Up to Cycle 2 Day 2, 61% of the subjects had at least 1 treatment-emergent adverse event, 36% were drug-related. One subject (3%) reported a Grade 3 adverse event (no Grade 4 events) and no serious adverse events were reported. No Grade 3 or 4 serious adverse events or drug-related serious adverse events were reported. No adverse events leading to discontinuation of abiraterone acetate therapy were reported and no deaths were reported. The single Grade 3 adverse event was an increase in blood alkaline phosphatase and was considered unrelated to study drug, not serious, and ongoing.

STUDY LIMITATIONS: For this study, a typical Thorough QT design, as per the ICH-E14 guideline, was not used for several reasons. First, a supratherapeutic dose could not be administered to patients because the safety and tolerability of doses exceeding 1000 mg once daily had not been established. Secondly, a placebo arm was not possible due to the ethical issues associated with prolonged dosing of this population with a placebo. Finally, having a positive control arm was not appropriate due to the patients' compromised health state. For these reasons, an Intensive QT design was used, as an alternative design recommended in the ICH E14 guidance.

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