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-BE

Title of Study: A Pharmacokinetics Study to Assess the Oral Administration of CB7630 (abiraterone acetate) Capsule Formulation and Tablet Formulation in Patients with Prostate Cancer

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Publication (Reference): None

Study Period: 11 June 2007 to 22 January 2010

Phase of Development: 1

Objectives: The primary objective of this study was to evaluate the pharmacokinetics of abiraterone acetate administered in capsule formulation with that in tablet formulation under fasted and fed conditions in subjects with prostate cancer.

Secondary objectives were to: 1) evaluate safety and tolerability of daily administration of abiraterone acetate tablet; 2) assess antitumor activities of daily administration of abiraterone acetate tablet; and 3) evaluate the role of circulating tumor cell (CTC) enumeration (optional) and tumor characterization (optional) in the assessment of prognosis and treatment response in the study population.

The main purpose of this abbreviated study report is to present the safety and tolerability data of abiraterone acetate in this study up to 22 January 2010.

Methodology: This was a Phase 1 multi-center, open-label, 2–arm study with a 4-stage design to evaluate the pharmacokinetics of abiraterone acetate administered in a capsule formulation and in a tablet formulation under fed and fasted conditions in subjects with adenocarcinoma of the prostate. Eligible subjects were enrolled sequentially alternating between Arms 1 (fed) and 2 (fasted). The study had a screening period of 14 days prior to Day 1 of Stage I. Stage I was a single dose pharmacokinetic study, with a cross-over design for comparison of capsules and tablets and parallel design for comparison of fed versus fasting. In Group 1, subjects received capsules (four 250 mg capsules of abiraterone acetate) on Day 1 and tablets (four 250 mg tablets of abiraterone acetate) on Day 8 and in Group 2, subjects received tablets on Day 1 and capsules on Day 8 under fed (Arm 1) condition. A similar design was used for subjects under fasted condition (Arm 2). Fasted condition was defined as an overnight fast for at least 10 hours and continued fast for 4 hours after drug administration. Fed condition was defined as an overnight fast followed by a meal of 800 to 1000 calories within approximately 30 minutes before drug administration and continued fast for 4 hours. Stage II was a daily dose study of abiraterone acetate tablets (four 250 mg tablets) under fed versus fasted conditions. Subjects were to receive daily doses of abiraterone

acetate under fed or fasted conditions until disease progression, death, or availability of abiraterone acetate through healthcare provider(s) or the development program ceased. Fasted condition was defined as an overnight fast and study drug administration 1 hour before or 2 hours after a meal. Fed condition was defined as a normal breakfast in the morning or a meal during the day followed by study drug administration. Stage III and Stage IV were conducted to evaluate safety and to measure antitumor activity of the abiraterone acetate tablets (four 250 mg tablets) under fasted condition. Subjects who had completed 12 cycles of abiraterone acetate in Stage III and continued to receive clinical benefit were to enter Stage IV for additional 12 cycles (total 24 cycles). Each cycle was of 28±7 days. Subjects in Stage III and Stage IV were concurrently taking prednisolone/prednisone 5 mg twice daily or dexamethasone 0.5 mg once daily. After the end of the study visit, subjects were to be followed up every 3 months for disease progression and survival for up to 3 years.

Number of Subjects (planned and analyzed): Planned: Twelve to 20 subjects for the crossover bioavailability study were to be enrolled into each of the 2 arms (6 to 10 per group) for Stage I, and consequently a total of 24 to 40 subjects were to be enrolled in the study. Analyzed: Of the 33 subjects enrolled in the study, 31 received at least 1 dose of abiraterone acetate and comprised the safety analysis set. Twenty-nine subjects met criteria for prostate specific antigen (PSA) evaluations (ie, had baseline and at least 1 post-baseline PSA assessment) and comprised the PSA-evaluable population used to determine the antitumor activity of abiraterone acetate.

Diagnosis and Main Criteria for Inclusion: Men with adenocarcinoma of the prostate undergoing androgen deprivation therapy and with serum testosterone levels of less than 50 ng/dL were eligible for this study. Eastern Cooperative Oncology Group (ECOG) performance status had to be less than 2 (or Karnofsky Performance Status of greater than or equal to 50%). Subjects were not to receive radiotherapy, chemotherapy, or immunotherapy within 30 days of administration of study drug, and toxicities related to prior chemotherapy and radiotherapy had to resolve to a National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, Version 3.0) Grade 1 or less. Subjects with adrenal insufficiency or hyperaldosteronism were excluded from the study. Subjects with New York Heart Association (NYHA) classification of III or IV heart disease or with any other medical conditions that could interfere with their participation in the study were excluded.

Test Product, Dose and Mode of Administration, Batch No.: Abitraterone acetate 250 mg (batch numbers: 0079C, A06490, 9405.001, 9405.003, 9405.004, and 9405.006) was supplied as tablets and capsules for oral administration. Subjects received abiraterone acetate 1000 mg (4×250 mg as capsules or tablets) once daily. Starting with Stage III, oral dosing with prednisone/prednisolone 5 mg twice daily or dexamethasone 0.5 mg once daily was initiated. Commercially available prednisone/prednisolone and dexamethasone were used.

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

Duration of Treatment: In Stage I, Group 1 subjects received abiraterone acetate (1000 mg) as capsules (4x250 mg) on Day 1 and as tablets (4x250 mg) on Day 8, and Group 2 subjects received the same dose as tablets on Day 1 and as capsules on Day 8 under fed (Arm 1) condition. A similar design was used for subjects under fasted condition (Arm 2). In Stage II, subjects received daily doses of abiraterone acetate (1000 mg) as tablets (4x250 mg) under fed versus fasted condition. In Stages III and IV, subjects received 12 cycles each (28±7 days/cycle) of abiraterone acetate (1000 mg once daily, total of 24 cycles) under fasted condition.

Criteria for Evaluation: Pharmacokinetics: For the determination of plasma concentrations of abiraterone acetate and abiraterone, blood samples were taken during Stage I on Days 1 and 8 (capsules/tablets versus tablets/capsules) under fed (Arm 1) and fasting (Arm 2) conditions. Blood samples were taken predose and 1, 2, 4, 6, 8, 24, 48 and 72 hrs postdose. Efficacy: The antitumor activities of abiraterone acetate were evaluated by measuring PSA. Prostate specific antigen response rates, time to PSA response, and time to PSA progression were analyzed in subjects with baseline and at least 1 post-baseline PSA measurement. Eastern Cooperative Oncology Group (ECOG) performance status was also measured. Optional efficacy parameters included CTC enumeration and tumor characterization. Safety: Safety and tolerability were evaluated by assessment of adverse events, clinical laboratory tests (hematology, chemistry, and

urinalysis), vital sign measurements (pulse and blood pressure), physical examination, 12-lead electrocardiograms (ECGs), and tumor imaging (chest X-ray, computed tomography scan or magnetic resonance imaging) and bone scans.

Statistical Methods: Sample size determination: No formal justification for the sample size was performed. Pharmacokinetics: The bioavailability of both formulations of abiraterone acetate was based upon the 90% confidence intervals (CIs) of the relative means (tablet or capsule) of back-transformed values of area under the curve (AUC) and maximum concentration (C_{max}). Both formulations were to be considered equivalent if the 90% confidence limits were within a 0.80 to 1.25 range (80% to 125%) for AUC and within a 0.75 to 1.33 range (75% to 133%) for other parameters. Efficacy: All CIs for the estimations were reported using 2-sided 95% CIs, unless otherwise specified. Continuous endpoints were summarized using descriptive statistics, which included the number of subjects with a valid measurement (n), mean, standard deviation, median, and range. Descriptive statistics were used to summarize CTC enumeration and tumor characterization. Binary and multinomial endpoints were summarized using frequencies and percentages. Percentages were calculated by dividing the number of subjects with the characteristic of interest by the number of subjects in the analysis population. The exact (Clopper-Pearson) 95% confidence limits were provided for the PSA response rate estimate. A waterfall graph was produced for the maximal PSA decline. The Kaplan-Meier product-limit method was used to estimate the median time-to-PSA progression. The corresponding 95% CI for the median time-to-PSA progression estimate was calculated. ECOG performance status was summarized using descriptive statistics. Safety: The safety of abiraterone acetate was evaluated from the signing of the informed consent through post-treatment (ie, 30 days after the last dose of abiraterone acetate) by examining the incidence, severity, relationship to study medication, and type of adverse events; changes in clinical laboratory test results, physical examination and vital sign measurements; concomitant medication/therapy; 12-lead ECGs; and tumor images and bone scans. Data were summarized using descriptive statistics.

RESULTS:

STUDY POPULATION: Thirty-three subjects were enrolled in this study, and 31 subjects were treated with abiraterone acetate. All subjects had adenocarcinoma of the prostate, and the most common site of metastasis was bone (71%). The median age of the study population was 70 years. All treated subjects (31 [100%]) received prior androgen deprivation therapy for prostate cancer as mandated by the protocol. Of these, 30 subjects (97%) received luteinizing-hormone-releasing hormone. Twenty-four (77%) subjects had prior radiotherapy, and 20 (65%) subjects had prior chemotherapy for the treatment of prostate cancer with most (55%) subjects receiving prior docetaxel therapy.

PHARMACOKINETIC RESULTS: Significant increases in drug exposures (AUC_{last}) and maximum drug concentrations (C_{max}) were observed when abiraterone acetate was administered concomitantly with food, in comparison with the fasting state, for both the capsule and tablet formulations. Under fed conditions, tablets and capsules resulted in similar, but not equivalent, exposures to abiraterone. Likewise, under fasted conditions, tablets and capsules resulted in similar, but not equivalent, exposures. However, the highly variable results preclude definitive conclusions. In addition, disposition of the study drug was similar with tablets and capsules under fed and fasted conditions.

EFFICACY RESULTS: Antitumor activity was assessed on the basis of declines in PSA levels post-baseline. A decline in PSA levels of 50% or greater was confirmed in 48% of PSA evaluable subjects. The median time to PSA response was 1.4 months (43 days; 95% CI: 38.00, 48.00), and the median duration of response was 7.4 months (225 days). The median time to PSA progression was 8.7 months (264 days). Optional secondary endpoints, CTC enumeration and tumor characterization, were not evaluated.

SAFETY RESULTS: The median duration of treatment with abiraterone acetate was 23.3 weeks (5.4 months), and the longest treatment duration was 94 weeks. Ninety percent of subjects discontinued from treatment at the cut-off date. The primary reason for discontinuation of treatment was reported as progressive disease (58%).

The most frequently reported treatment-emergent adverse events were nausea (32%, all with a severity of Grade 1 or 2) followed by hypokalemia (23%; 6 subjects with a severity Grade 1, 1 with a severity Grade 4, and 1 with a severity Grade 5) and arthralgia (23%, all with a severity of Grade 1 or 2). The majority of abiraterone acetate treated-subjects (74%) experienced at least 1 drug-related treatment-emergent adverse event. Hypokalemia (23%), increased blood pressure (16%), nausea (10%), fatigue (10%), and lethargy (10%) were the most common drug-related adverse events reported; hypokalemia and increased blood pressure are known mineralocorticoid-related toxicities. Grade 3 or 4 treatment-emergent adverse events were reported by 19% of subjects; spinal cord compression was reported by 2 (6%) subjects, and all other Grade 3 or 4 adverse events (by preferred term) were reported by no more than 1 subject.

Two subjects died within 30 days of the last dose of abiraterone acetate. One subject died of a cardiac arrest that was assessed by the investigator as unrelated to the study medication. The second subject experienced a serious Grade 5 adverse event of hypokalemia and died. The Grade 5 hypokalemia was assessed by the investigator as probably related to the study medication. In response to the Grade 5 hypokalemia, the following changes in study conduct were implemented: 1) Treatment with prednisolone/prednisone 5 mg twice daily or dexamethasone 0.5 mg once daily was initiated; 2) Potassium supplementation was initiated when serum potassium levels were 3.5 mM or lower. Treatment included the intravenous administration of potassium when serum potassium levels were less than 3.0 mM.; 3) Frequent monitoring of electrolytes was initiated; and 4) Cardiac monitoring was initiated for subjects with serum potassium levels less than 3.0 mM.

Treatment-emergent serious adverse events were reported in 29% of abiraterone acetate-treated subjects. Of these, 1 subject experienced a Grade 4 serious adverse event of hypokalemia. In addition, 1 subject experienced a Grade 5 serious adverse event of hypokalemia (as noted above). Four (13%) subjects reported adverse events leading to discontinuation of study treatment. No subject discontinued study treatment due to a drug-related adverse event.

Sixty-eight percent of subjects reported treatment-emergent adverse events of special interest (ie, adverse events related to the known pharmacologic mechanism of action of abiraterone acetate which leads to mineralocorticoid excess [eg, hypokalemia, hypertension, fluid retention/edema, etc.] as well as adverse event related to liver function abnormalities and cardiac disorders). The most commonly reported treatment-emergent adverse events of special interest were hypokalemia (23%), increased blood pressure (16%), fluid retention (10%), and edema peripheral (10%). The majority of these treatment-emergent adverse events of special interest were Grade 1 or 2 severity events.

With the exception of alkaline phosphatase, few (2 or less) subjects experienced Grade 3 or 4 chemistry abnormalities. Five subjects had vital sign abnormalities reported (change in pulse rate and/or blood pressure).

STUDY LIMITATIONS: The pharmacokinetic variability of abiraterone acetate and the small number of subjects evaluated are the known limitations of this study.

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