SYNOPSIS

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Name of Sponsor/Company	Cougar Biotechnology, Inc.
Name of Finished Product	Not applicable
Name of Active Ingredient(s)	Abiraterone acetate (JNJ-212082)

Protocol No.: COU-AA-015

Title of Study: An Abiraterone Acetate Plus Prednisone Drug-Drug Interaction Study with Dextromethorphan and Theophylline in Patients with Metastatic Castration-Resistant Prostate Cancer

Study Name: COU-AA-015

NCT No.: NCT 01017939

Principal Investigators:

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Study Center(s):

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- Tower Cancer Research Foundation, 9090 Wilshire Blvd, Suite 200, Beverly Hills, CA 90211
- South Texas Accelerated Research Therapeutics, LLC, 4383 Medical Drive, 4th Floor, San Antonio, TX 78229

Publication (Reference): Not applicable

Study Period: The study was initiated on 2 February 2010. The database freeze occurred on 12 August 2010.

Phase of Development: Phase 1b

Objectives:

Primary Objectives

- To evaluate the effects of multiple doses of abiraterone acetate plus prednisone on the pharmacokinetics of a single dose of dextromethorphan HBr in patients with metastatic castration-resistant prostate cancer (CRPC)
- To evaluate the effects of multiple doses of abiraterone acetate plus prednisone on the pharmacokinetics of a single dose of theophylline in patients with metastatic castration-resistant prostate cancer (CRPC)

Secondary objective

- To assess safety

Methodology: This was a multicenter, open–label, drug-drug interaction study of abiraterone acetate and prednisone in subjects with metastatic CRPC who were medically or surgically castrated. The protocol defined 2 groups:

- Group A assessed the effect of multiple doses of abiraterone acetate plus prednisone on CYP2D6 using dextromethorphan HBr as a probe drug (only on extensive metabolizers as determined by genomic testing)
- Group B assessed the effect of multiple doses of abiraterone acetate plus prednisone on CYP1A2 using theophylline as a probe drug on those who did not test as extensive metabolizers for CYP2D6

Number of Subjects (planned and analyzed): The planned enrollment was 37 subjects. The total number of subjects enrolled were 34: 18 in Group A (dextromethorphan) and 16 in Group B (theophylline).

Diagnosis and Main Criteria for Inclusion: Subjects with metastatic CRPC who were medically or surgically castrated.

Test Product, Dose and Mode of Administration, Batch No.: Subjects were instructed to take four 250 mg tablets of abiraterone acetate orally (PO) at least 1 hour before a meal or 2 hours after a meal. The abiraterone acetate supply used in the study was from Lot Number 9405.028. Subjects in Group A received 2 single doses of dextromethorphan HBr (30 mg): one on Cycle 1 Day -8 and one on Cycle 1 Day 8 under fasting conditions (no food intake for at least 8 hours prior to dosing). Subjects in Group B received 2 single doses of theophylline (100 mg): one on Cycle 1 Day -8 and one on Cycle 1 Day 8 under fasting conditions (no food intake for at least 8 hours prior to dosing).

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

Duration of Treatment: Abiraterone acetate and prednisone were taken daily, starting on Cycle 1 Day 1, and continuing until disease progression. Dextromethorphan (Group A) and theophylline (Group B) were administered as 2 single doses, one on Cycle 1 Day -8 and one on Cycle 1 Day 8.

Criteria for Evaluation:

Pharmacokinetic Evaluations: For each subject, the following pharmacokinetic parameters of dextromethorphan (parent) and dextrorphan (metabolite) (Group A) or theophylline (Group B), were calculated, whenever possible, by non-compartmental methods using WinNonlin Version 5.0 or higher: C_{max}, t_{max}, AUC_{24}, AUC_{last}, AUC_{∞}, λ_z, and $t_{1/2}$. In addition, C_{max}, AUC_{24}, AUC_{last}, and AUC_{∞} were calculated for the ratio of dextromethorphan (parent) and dextrorphan (metabolite), in Group A.

Safety Evaluations: Safety was evaluated by adverse events, clinical laboratory testing, ECGs, and vital signs and physical examinations. All observed or volunteered adverse events were recorded on the adverse event page(s) of the CRF. The incidences of treatment-emergent adverse events (TEAEs), drug-related TEAEs, and treatment-emergent serious adverse events were summarized by system organ class (SOC), preferred term (PT), and by NCI CTCAE toxicity grade. All TEAEs were analyzed in the following 3 periods:

- Period 1: Cycle 1 Day -8 to Cycle 1 Day 1; treatment = probe drug
- Period 2: Cycle 1 Day 1 to Cycle 1 Day 8; treatment = abiraterone acetate + prednisone
- Period 3: Cycle 1 Day 8 to Cycle 1 Day 15; treatment = abiraterone acetate + prednisone + probe drug.

Statistical Methods: Statistical analysis was performed using Statistical Analysis Software (SAS®) Version 9.1 or greater. All continuous endpoints were summarized using descriptive statistics which included the number of subjects, mean, standard deviation, median, minimum, and maximum. All categorical endpoints were summarized using frequencies and percentages.

For Group A, the PK evaluation of drug-drug interaction was based on the ratio of mean PK parameters (C_{max} and AUCs) of dextromethorphan, dextrorphan and parent/metabolite with and without co-administration of abiraterone acetate and prednisone, and 90% confidence intervals for the ratio of means

was estimated using the least square means and intra-subject coefficient of variance from a mixed effects modeling of log-transformed PK parameters.

For Group B, all subjects with at least one PK parameter estimate of theophylline were included in descriptive statistics. The estimation of the ratio of mean theophylline PK parameters with and without co-administration of abiraterone acetate and prednisone was based on the ratio of mean PK parameters (C_{max} and AUCs) of theophylline with and without co-administration of abiraterone acetate and prednisone and 90% confidence intervals for the ratio of means was estimated using the least square means and intra-subject coefficient of variance from a mixed effects modeling of log-transformed PK parameters.

RESULTS:

Study Population

Thirty-four subjects participated in Study COU-AA-015, 18 subjects in Group A (dextromethorphan) and 16 subjects in Group B (theophylline). No subject discontinued from the study. The majority of subjects were white (94%) in both groups combined. The median age of the subjects, in both groups combined, was 70 years (range 44 to 81 years).

Pharmacokinetic Results

Mean systemic exposure to dextromethorphan was approximately 100% higher when dextromethorphan was co-administered with abiraterone acetate. The median t_{max} and mean $t_{1/2}$ of dextromethorphan were comparable, suggesting that the disposition characteristics between treatments are similar. For dextrorphan, the active metabolite of dextromethorphan, the mean C_{max} values were similar whereas AUC values were approximately 33% higher when dextromethorphan was co-administered with abiraterone acetate. The median t_{max} and mean $t_{1/2}$ of dextrorphan were comparable. The ratio of dextromethorphan/dextrorphan exposure parameters was similar to that observed for dextrorphan (approximately 33% increase in exposure).

Mean systemic exposure to theophylline was similar when theophylline was co-administered with abiraterone acetate and when administered alone. The median t_{max} and mean $t_{1/2}$ of theophylline were comparable. Additional analysis of baseline-adjusted theophylline data was performed due to unexpected observation of pre-dose theophylline concentrations (5.03 ng/mL to 2020 ng/mL) for all patients in at least one treatment period. The results from this additional analysis were similar to the planned analysis.

Safety Results:

In both groups, majority of the TEAEs were of Grades 1 or 2. Drug related TEAEs occurred in both groups (4 subjects in Group A and 5 subjects in Group B). There were no reports of drug-related TEAEs of Grade 3 or 4 severity for either Group A or Group B. Serious adverse events, deaths, and discontinuations due to adverse events were not reported for any subject in either group. Adverse events of special interest occurred in both groups. One of the 4 subjects during Period 3 in Group B experienced a Grade 3 increased alkaline phosphatase.

Study Limitations:

No notable study limitations were identified by the Sponsor.

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