

**Janssen Research & Development**

**Clinical Study Report  
Protocol COU-AA-301; Phase 3**

**JNJ-212082 (abiraterone acetate)**

**Redaction and Removal of Information in This Document**

- Information (including individual data listings, where applicable) has been removed or redacted to protect the privacy of patients, study subjects, and all named persons associated with the study.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

---

**Confidentiality Statement**

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you that is indicated as *privileged* or *confidential*.

## SYNOPSIS

**Issue Date:** 02 December 2010

**Document No.:** EDMS-ERI-19095535

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

**Protocol No.:** COU-AA-301

**Title of Study:** A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

**EudraCT Number:** 2007-005837-13

**Clinical Registry Number:** NCT-00638690

**Coordinating Investigators:** [REDACTED] M.D., Ph.D., M.B.Ch.B., [REDACTED]  
[REDACTED] UK; [REDACTED] M.D. [REDACTED]  
[REDACTED] USA.

**Publication (Reference):** None

**Study Period:** Study start: 8 May 2008 (first subject enrolled); Last subject enrolled: 28 July 2009; Study clinical cutoff: 22 January 2010.

**Phase of Development:** 3

**Objectives:** The primary objective of the study was to demonstrate that treatment with abiraterone acetate improves survival among men with metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed on or after 1 or 2 chemotherapy regimens, one of which contained the taxane docetaxel. Secondary objectives were to further evaluate the safety profile of abiraterone acetate and prednisone, further characterize the pharmacokinetics of abiraterone acetate when administered concurrently with prednisone, further explore the potential utility of circulating tumor cells (CTCs) as a surrogate for clinical benefit, and to evaluate the impact of abiraterone acetate and prednisone on functional status and symptom measures.

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints were time to prostate-specific antigen (PSA) progression, radiographic progression-free survival (rPFS), and PSA response rate. Other endpoints included objective tumor response, proportion of subjects experiencing pain palliation, time to pain progression, time to first skeletal-related event, modified progression-free survival based on criteria for discontinuation of study treatment, proportion of patients achieving a decline in CTCs/7.5mL to <5, and functional status and symptom measures (total score and each subscale as assessed by Functional Assessment of Cancer Therapy-Prostate [FACT-P]).

**Methods:** This was a Phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study conducted at 147 sites in the United States (U.S.), Europe, Australia, and Canada comparing the efficacy and safety of abiraterone acetate and prednisone with placebo and prednisone to treat men with mCRPC whose disease had progressed on or after 1 or 2 chemotherapy regimens, one of which contained the taxane docetaxel. Planned enrollment was approximately 1,158 subjects. Subjects were stratified according to baseline Eastern Cooperative Oncology Group (ECOG) performance status score (0-1 versus 2), worst pain over the past 24 hours on the Brief Pain Inventory - Short Form (BPI-SF) (0-3 [absent] versus 4-10 [present]), 1 versus 2 prior chemotherapy regimens, and type of progression (PSA progression only versus radiographic progression with or without PSA progression) and were then randomly assigned in a 2:1 ratio to receive abiraterone acetate and prednisone or placebo and prednisone, respectively. Eligible

subjects received abiraterone acetate 1 g (administered as 4 x 250-mg tablets) once daily continuously or 4 matching placebo tablets orally once daily continuously at least 1 hour before or 2 hours after a meal, and prednisone 5 mg orally twice daily. In regions where prednisone was not marketed, prednisolone 5 mg orally twice daily was provided. While treatment was administered on a continuous schedule, each cycle of treatment was 28 days. The study consisted of a screening period (within 14 days prior to Cycle 1 Day 1), treatment period (until documented disease progression or unacceptable toxicity), and a follow-up period (follow up for survival every 3 months up to 60 months [5 years]). Safety and dosing compliance were evaluated during the Cycle 1 Day 15 visit, on Day 1 of each subsequent cycle, at treatment discontinuation if applicable, and at the end-of-study visit. In addition, approximately 150 to 200 subjects were scheduled to be enrolled at selected sites for the pharmacokinetic assessment, with approximately 100 to 133 of these subjects in the group that was assigned to receive abiraterone acetate. An Independent Data Monitoring Committee (IDMC) was formed to monitor the safety at regular intervals, and to evaluate efficacy and safety results at the time of the interim analysis. One interim analysis of OS was to be conducted after approximately 534 death events were observed (67% of 797 total events) and the planned final analysis was to occur after 797 total deaths. The IDMC review is further described in the RESULTS section below.

**Number of Subjects (planned and analyzed):**

Subjects planned: 1,158 subjects (772 subjects: abiraterone acetate; 386 subjects: placebo).

Subjects randomized: 1,195 subjects (797 subjects: abiraterone acetate; 398 subjects: placebo).

Subjects analyzed: Intent-to-treat (ITT)/efficacy population: 1,195 subjects; safety population: 1,185 subjects.

**Diagnosis and Main Criteria for Inclusion:** Eligible subjects included consenting men (at least 18 years of age) with histologically- or cytologically-confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology. Subjects were required to have at least 1 but not more than 2 different cytotoxic chemotherapy regimens for mCRPC (one of which must have contained docetaxel). Subjects were to have documented prostate cancer progression, as assessed by the investigator, with 1 of the following: PSA progression according to Prostate-specific Antigen Working Group criteria or radiographic progression in soft tissue or bone with or without PSA progression. Subjects were included if they had ongoing androgen deprivation with serum testosterone <50 ng/dL (<2.0 nM); an ECOG performance status score of 2 or less; and hematology and chemistry laboratory test concentrations that met predefined criteria. Subjects were excluded if they had serious or uncontrolled co-existent non-malignant disease (including active and uncontrolled infection); abnormal liver transaminase test concentrations (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] <2.5 x upper limit of normal [ULN] permitted, AST or ALT ≤5 x ULN permitted for subjects with known liver metastasis); uncontrolled hypertension; active or symptomatic viral hepatitis or chronic liver disease; history of pituitary or adrenal dysfunction; clinically significant heart disease; prior therapy with abiraterone acetate or other CYP17 inhibitor(s), or investigational agent(s) targeting the androgen receptor (AR); prior therapy with ketoconazole for prostate cancer; or medical condition or comorbidity that could have interfered with their participation in the study.

**Test Product, Dose and Mode of Administration, Batch No.:** Abiraterone acetate, 1 g/day (4 x 250-mg tablets) given orally; batch numbers: 9405.008, 9405.009, 9405.010, 9405.011, 9405.012, 9405.013A, 9405.016, 9405.019, 9405.020, 9405.024, 9405.025, 9405.028, R0304001, C1641001.

**Reference Therapy, Dose and Mode of Administration, Batch No.:** Placebo for abiraterone acetate 250-mg tablets matching abiraterone acetate tablets in size, color, and shape; batch numbers: 9410.001, 9410.004, and C1693001.

**Duration of Treatment:** Subjects were to receive treatment until documented disease progression. In this study, disease progression was defined as having 1) radiographic progression, 2) PSA progression, and 3) clinical progression. Study treatment could be discontinued in the event of unacceptable toxicity or for initiation of new antitumor therapy at the discretion of the investigator, for dosing noncompliance, subject choice, or for administration of prohibited medications.

**Criteria for Evaluation:** Efficacy assessments included: PSA concentrations to assess PSA response rate and time to PSA progression, radiographic imaging to assess tumor response and PFS, skeletal-related

events, BPI-SF and analgesic usage score to assess the number of subjects experiencing pain palliation, and time to pain progression. Safety assessments included medical history; vital sign measurements; body weight; physical examination; review of concomitant therapy and procedures; review of adverse events (AEs) and serious adverse events (SAEs), including laboratory test AEs; serum chemistry, hematology, and coagulation and serum lipids studies; urinalysis; electrocardiograms (ECG) findings; and measurement of cardiac ejection fraction. Other assessments included functional status using FACT-P questionnaire; fatigue evaluated by the Brief Fatigue Inventory (BFI) instrument; medical resource utilization (MRU) information; and CTC enumeration. Pharmacokinetic and additional ECG assessments were to be performed on approximately 150 to 200 subjects at selected study centers; these data will be summarized in a separate report.

**Statistical Methods:** The planned sample size of approximately 1,158 subjects (772 subjects: abiraterone acetate; 386 subjects: placebo) provided 85% power to detect a 20% decrease in the risk of death for the abiraterone acetate-treated group (hazard ratio [HR]=0.80). This sample size was calculated by assuming the following: a median survival of 15 months for the abiraterone acetate group and a median survival of 12 months for the placebo group; a 2-tailed significance level of 0.05; an enrollment period of approximately 13 months; and a study duration of approximately 30 months to observe the required 797 total events. One interim analysis and 1 final analysis were planned for the study using group sequential design. Distributions of time-to-event variables and associated 95% confidence intervals (CI) were analyzed using Kaplan-Meier estimates of survival distributions. The stratified log-rank test was used as the primary analysis for treatment comparison. Prostate-specific antigen or radiographic response rate was defined as the proportion of subjects fulfilling the respective criteria for response. The relative risk (treatment:control) was reported along with the associated 95% CI. Statistical inference was evaluated using the Chi-square statistic; the Fisher's exact test was used if the expected counts in some cells were small. Sensitivity analyses for OS using the non-stratified log-rank test and Cox proportional hazards model were also performed as supportive analyses. Subgroup analyses were carried out to assess whether or not treatment effects were consistent across the subgroups evaluated.

## **RESULTS:**

**IDMC REVIEW OF INTERIM EFFICACY AND SAFETY RESULTS:** A protocol-specified interim analysis of OS was to be conducted after approximately 534 death events were observed (67% of 797 total events). Clinical cutoff for the interim analysis was reached on 22 January 2010, at which time 552 deaths had been observed. The database was locked on 11 August 2010 for the IDMC review of efficacy and safety. On 20 August 2010, the IDMC met to review the efficacy and safety results of the interim analysis. The IDMC indicated that there were no major safety concerns that would warrant a change in study management. Upon review of the efficacy data, the IDMC concluded that the prespecified efficacy boundary had been crossed, based on 552 death events observed at the time of analysis (nominal alpha level, 0.0141), and that there was significant benefit in OS for subjects receiving abiraterone acetate and prednisone/prednisolone. Based on these recommendations by the IDMC, the blinded portion of the study was terminated. The study protocol was then amended to allow subjects in the placebo group who were either still participating in the treatment phase or were in the long-term survival follow-up phase to receive abiraterone acetate provided that they met the criteria specified in the amended protocol. The data summarized below are based on the analysis described above. These results constitute the primary analysis of the study data; the planned final analysis was to occur after 797 total deaths.

**DISCONTINUATION OF STUDY TREATMENT:** The proportion of subjects who discontinued study treatment was lower in the abiraterone acetate group than in the placebo group (72% versus 86%). The most common reason for discontinuation for both groups was disease progression (28% in both groups). Twelve percent (12%) of subjects in the abiraterone acetate group and 18% of subjects in the placebo group discontinued treatment due to AEs.

**DEMOGRAPHIC AND BASELINE CHARACTERISTICS:** Demographic and disease baseline characteristics, including the stratification factors of ECOG performance status score, type of disease progression, and presence or absence of pain, were balanced between the 2 groups. Ninety-three percent (93%) of the subjects in both groups were white. The median age was 69 years in both groups. Ten percent

(10%) of subjects in the abiraterone acetate group and 11% of subjects in the placebo group had a baseline ECOG performance status score of 2. Most subjects (70% and 69% in the abiraterone acetate and placebo groups, respectively) had radiographic progression with or without PSA progression. Forty-five percent (45%) of subjects in both groups had pain at baseline. Eighty-nine percent (89%) of subjects in the abiraterone acetate group and 90% of subjects in the placebo group had bone metastasis. Liver metastasis was reported in 11% of subjects in the abiraterone acetate group and 8% of subjects in the placebo group. Baseline central laboratory test concentrations, BPI-SF pain scores, and analgesic usage scores were similar in the 2 groups. The number of prior cytotoxic chemotherapy regimens (one of the stratification factors) was balanced between the 2 groups. Thirty percent (30%) of subjects in the abiraterone acetate group and 31% of subjects in the placebo group received 2 prior cytotoxics.

Fifteen percent (15%) of subjects in both groups had major protocol deviations during the study. Enrollment and entry criteria deviations were the most common, accounting for 8% of subjects in the abiraterone acetate group and 9% of subjects in the placebo group. The most frequent criterion violated was the use of prior ketoconazole (2% of subjects in both groups). The other listed criteria were violated in 1% of subjects or less. The most common major protocol deviation after enrollment and entry criteria deviations was the use of prohibited concurrent medications (5% and 4% of subjects in the abiraterone acetate and placebo groups, respectively), such as 5-alpha reductase inhibitors, non-steroidal antiandrogens, spironolactone, and radioisotopes. The major protocol deviations were distributed across many specific criteria and were comparable between the 2 groups. Placed into the context of a study with robust efficacy where benefit was seen across all subgroups, it is anticipated that the deviations should have no impact on the interpretation of the study results.

**EFFICACY RESULTS:** All efficacy analyses were based on the ITT population, which included all randomized subjects. The study met its primary endpoint at the prespecified significance level (0.0141) required to cross the efficacy boundary for the interim analysis based on 552 deaths at the clinical data cutoff. Treatment with abiraterone acetate decreased the risk of death by 35% compared with placebo (HR=0.646; 95% CI: 0.543, 0.768;  $p<0.0001$ ). Median survival improved by 36% (450.0 days [14.8 months] in the abiraterone acetate group and 332.0 days [10.9 months] in the placebo group). All sensitivity analyses for OS confirmed these results. Subgroup analyses support the robustness of the results.

Results from the analyses of the secondary efficacy endpoints demonstrate the consistency of the results. The results from all 3 endpoints remained significant after adjusting for multiple testing.

- Treatment with abiraterone acetate decreased the risk of PSA progression by 42% compared with placebo (HR=0.580; 95% CI: 0.462, 0.728;  $p<0.0001$ ). The median time to PSA progression was 309.0 days (10.2 months) in the abiraterone acetate group and 200.0 days (6.6 months) in the placebo group.
- Treatment with abiraterone acetate decreased the risk of radiographically documented disease progression or death by 33% compared with placebo (HR=0.673; 95% CI: 0.585, 0.776;  $p<0.0001$ ). The median rPFS was 171.0 days (5.6 months) in the abiraterone acetate group and 110.0 days (3.6 months) in the placebo group.
- The proportion of subjects with a confirmed PSA response was greater in the abiraterone acetate group than in the placebo group (29% versus 6%;  $p<0.0001$ ). Total response (confirmed and unconfirmed) was also higher in the abiraterone acetate group than in the placebo group (38% versus 10%;  $p<0.0001$ ).

The results of analyses that measure the morbidities of mCRPC also favored the abiraterone acetate group.

- Objective response rate was greater in the abiraterone acetate group than in the placebo group (14% versus 3%,  $p<0.0001$ ).
- The proportion of subjects who had a pain palliation response was greater in the abiraterone acetate group than in the placebo group (44% versus 27%,  $p=0.0002$ ).

- At 6, 12, and 18 months, a lower proportion of subjects in the abiraterone acetate group had pain progression compared with the placebo group.
- At 6, 12, and 18 months, a lower proportion of subjects in the abiraterone acetate group had skeletal-related events compared with the placebo group. The time to first skeletal-related event at the 25th percentile in the abiraterone acetate group was twice that of the placebo group (301.0 days [9.9 months] versus 150.0 days [4.9 months]).

**SAFETY RESULTS:** The safety results from this study support an acceptable safety profile of abiraterone acetate with prednisone/prednisolone for the treatment of mCRPC in patients whose disease has progressed on or after 1 or 2 chemotherapy regimens, at least one of which contained the taxane docetaxel.

- Compared with placebo, treatment with abiraterone acetate does not increase the overall incidence of AEs, Grade 3 or 4 AEs, SAEs, AEs leading to treatment discontinuation, or AEs with an outcome of death.
- Mineralocorticoid-related toxicities, ie, preferred terms of edema peripheral (25% versus 17%), hypokalemia (17% versus 8%), and hypertension (9% versus 7%), were reported more frequently in the abiraterone acetate group versus the placebo group. Most of these events were Grade 1 or 2 and infrequently interfered with abiraterone acetate treatment, as evidenced by low rates of dose reductions (1 [0.1%] subject for each term) and no treatment discontinuations or deaths due to any of the 3 terms. The standardized event rate for all grades of the fluid retention/edema Standardized MedDRA Queries (SMQ) category was 71 events/100 patient-years (P-Y) in the abiraterone acetate group and 65 events/100 P-Y in the placebo group. For all grades of the hypokalemia SMQ category, the standardized event rate was 47 events/100 P-Y in the abiraterone acetate group and 29 events/100 P-Y in the placebo group. The standardized event rate for all grades of the hypertension SMQ category was 19 events/100 P-Y in the abiraterone acetate group and 20 events/100 P-Y in the placebo group.
- The most frequently reported AE in both groups was fatigue, which was reported in 44% and 43% of subjects in the abiraterone acetate and placebo groups, respectively.
- Urinary tract infection (UTI) was more frequent in the abiraterone acetate group than in the placebo group (12% versus 7%). Most of these events were Grade 1 or 2. Serious adverse events of UTI were infrequent, reported in 2% of subjects in the abiraterone acetate group and 1% of subjects in the placebo group. The standardized event rate for UTI was 24 events/100 P-Y in the abiraterone acetate group and 18 events/100 P-Y in the placebo group.
- Adverse events classified in the cardiac disorders SMQ were reported in 13% of subjects in the abiraterone acetate group and 11% of subjects in the placebo group. The rate of treatment discontinuation due to AEs classified in the Cardiac Disorders SOC was low in both groups (2% in each group), as was the rate of cardiac-related deaths (1% in each group). The standardized event rate for all grades of the cardiac disorders SMQ category was 33 events/100 P-Y in the abiraterone acetate group and 28 events/100 P-Y in the placebo group.
- Hepatotoxicity AEs (ie, AEs classified in the liver function test abnormalities SMQ category) were reported in 10% of subjects in the abiraterone acetate group and 8% of subjects in the placebo group. The standardized event rate for all grades of the liver function test abnormalities SMQ category was 33 events/100 P-Y in the abiraterone acetate group and 42 events/100 P-Y in the placebo group. Treatment discontinuations due to ALP increase, AST increase, ALT increase, or hyperbilirubinemia were each reported in less than 1% of subjects in each group. No subject in either group had AEs of ALP increase, AST increase, ALT increase, or hyperbilirubinemia with an outcome of death. The incidence of Grade 4 liver function test abnormalities was minimized by implementation of a protocol amendment that required more frequent monitoring during the first 12 weeks, interruption of treatment for subjects with Grade 3 or higher liver function test abnormalities, and no rechallenge for subjects with Grade 4 liver function test abnormalities.

**STUDY LIMITATIONS:** The results of this study are applicable only to the population included in the study. The incidence rates for prostate cancer are significantly higher in African Americans than in whites;

however, African Americans comprised only 4% of the subject population of this study. In addition, this study excluded subjects who had been treated with prior ketoconazole.

CONCLUSION: Persistent androgen synthesis and resultant stimulation of tumor cells is detrimental for men with mCRPC, even after they have received chemotherapy. Abiraterone acetate treatment provides a new approach to address this unmet medical need. This is the first study to demonstrate an overall survival benefit with the use of a noncytotoxic agent in mCRPC following docetaxel administration. This study confirms the scientific hypothesis that blocking persistent or up-regulated androgen synthesis in mCRPC by inhibiting CYP17 has the potential to extend the lives of men with metastatic prostate cancer.