SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	ZYTIGA®
Name of Active Ingredient(s)	abiraterone acetate

Status: Approved
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Prepared by: Janssen Research & Development, LLC

Protocol No.: Protocol COU-AA-302

Title of Study: A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer

EudraCT Number: 2008-008004-41

Clinical Registry No.: NCT-00887198

Principal Investigator: Charles J. Ryan, M.D., University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, Urologic Oncology Program, [redacted], USA.

Study Center(s): 151 sites worldwide in the United States, Europe, Australia, and Canada.

Publication (Reference): None

Study Period: Study start (first subject enrolled): 28 April 2009; last subject enrolled: 23 June 2010. The cutoff date for the independent review of radiographic progression-free survival (rPFS) and the first interim analysis of overall survival (OS) was 20 December 2010. The cutoff date for the second interim analysis of OS was 20 December 2011.

Phase of Development: 3

Objectives: The primary objective was to compare the clinical benefit of abiraterone acetate plus prednisone to placebo plus prednisone in men with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC), who were asymptomatic or mildly symptomatic. Secondary objectives were to establish additional clinically relevant improvements in prostate cancer subjects treated with abiraterone acetate in comparison with placebo, to characterize the safety profile of abiraterone acetate in this subject population, and to characterize the pharmacokinetics of abiraterone acetate when administered concurrently with prednisone.

The co-primary efficacy endpoints of this study were radiographic progression-free survival (rPFS) and overall survival (OS). Secondary efficacy endpoints were time to opiate use for cancer-related pain; time to initiation of cytotoxic chemotherapy for metastatic prostate cancer; time to first clinical deterioration, as assessed by the Eastern Cooperative Oncology Group (ECOG) performance status grade, and time to prostate-specific antigen (PSA) progression (according to adapted Prostate Cancer Clinical Trials Working Group-2 [PCWG2] criteria). Patient-reported outcomes were captured using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the Brief Pain Intensity-Short Form (BPI-SF). Analgesic usage score was used to measure time to pain progression. Medical resource utilization (MRU) information was also assessed and is included in a separate report. Pharmacokinetic measurements and biomarker information (TMPRSS2-ERG and other biomarkers in primary tumor tissue or in circulating tumor cells [CTCs]) were collected at selected sites. The results from the population pharmacokinetic modeling analyses and biomarker data will be summarized in separate reports.

Methodology: This is a multinational, randomized, double-blind, placebo-controlled, Phase 3 study conducted at 151 study sites. The study was designed to compare the efficacy and safety of abiraterone acetate plus prednisone with that of placebo plus prednisone in medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who have not received cytotoxic chemotherapy. Subjects were stratified according to ECOG performance status Grade (0 versus 1) and were randomly assigned (1:1) to receive abiraterone acetate plus prednisone or placebo plus prednisone. Prednisolone was used in Europe; it was used in Australia when prednisone

was not available. Eligible subjects received 1,000 mg of abiraterone acetate (administered as 4 x 250 mg tablets) or 4 placebo tablets once daily plus prednisone 5 mg twice daily. Food was not to be consumed for at least 2 hours before and for at least 1 hour after the dose of study drug. The study consisted of a Screening Period (within 14 days before Cycle 1 Day 1), a Treatment Period (starting at the first dose on Cycle 1 Day 1 and ending with the End-of-Study Treatment Visit), and a Follow-up Period (follow-up for survival every 3 months up to 5 years). Each treatment cycle was 28 calendar days. An Independent Data Monitoring Committee (IDMC) evaluated safety at regular intervals and efficacy and safety at the time of the pre-specified interim analyses.

Number of Subjects (planned and analyzed): Subjects planned: 1,000 subjects. Subjects randomized (intent-to-treat [ITT]): 1,088 subjects (546 subjects: abiraterone acetate plus prednisone; 542 subjects: placebo plus prednisone). Safety population: 1,082 subjects (542 subjects: abiraterone acetate plus prednisone; 540 subjects: placebo plus prednisone).

Diagnosis and Main Criteria for Inclusion: Men who were at least 18 years of age with histologically or cytologically confirmed adenocarcinoma of the prostate were eligible for enrollment. Investigator-assessed prostate cancer progression was required by either PSA progression (according to adapted PCWG2 criteria) or radiographic progression (according to modified Response Evaluation Criteria in Solid Tumors [RECIST] criteria). Laboratory evidence of ongoing androgen deprivation (serum testosterone <50 ng/dL [<2.0 nM]) and an ECOG performance status Grade 0 or 1 were required for enrollment. Men were excluded from participation if they had serious or uncontrolled co-existent nonmalignant disease (including active and uncontrolled infection); prior cytotoxic chemotherapy or biologic therapy for CRPC; liver, visceral organ, or brain metastasis; used opiate analgesics for cancer-related pain within 4 weeks of Cycle 1 Day 1; or abnormal liver transaminase test values (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] <2.5 x the upper limit of normal [ULN] were permitted).

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate, 1,000 mg/day (4 x 250 mg tablets) given orally; batch numbers: A05511-031B01, A06490-009B01, A06490-004B01, A06490-007B01, R0314A001, R0304A001, C1797A001, NXZ, HGX, CFSK, CFSN, CBXC, CXPW, CXPV, FBZC, CMZK, and FFSY. Prednisone, 5 mg twice per day.

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: A06490-005B01, A06490-006B01, A06490-010B01, CHBD, CPBG, and FHNP.

Duration of Treatment: Subjects were to receive treatment until documented disease progression. Study drug was to be discontinued prior to documented radiographic progression if the investigator determined that the subject had experienced unequivocal clinical progression (due to cancer pain requiring immediate administration of chronic opiate analgesics, deterioration of ECOG performance status to Grade 3, or immediate need to initiate cytotoxic chemotherapy, or have either radiation therapy or surgical intervention for prostate cancer). Treatment also was to have been discontinued due to unacceptable toxicity or subject choice. Follow-up for survival was to occur every 3 months up to 5 years after subjects discontinued study drug.

Criteria for Evaluation: Efficacy assessments included sequential radiographic imaging to assess rPFS (computed tomography [CT] or magnetic resonance imaging [MRI] and bone scan) and assessment of survival status. The following evaluations also were performed: recording of concomitant or subsequent medication to determine time to opiate use for cancer-related pain and time to initiation of cytotoxic chemotherapy for metastatic prostate cancer, review of medical history, physical examination for determination of time to clinical deterioration in ECOG performance status by ≥1 grade, and measuring serum PSA concentrations to identify PSA progression. Safety assessments included a review of medical history, measurement of vital signs, physical examinations, review of concomitant therapy and procedures, and a review of adverse events (AEs), serious adverse events (SAEs), and deaths. Laboratory testing was performed to identify abnormalities in blood chemistries, hematologic parameters, coagulation studies, serum lipid concentrations, and kidney function. Cardiac safety was monitored through serial electrocardiograms (ECGs). Left ventricular ejection fraction (LVEF) was measured at baseline only via multiple gated acquisition (MUGA) scan, or echocardiogram (ECHO), if MUGA was unavailable.

Statistical Methods: The overall level of significance for the study was 0.05 allocated between the co-primary endpoints of rPFS (0.01) and OS (0.04). Enrollment of the 1,000 subjects was estimated to take 20 months, assuming an enrollment rate of 50 subjects per month. A single analysis was planned for the co-primary endpoint of rPFS, after 378 rPFS events occurred. This would provide 91% power to detect a median rPFS of 4 months in the placebo group compared with 6 months in the abiraterone acetate group (hazard ratio [HR]=0.667) at a 2-tailed level

of significance of 0.01. For the co-primary endpoint of OS, 773 events were required to detect a difference between a median OS of 22 months in the placebo group and a median OS of 27.5 months in the abiraterone acetate group (HR=0.80) at a 2-tailed significance level of 0.04 with a power of 85%. Three interim analyses were planned for OS after when approximately 15% (in conjunction with the primary rPFS analysis), 40%, and 55% of the total events were observed. A final analysis is planned for OS after 100% of the events are observed. The interim analyses were incorporated for the OS endpoint by group sequential design using the O'Brien-Fleming boundaries as implemented by the Lan-DeMets alpha spending method. The primary statistical method of comparison for the primary and secondary endpoints was the stratified log-rank test.

RESULTS:

Discontinuation of Study Treatment: Sixty-nine percent (69%) of subjects in the abiraterone acetate group and 84% of subjects in the placebo group discontinued treatment. Twenty-one percent (21%) of subjects in the abiraterone acetate group and 30% of subjects in the placebo group discontinued treatment due to radiographic progression only; 21% and 25% of subjects, respectively, discontinued due to unequivocal clinical progression only. The proportion of subjects who discontinued treatment due to unequivocal clinical progression without evidence of radiographic progression was balanced between the groups (39% in each treatment group): 111/283 subjects in the abiraterone acetate group and 136/351 subjects in the placebo group.

Demographics and Baseline Characteristics: The median age was 71 years in the abiraterone acetate group and 70 years in the placebo group. Twenty-five percent (25%) of subjects in the abiraterone acetate group were <65 years, compared with 29% of subjects in the placebo group; 34% versus 30% of subjects were ≥75 years, respectively. Twenty-five percent (25%) of subjects in the abiraterone acetate group and 26% of subjects in the placebo group had presented with metastatic disease (M1) at diagnosis. Eighty-three percent (83%) of subjects in the abiraterone acetate group and 80% of subjects in the placebo group had bone metastases at study entry. Baseline PSA concentrations were 42.0 ng/mL for the abiraterone acetate group and 37.7 ng/mL for the placebo group.

Efficacy Results:

- At the time of the primary rPFS analysis and first interim analysis of OS (20 December 2010):
  - Treatment with abiraterone acetate plus prednisone decreased the risk of radiographic progression or death by 58% compared with placebo plus prednisone (HR=0.425; p<0.0001). The study met its nominal significance level for this co-primary endpoint (0.01) of the independent review of rPFS. The median rPFS was not reached in the abiraterone acetate group and was 8.3 months in the placebo group. The treatment effect of abiraterone acetate plus prednisone on rPFS was favorable and significant across all subgroups. Analysis of the investigator review of rPFS was similar to and highly consistent with the independent review.
  - Ninety-eight (98) deaths had occurred; there was no difference in OS between the treatment groups.
- At the time of the second interim analysis (20 December 2011):
  - The investigator review of rPFS was consistent with the primary independent review of rPFS analysis from 20 December 2010. The median rPFS for the abiraterone acetate group was nearly double that of the placebo group.
  - Treatment with abiraterone acetate plus prednisone resulted in a 25% decrease in the risk of death compared with placebo plus prednisone (HR=0.752; p=0.0097) but did not reach the prespecified statistical significance level based on the O'Brien-Fleming efficacy boundary (nominal significance level of 0.0008) when the IDMC unanimously recommended unblinding the treatment and allowing subjects in the placebo group to receive abiraterone acetate. The median OS had not been reached for the abiraterone acetate group and was 27.2 months in the placebo group. The point estimates of the treatment effect of abiraterone acetate on OS were favorable for all subgroups (all HR<1.0).
  - All of the clinically relevant secondary efficacy endpoints significantly favored treatment with abiraterone acetate over treatment with placebo and remained significant after adjusting using the Hochberg's procedure (time to opiate use for prostate cancer, time to initiation of cytotoxic chemotherapy for prostate cancer, time to deterioration in ECOG performance status grade, time to PSA progression (p≤0.0053 for all endpoints).

- The results of other efficacy analyses that measure the progression of mCRPC also favored the abiraterone acetate group. Confirmed PSA response was statistically significant ($p<0.0001$); the HR for analgesic progression was 0.687 ($p=0.0026$).
- All patient-reported outcome (PRO) measures of pain using BPI-SF favored the abiraterone acetate group. Significant results favoring abiraterone acetate were observed for the FACT-P Total Score and its subscales, except for the Social and Family Well-Being subscale (SFWB).

Safety Results:

- Grade 3 or 4 AEs were reported in 48% of subjects in the abiraterone acetate group versus 42% of subjects in the placebo group; SAEs were reported in 33% versus 26% of subjects; AEs with an outcome of death were reported in 4% versus 2% of subjects; and AEs that led to treatment discontinuation were reported in 10% versus 9% of subjects, respectively.
- The most frequently reported AEs (reported in ≥20% of subjects in either the abiraterone acetate or placebo group) were fatigue, back pain, arthralgia, peripheral edema, nausea, constipation, hot flush, diarrhea, bone pain, and hypertension.
- Hepatotoxicity AEs were reported in 18% of subjects in the abiraterone acetate group and 11% of subjects in the placebo group; Grade 3 or 4 hepatotoxicity AEs were reported in 8% and 3% of subjects, respectively. AEs classified in the System Organ Class (SOC) of Investigations led to dose modification or interruption for 6% of subjects in the abiraterone acetate group and 1% of subjects in the placebo group; treatment discontinuations due to hepatotoxicity AEs were reported in 2.2% and 0.2% of subjects, respectively. No subject in either treatment group had hepatotoxicity-related AEs with an outcome of death.
- Adverse events classified as cardiac disorders were reported in 19% of subjects in the abiraterone acetate group and 16% of subjects in the placebo group. After standardizing for the difference in duration of treatment exposure, an excess of 2 cardiac disorder events/100 P-Y (for all grades) was observed in the placebo group (27 in the abiraterone acetate group and 29 the placebo group). Treatment discontinuations due to AEs in the SOC of Cardiac Disorders were reported in 0.6% of subjects in the abiraterone acetate group and 0.4% of subjects in the placebo group; cardiac-related deaths were also reported in 0.6% and 0.4% of subjects, respectively. For the subcategory cardiac failure, the incidences of all AEs (2.0% versus 0.4%) and Grade 3 or higher AEs (1% versus 0) were higher in the abiraterone acetate group compared with the placebo group. An excess of 3.2 cardiac failure events/100 P-Y was observed in the abiraterone acetate group (3.6 in the abiraterone acetate group and 0.4 in the placebo group).
- Mineralocorticoid-related toxicities were reported more frequently in the abiraterone acetate group than in the placebo group, ie, the preferred terms of hypertension (22% versus 13%), edema peripheral (25% versus 20%), and hypokalemia (17% versus 13%), respectively. The standardized event rate (events/100 P-Y) for all grades of hypertension was 24 in the abiraterone acetate group versus 20 in the placebo group, for fluid retention/edema was 38 versus 44, respectively, and for hypokalemia was 24 versus 22, respectively. Most of these events were Grade 1 or 2 and infrequently interfered with abiraterone acetate treatment, suggested by the following:
  - In both treatment groups, dose reductions or interruptions occurred at a rate of approximately 1% of subjects.
  - In both treatment groups, treatment discontinuations occurred in <0.5% of subjects.
  - There were no deaths in either treatment group due to any of the 3 events (hypertension, edema peripheral, or hypokalemia).

Study Limitations: The results of this study are applicable only to the population included in the study.

Conclusion: For chemotherapy-naïve mCRPC patients, Study COU-AA-302 establishes that treatment with abiraterone acetate plus prednisone offers better outcomes than those observed for patients treated with placebo plus prednisone. Treatment with abiraterone acetate plus prednisone substantially delays disease progression and its undesirable manifestations, and improves survival. These favorable outcomes for patients treated with abiraterone acetate plus prednisone are achieved while preserving quality of life. The safety profile was similar to that observed with abiraterone acetate plus prednisone in subjects in the post-docetaxel setting and usually does not interfere with treatment.