

SYNOPSIS

<u>Name of Sponsor/Company</u>	Janssen Research & Development*
<u>Name of Finished Product</u>	ZYTIGA®
<u>Name of Active Ingredient(s)</u>	JNJ-212082 (abiraterone acetate)

* Janssen Research & Development is a global organization that operates through different legal entities in various countries. Therefore, the legal entity acting as the sponsor for Janssen Research & Development studies may vary, such as, but not limited to Janssen Biotech, Inc.; Janssen Products, LP; Janssen Biologics, BV; Janssen-Cilag International NV; Janssen, Inc; Janssen Infectious Diseases BVBA; Janssen R&D Ireland; or Janssen Research & Development, LLC. The term “sponsor” is used to represent these various legal entities as identified on the Sponsor List.

Status: Approved
Date: 18 July 2013
Prepared by: Janssen Research & Development, LLC

Protocol No.: ABI-PRO-3002

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (JNJ-212082) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients with Metastatic Castration-Resistant Prostate Cancer

NCT No.: NCT01591122

Clinical Registry No.: CR100011

Coordinating Investigator: Yinghao Sun, MD - Shanghai Changhai Hospital, [REDACTED]
[REDACTED] China

Study Center(s): The study was conducted in 42 sites in China (26 sites), Russia (15 sites), Malaysia (2 sites), and Thailand (2 sites).

Publication (Reference): None

Study Period: 15 March 2012-18 March 2013. Database lock for interim analysis: 29 April 2013.

Phase of Development: 3

Objectives: The primary objective of this study was to compare the clinical benefit, as measured by an improvement in time to prostate specific antigen (PSA) progression (TTPP), of abiraterone acetate plus prednisone versus placebo plus prednisone in subjects with chemotherapy-naïve metastatic castration resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic. Secondary objectives were to establish additional clinically relevant improvements in prostate cancer subjects treated with abiraterone acetate in comparison to placebo and to characterize the safety profile of abiraterone acetate with concurrent prednisone in this subject population.

Methodology: This was a multinational, randomized, double-blind, placebo-controlled Phase 3 study conducted at 42 study sites in Asia (China, Malaysia, and Thailand) and Europe (Russia). 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 region (Asia versus Europe) and Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade (0 versus 1) and were randomly assigned (1:1) to receive either abiraterone acetate plus prednisone

(China) or prednisolone (Russia, Malaysia, and Thailand; hereafter referred to as prednisone) or placebo plus prednisone. Eligible subjects received 1,000 mg abiraterone acetate (administered as 4 x 250 mg tablets) or 4 placebo tablets once daily plus prednisone 5 mg twice daily on an empty stomach. 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 28 days prior to randomization on 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 consecutive days. An Independent Data Monitoring Committee (IDMC) evaluated safety at regular intervals and efficacy and safety at the time of the pre-specified interim analysis.

Number of Subjects (planned and analyzed): Subjects planned: 290 subjects. Subjects randomized (intent-to-treat [ITT]) and safety analysis set: 313 subjects (157 subjects: abiraterone acetate plus prednisone; 156 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. Laboratory evidence of ongoing androgen deprivation (serum testosterone <50 ng/dL [<1.7 nmol/L]) was required. Investigator-assessed prostate cancer progression was documented by either PSA progression (according to adapted Prostate Cancer Working Group 2 [PCWG2] criteria) or radiographic progression (according to modified Response Evaluation Criteria in Solid Tumors [RECIST] criteria). An ECOG PS Grade 0 or 1 was required for enrollment. Men were excluded from participation if they had prior cytotoxic chemotherapy or biologic therapy for mCRPC; liver, visceral organ, or brain metastasis; 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: GGZC, FFTN, HTWK, and GGZB.

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: HHKM, FHNS, and HHKK.

Prednisone/Prednisolone 5 mg tablets used in the study were sourced locally.

Duration of Treatment: Subjects were to receive treatment until documented disease progression. Study drug was to be discontinued if the investigator determined that the subject had experienced PSA progression (PSA increase $\geq 25\%$ and ≥ 2 ng/mL above the nadir with confirmation ≥ 3 weeks later), radiographic progression (confirmed progression on bone scan or soft tissue disease progression by modified RECIST criteria), or clinical progression (confirmed pain progression as assessed by a Brief Pain Inventory-Short Form [BPI-SF] value of ≥ 4 , development of a skeletal related event, any increase in prednisone dose or change to a more potent glucocorticoid, or initiation of a new systemic anti-cancer therapy). Treatment also was to have been discontinued due to unacceptable toxicity or subject choice.

Criteria for Evaluation: Efficacy assessments included measurement of serum PSA concentrations to assess disease progression and assessment of survival status. The following evaluations also were performed: overall survival, overall response rate, recording of concomitant or subsequent medication, time to initiation of cytotoxic chemotherapy for metastatic prostate cancer, patient-reported outcome questionnaires to determine time to pain progression and analgesic usage score to measure time to analgesic progression, review of medical history, and physical examination for determination of time to clinical deterioration in ECOG PS grade.

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), AEs and SAEs leading to discontinuation, AE and SAEs of special interest, and deaths. Laboratory testing was performed to identify abnormalities in blood chemistries, hematologic parameters, coagulation studies, and serum lipid concentrations. 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: Assuming an exponential distribution for TTPP with a hazard ratio (HR) of 0.62 (median TTPP 4 months for placebo versus 6.5 months in the abiraterone acetate group), a 2-sided alpha of 0.05 and a power of 90%, 181 progression events will be required to detect a difference in the planned HR. With an enrollment rate of 20 subjects per month over 14.5 months, approximately 290 subjects will be enrolled. One interim analysis was planned when approximately 50% of TTPP events (91 events) were expected to be observed. The alpha spending for the interim analysis was to be based on the Pocock boundary as implemented by Lan-DeMets alpha spending method. With 50% events observed at interim analysis, the cumulative Pocock alpha spending was anticipated to be 0.0310 and 0.0500 for the interim and final analyses, respectively. A final analysis was planned for the primary endpoint of TTPP after 181 PSA progression events occurred. The primary statistical method of comparison for the primary and secondary endpoints was the stratified log-rank test.

RESULTS:

Discontinuation of Study Treatment: As of the clinical cut-off date of 18 March 2013, 12% of subjects in the abiraterone acetate group and 28% of subjects in the placebo group discontinued treatment. Disease progression was the main reason for discontinuation in over half of the subjects in the 2 treatment groups (12/19 [63%] in abiraterone acetate group and 24/44 [55%] in the placebo group).

Demographics and Baseline Characteristics: The median age was 71 years in the abiraterone acetate group and 72 years in the placebo group. Sixty-four percent of subjects in the abiraterone acetate group and 57% of subjects in the placebo group had metastatic disease (M1) at initial diagnosis. At initial diagnosis, 54% of subjects in the abiraterone acetate group and 56% of subjects in the placebo group had a Gleason Score ≥ 8 . Median PSA levels at baseline were 48.6 ug/mL for the abiraterone acetate group and 55.7 ug/mL for the placebo group. Median time from initial diagnosis to first dose was 2.6 years and 3.1 years for the abiraterone acetate group and placebo group, respectively.

Efficacy Results:

Per INT-1 protocol amendment, an interim analysis was planned when approximately 50% of TTPP events (91 events) were observed. This interim analysis was conducted with 94 TTPP events. The IDMC reviewed the safety and efficacy data from this interim analysis and recommended stopping the study based on having met the pre-defined stopping criteria with a greater reduction in TTPP in the abiraterone acetate group relative to placebo.

At the time of interim analysis, the median duration of treatment was 3.8 months in the abiraterone acetate group and 3.4 months in the placebo group. The median follow-up for randomized subjects was 3.9 months.

- There was a 58% reduction in the risk of PSA progression in subjects treated with abiraterone acetate plus prednisone compared with subjects treated with placebo plus prednisone (HR=0.418; $p < 0.0001$).
- The PSA response rate (67%) was significantly higher (relative risk=2.4; $p < 0.0001$) for subjects treated with abiraterone acetate plus prednisone compared with subjects treated with placebo plus prednisone (31%).

- The objective response rate (complete response [CR] + partial response [PR]) showed that subjects treated with abiraterone acetate plus prednisone were 4.8 times (22.9%) more likely to achieve a response than subjects treated with placebo plus prednisone (4.8%) (p=0.0369). All responses were PRs.
- Other secondary endpoints of overall survival, time to initiation of cytotoxic chemotherapy, and time to ECOG PS deterioration have not matured to the point for meaningful analysis due to the low numbers of events.
- Patient-reported outcomes measures related to pain palliation favored abiraterone acetate plus prednisone treatment (time to pain intensity progression HR=0.608; p=0.2228, time to pain interference progression HR= 0.620; p=0.0481; time to analgesic progression HR=0.599; p=0.3860) at the time of this interim analysis.
- Patient-reported outcomes measures related to patient well-being using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) instrument showed no detrimental effects of administration of abiraterone acetate plus prednisone. In some subscales, improvements were trending in favor of the abiraterone acetate group compared with the placebo group at the time of this interim analysis.

Safety Results:

- The most frequently reported AEs (reported in $\geq 10\%$ of subjects in either the abiraterone acetate or placebo group) were bone pain, arthralgia, back pain, pain in extremity, and hypertension.
- Grade 3 or 4 AEs were reported in 17% of subjects in the abiraterone acetate group versus 21% of subjects in the placebo group; SAEs were reported in 4% versus 7% of subjects; AEs with an outcome of death were reported in 3% versus 4% of subjects; and AEs that led to treatment discontinuation were reported in 3% versus 5% of subjects.
- Hepatotoxicity AEs were reported in 19% of subjects in the abiraterone acetate group and 20% of subjects in the placebo group. Grade 3 ALT increases were reported in 3% of subjects in the abiraterone acetate group and no subjects in the placebo group; Grade 3 AST increases were reported in 2% of subjects in the abiraterone acetate group and 0.6% of subjects in the placebo group. Two subjects in the abiraterone acetate group had reported Grade 3 ALT and AST increases. Appropriate protocol-specified dose modifications and discontinuations due to AEs of Grade 3 or 4 ALT or AST increases were implemented. No deaths occurred due to hepatotoxicity. No subjects had liver function test abnormalities that met Hy's law criteria.
- Adverse events classified as cardiac disorders were reported in 10% of subjects in the abiraterone acetate group and 4% of subjects in the placebo group. All cardiac disorder events with the exception of 1 reported Grade 4 event, were Grade 1 or 2 in severity. Within the cardiac disorder subcategories, the incidence in the abiraterone acetate and placebo groups was the following: arrhythmias (7% versus 3%), ischemic heart disease (3% versus 0%), other cardiac disorders (1% versus 2%), and cardiac failure (0.6% versus 0%). Serious adverse events under cardiac disorders were reported in 1.9% of subjects in the abiraterone acetate group and 0.6% of subjects in the placebo group. Cardiac disorder SAEs, by subcategory were reported as follows: arrhythmias (1 subject in each treatment group), ischemic heart disease (2 subjects in the abiraterone acetate group), and cardiac failure (1 subject in the abiraterone acetate group). One subject (abiraterone acetate group) experienced an SAE of Grade 4 congestive cardiac failure secondary to Grade 3 lung infection and died with a primary cause of multiorgan failure; this subject also had 2 reported events of Grade 2 atrial flutter (with recovery) before the lung infection occurred. One subject in the placebo group had a reported Grade 5 AE of sudden death. Adverse events under the cardiac disorders category led to dose modification or interruption for 1% of subjects in the abiraterone acetate group and 0% of

subjects in the placebo group. With the exception of 1 subject in the placebo group who died suddenly (Grade 5 sudden death), no subjects discontinued study drugs due to a cardiac-related AE.

- Mineralocorticoid-related toxicities were reported at a slightly higher incidence in the abiraterone acetate group compared with the placebo group: hypertension (15% versus 14%), fluid retention/edema (5% versus 3%), and hypokalemia (8% versus 5%). Grade 3 hypertension was reported in 3% of subjects in the abiraterone acetate group and 4% of subjects in the placebo group. All events of fluid retention/edema were Grade 1 or 2 in severity. Grade 3 hypokalemia was reported for 3 subjects in the abiraterone acetate group, although 1 subject had a reported Grade 3 event that was not consistent with the laboratory data (Grade 2). Grade 4 hypokalemia was reported for 1 subject in the abiraterone acetate group and led to discontinuation of study drugs. No SAEs related to hypertension or hypokalemia or peripheral edema, were reported. There were no deaths in either treatment group due to any of the 3 events (hypertension, edema peripheral, or hypokalemia).
- Anemia was reported as an AE in 6% of subjects in the abiraterone acetate group and 8% of subjects in the placebo group. Grade 3 anemia was reported in 0.6% of subjects in the abiraterone acetate group and 3% of subjects in the placebo group; no Grade 4 events of anemia were reported in either treatment group.
- No osteoporosis and osteoporosis-related AEs were reported in the abiraterone acetate group. One subject in the placebo group experienced an SAE of Grade 4 thoracic vertebral fracture, which along with Grade 4 paraplegia and Grade 2 urinary incontinence led to discontinuation of study drugs. No cataract or sexual dysfunction-related AEs were reported in this study.
- Electrocardiogram QTc results were inconsistent and difficult to interpret; variability in ECG recording methods and small sample sizes were contributing factors. With the exception of 2 subjects, ECG changes from baseline (QTc > 60 msec or actual QTc > 500 msec) were considered not clinically significant by the investigators.
- The safety profile for Study ABI-PRO-3002 was consistent with the safety profile for Study COU-AA-302; no new safety concerns were identified at the time of this interim analysis.

Study Limitation: The duration of subject follow-up data is limited (3.9 months) the data for several of the secondary endpoints are not mature subsequent to the early unblinding of the study by the IDMC. No notable study limitations were identified by the Sponsor in the design of the study or its conduct.

Conclusion:

This interim analysis of Study ABI-PRO-3002 confirms a favorable benefit to risk ratio of abiraterone acetate plus prednisone in men with mCRPC who were asymptomatic or mildly symptomatic. The efficacy and safety results of Study ABI-PRO-3002 were consistent with the results from Study COU-AA-302. Subgroup analyses also demonstrated a general consistency of efficacy and safety.

Disclaimer

Information in this posting shall not be considered to be a claim for any product, whether marketed or under development. In case of a marketed product, some of the information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.