

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-AAA (abiraterone acetate)

Protocol No.: COU-AA-201**Title of Study:** A Phase 2 Open-Label, Randomized, Multi-center Study of Neoadjuvant Abiraterone Acetate (CB7630) Plus Leuprolide Acetate and Prednisone Versus Leuprolide Acetate Alone in Men With Localized High Risk Prostate Cancer**NCT No.:** NCT00924469**Clinical Registry No.:** COU-AA-201**Principal Investigator:** Mary-Ellen Taplin, MD, Dana-Farber Cancer Institute, [REDACTED], USA**Study Centers:** [REDACTED] Houston Texas- [REDACTED]
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[REDACTED] Boston, MA [REDACTED]**Publication (Reference):** None**Study Period:** 11 November 2009 to 05 March 2012**Phase of Development:** 2**Objectives:** The primary objective of the study was to compare serum and prostate tissue concentrations of testosterone and dihydrotestosterone (DHT) and the androgen precursors, dihydroepiandrosterone (DHEA) and androstenedione, after 12 weeks of treatment with either abiraterone acetate plus leuprolide acetate, and prednisone or leuprolide acetate alone.

The secondary objectives of the study were to:

- Analyze serum and prostate tissue concentrations of androgens (testosterone and DHT), androgen precursors (DHEA and androstenedione) and the serum androgen metabolite 5 α -androstane-3 α , 17 β -diol glucuronide, after 24 weeks of combined abiraterone acetate, prednisone, and leuprolide acetate treatment (prostatectomy specimen)
- Assess the rate of pathologic complete response at prostatectomy after abiraterone acetate, prednisone, and leuprolide acetate treatment
- Evaluate prostate-specific antigen (PSA) response (proportion with PSA \leq 0.2 ng/mL) after 12 and 24 weeks of androgen deprivation therapy (ADT)
- Evaluate (molecular) expression of androgen receptor (AR) regulated genes (AR, TMPRSS2/ERG, UBEC2, Cdk1, cyclin B1, ERG, cell-division cycle 20 [CDC20], CKS2 and androgen metabolic enzymes) and tumor immunohistochemistry (AR, PSA, UBEC2, Ki-67, AKR1C3, cleaved caspase 3, TUNEL staining, CYP17, and other androgen metabolic enzymes). Determine molecular and protein expression correlation with intracellular androgen levels and pathologic response to ADT.

Methodology: This was an open-label, multicenter, Phase 2, randomized study. Approximately 58 men (29 subjects per treatment) with localized and intermediate to high risk prostate cancer with at least 3 positive core biopsies and who were suitable for prostatectomy were planned to be enrolled in the study. The study consisted of 4 phases: screening, treatment, prostatectomy, and end of study (EOS) visit. The duration of the treatment phase was 24 weeks, concluded by an end-of-treatment visit.

Subjects were randomly assigned in 1:1 ratio to either Group 1 or Group 2 after the investigator verified that all eligibility criteria were met. Subjects in Group 1 received treatment for 24 weeks with abiraterone acetate (1,000 mg orally daily as 4 x 250 mg tablets), leuprolide acetate (22.5 mg every 12 weeks [or 7.5 mg every 4 weeks with a ± 2 day window]), and prednisone (5 mg orally daily). Subjects in Group 2 received leuprolide acetate alone for 12 weeks, and then abiraterone acetate, leuprolide acetate, and prednisone for the next 12 weeks. Subjects were stratified per a risk factor with 2 levels: High Risk: Gleason score ≥ 8 or prostate specific antigen (PSA) ≥ 20 ng/mL and Intermediate Risk: Gleason score ≤ 7 and PSA < 20 ng/mL.

Number of Subjects (planned and analyzed): Planned: Approximately 58 men (29 subjects per treatment) with localized and intermediate to high risk prostate cancer with at least 3 positive core biopsies and who were suitable for prostatectomy were planned to be enrolled in the study.

Analyzed: Fifty-eight subjects (30 subjects in Group 1 and 28 subjects in Group 2) were randomized and treated with the study drug. Fifty-four subjects completed the study.

Diagnosis and Main Criteria for Inclusion: Males of at least 18 years of age with a PSA response rate of > 10 ng/mL, or PSA velocity > 2 ng/mL/year, or Gleason score of ≥ 7 or Gleason score of 6, if either PSA ≥ 10 ng/ml or PSA velocity ≥ 2 ng/ml/year. Subjects who did not meet any of the inclusion criteria were not to be enrolled in this study.

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate 1,000 mg (4 x 250 mg tablets every day), orally every day at least 1 hour before or 2 hours after a meal. Prednisone 5 mg tablets every day, orally taken with food (morning). Batch numbers for abiraterone acetate: 9405.022, 9405.024, 9405.028, C1797A001, CBXC, CNTC, DPXX.

Reference Therapy, Dose and Mode of Administration, Batch No.: Leuprolide acetate 22.5 mg intramuscularly (IM) every 12 weeks (or at a dose of 7.5 mg IM every 4 weeks).

Duration of Treatment: The planned duration of the study for each subject consisted of a 24-week treatment phase, followed by a prostatectomy and an EOS visit conducted 4 to 8 weeks after prostatectomy.

Criteria for Evaluation:

Efficacy: Efficacy evaluations were based upon the prostate tissue and serum concentrations of testosterone, DHT, DHEA, and androstenedione, serum concentrations of other androgens (DHEA-S, estradiol, progesterone, 5α -androstane- 3α , 17β -diol glucuronide), PSA response rate, and pathological complete or near complete response.

Safety: Safety evaluations were based upon the type, incidence, and severity of adverse events (AEs) reported throughout the study, and on changes in vital sign measurements, physical examinations, electrocardiograms (ECGs), and clinical laboratory tests. Safety was monitored throughout the study beginning at the time of the signing of the informed consent and ending with the completion of the last study procedure.

Statistical Methods:

Sample size: A sample size of 24 subjects per treatment group with evaluable core biopsies was needed for this study. This sample size could provide 80% power with Type 1 error of 10% to detect a mean prostate tissue DHT mean concentration difference of at least 0.97 ng/mL, between the 2 treatment groups after 12 weeks of treatment, assuming the mean DHT concentration in Group 2 is 1.92 ng/mL and 0.95 ng/mL in Group 1. The calculation was based on an assumed standard deviation of 1.35 ng/mL and a 2-sided 2-sample t-test.

In addition, the sample size of 24 subjects per treatment group could also provide 77% power with Type 1 error of 10% unadjusted for multiplicity, to detect a mean difference of at least 0.35 ng/mL in prostate tissue testosterone concentrations between the 2 treatment groups after 12 weeks of treatment. The calculation was based on the assumptions of a mean prostate tissue testosterone concentration of 0.55 ng/mL in Group 2 and a common standard deviation of 0.5 ng/mL, and a 2-sided 2-sample t-test. In this study, 58 subjects were enrolled (30 subjects in Group 1 and 28 subjects in Group 2).

The analysis sets defined in this study were intent-to-treat (ITT) and safety population. No interim analysis was planned for this study.

Efficacy:

For the primary efficacy analysis, which included the prostate tissue concentrations of testosterone and DHT at Week 12, the adjusted group mean difference and the associated 90% confidence interval (CI) were estimated and compared using an analysis of variance with baseline risk as covariate. For secondary efficacy analyses, which included prostate tissue concentrations of testosterone and DHT at Week 24, tissue concentrations of DHEA and androstenedione, the adjusted group means and the associated 90% confidence interval (CI) were estimated and compared using an analysis of variance with baseline risk as covariate. For secondary efficacy analyses, which included serum concentrations of androgens, the difference in adjusted group means and the associated 90% CI was estimated and compared using analysis of covariance with stratification levels and baseline value as covariate. To meet the normality assumption on the random error for analysis, natural log-transformation was performed on the values prior to analysis.

Response rates were estimated and the corresponding 90% CI for the estimates was provided. The difference in response rates between treatment groups was analyzed using Cochran-Mantel-Haenszel test to adjust for the risk level.

Continuous endpoints were summarized using descriptive statistics (number, mean, standard deviation [SD], median, minimum, and maximum). Categorical 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.

Safety:

All subjects who received at least 1 dose of the study drug were included in the safety analysis. The analyses included the incidence of adverse events, evaluation of laboratory tests, vital signs, ECGs. Inferential statistics were not planned to be performed on safety data. Laboratory parameters, vital signs, physical examinations, and ECG measurements were summarized by descriptive statistics and change from baseline at each time point.

RESULTS:**Study Population:**

Fifty-eight subjects (30 subjects in Group 1 and 28 subjects in Group 2) were randomized and treated with the study drug. Fifty-four subjects (93.1%) completed the study. Two subjects in Group 1 were withdrawn from the study due to AEs. One subject in Group 2 was withdrawn from the study due to withdrawal of consent and another subject from the same group was withdrawn due to “other” reason (as the subject did not take the EOS visit due to [REDACTED] issue).

The median age was 58.0 years and 87.9% of the subjects were white. The median PSA at baseline for all subjects was 9.315 ng/mL. All subjects had a baseline Gleason score of ≥ 7 . Forty-three (74%) subjects were in the high risk prognostic group. All subjects who were randomized received at least 1 dose of the study drug.

Efficacy Results:

The primary efficacy endpoints included the prostate tissue testosterone and DHT concentrations measured at Week 12. Results showed that the difference of the mean prostate tissue testosterone concentrations between the 2 treatment groups at Week 12 was statistically significant ($p=0.0216$), and the mean DHT concentrations were significantly lower in Group 1 than that in Group 2 ($p<0.0001$).

The results of secondary efficacy endpoints showed that the difference of mean prostate tissue concentrations of DHEA and androstenedione, and mean serum concentrations of testosterone at Week 12 were statistically significant ($p<0.0001$) between treatment groups. At Week 24, mean prostate tissue and serum concentrations of testosterone and DHT, and prostate tissue concentrations of DHEA, and androstenedione were not statistically different between treatment groups.

The pathologic complete response rates after 24 weeks were not statistically different ($p=0.3427$) between the 2 treatment groups; however the total or near complete response rate in Group 1 was significantly higher than that in Group 2 at the significance level of 0.10 ($p=0.0799$). A significantly higher ($p<0.0001$) PSA response rate at Week 12 was observed in Group 1 than in Group 2.

Safety Results:

During the 24 weeks of study treatment, all subjects were reported to have at least 1 AE. Most AEs were Grade 1 or 2 in toxicity. Seven subjects (23%) in Group 1 and 9 subjects (32%) in Group 2 were reported to have Grade 3 or 4 AEs. The most frequently reported AEs were hot flush, aspartate aminotransferase (AST) increased, fatigue, and alanine aminotransferase (ALT) increased. One subject in Group 1 reported a Grade 4 AE of depression. The most frequently reported Grade 3 AEs were ALT increased and hypokalemia.

No deaths were reported during the study. Six subjects (20%) in Group 1 and 7 subjects (25%) in Group 2 had at least 1 serious adverse event (SAE). The only SAE reported for more than 1 subject was ALT increased, which was reported in 3 subjects (2 subjects in Group 1 and 1 subject in Group 2). Six subjects, 4 (14%) in Group 1 and 2 (7%) in Group 2, discontinued at least 1 of the study drugs (abiraterone acetate or leuprolide acetate or prednisone). The most frequently reported AE leading to discontinuation of study drug was ALT increased (3 subjects in Group 1 and 2 subjects in Group 2). The most frequently reported AE of special interest observed in both treatment groups was ALT increase (Grade 3), which was reported in 3 subjects (10%) in Group 1 and 2 subjects (7%) in Group 2.

Clinical Laboratory Tests:

After 12 weeks of treatment, 2 subjects in Group 1 and no subjects in Group 2 had Grade 3 ALT increases. In Group 1, one subject had a Grade 3 potassium decrease and 1 subject had a Grade 3 bilirubin increase. After 24 weeks of treatment, no additional subjects in Group 1 and 4 subjects in Group 2 had a Grade 3 ALT increase. One subject in Group 2 had a Grade 3 AST increase. No other additional Grade 3 laboratory abnormalities were reported after 24 weeks of treatment. No subject had laboratory abnormalities meeting all the criteria for Hy's law.

Other Safety Observations:

There were no clinically significant vital signs abnormalities. There were no major apparent or consistent treatment dose-related changes noted from baseline in the ECG parameters (QTc interval).

Study Limitations:

No notable study limitations were identified by the Sponsor.

Conclusions:

- Treatment with abiraterone acetate plus leuprolide acetate and prednisone significantly lowered the tissue testosterone and DHT levels at Week 12, compared with the treatment of leuprolide acetate alone.
- A significantly higher complete or near complete pathologic response rate was observed in subjects on the full 24 weeks of abiraterone acetate plus leuprolide acetate treatment compared to those on leuprolide acetate for 24 weeks with the addition of abiraterone acetate in the last 12 weeks of treatment.
- A significantly higher PSA response rate at Week 12 was observed in the subjects treated with abiraterone acetate plus leuprolide acetate and prednisone as compared with those treated with leuprolide acetate alone.
- There were no clinically significant effects of the study drugs on laboratory parameters, vital signs and ECG, and no increase in incidence of AE, including AEs of special interest (e.g. liver function test [LFT] abnormality, hypokalemia and cardiovascular related toxicity etc) was observed when abiraterone acetate was administered along with a lower dose of prednisone (i.e. 5 mg/day instead of 10 mg/day) as compared with safety data from the abiraterone acetate Phase 3 chemo-naïve study COU-AA-302.