Janssen Research & Development

Clinical Study Report Synopsis
[JNJ-212082; Phase 2]

JNJ-212082 (abiraterone acetate)

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SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.
Name of Finished Product	ZYTIGA®
Name of Active Ingredient(s)	JNJ-212082 (abiraterone acetate)

Status: Approved

Date: 23 March 2015

Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: JNJ-212082-JPN-202

Title of Study: A Phase 2 Study of JNJ-212082 (abiraterone acetate) in Metastatic Castration-Resistant Prostate Cancer Patients Who Have Received Docetaxel-based Chemotherapy

NCT No.: NCT01795703

Clinical Registry No.: CR017062

Coordinating Investigator(s): No coordinating investigator

Study Center(s): 18 sites in Japan

Publication (Reference): Satoh T, Uemura H, Tanabe K, et al. A phase 2 study of abiraterone acetate in Japanese men with metastatic castration-resistant prostate cancer who had received docetaxel-based chemotherapy. Jpn J Clin Oncol; 2014; 44(12): 1206-15.

Study Period: 4 June 2012 (first subject enrolled) to 15 October 2014 (last subject, last visit)

Phase of Development: 2

Objectives: The primary objective was to assess the proportion of subjects achieving a prostate-specific antigen (PSA) decline of ≥50% from baseline (PSA response) by 12 weeks of therapy in accordance with Prostate-Specific Antigen Working Group (PSAWG) criteria, in subjects with metastatic castration-resistant prostate cancer (mCRPC) who have previously received docetaxel-based chemotherapy.

The primary hypothesis of the study was that the lower limit of the two-sided 90% confidence interval (CI) of the proportion of study drug-treated subjects exhibiting a ≥50% PSA decline from baseline by 12 weeks of therapy in accordance with PSAWG criteria would be higher than 20%.

The secondary objectives were to assess the safety profile of abiraterone acetate with concurrent prednisolone in the study population; assess the radiographic objective response rate (RAD-ORR) in subjects with measurable lesions using response evaluation criteria in solid tumors (RECIST) Version 1.0; determine the duration of a ≥50% PSA decline and the proportion of subjects achieving PSA response (PSA response rate); assess clinical benefit, as determined by disease stabilization and by changes in Eastern Cooperative Oncology Group (ECOG) performance status (PS); assess the pharmacokinetics of abiraterone; assess serum PSA decline in accordance with Prostate Cancer Clinical Trials Working Group (PCWG2) criteria; assess overall survival; assess PSA-based progression-free survival (PSA-PFS); assess radiographic progression-free survival (RAD-PFS), and assess the circulating tumor cell (CTC) conversion rate.

The exploratory objectives were to explore the correlations among CTC enumerations, androgen receptor (AR) expression and mutations, chromosomal translocations, and PSA response, and to explore the

relationships between abiraterone acetate and biomarkers that could potentially affect the pharmacokinetics, safety, and efficacy of abiraterone acetate.

Methodology: This was a Phase 2, multi-center, open-label, single-arm study conducted at 18 sites in Japan to evaluate the safety and efficacy of abiraterone acetate in subjects with mCRPC who have previously received docetaxel-based chemotherapy. A target sample of 38 subjects was to be analyzed in this study. Eligible subjects received abiraterone acetate 1,000 mg (administered as 4×250 mg tablets) orally once daily at least 1 hour before a meal and 2 hours after a meal any time up to 10 PM every day, and 5 mg of prednisolone orally twice daily. Treatment was administered on a continuous schedule, and each cycle of treatment was 28 days. The study consisted of a screening period (within 14 days before Cycle 1 Day 1), a treatment period (until documented disease progression or unacceptable toxicity), and a follow-up period (follow-up for survival every 3 months up to 5 years or any date in accordance with the criteria added along with the switch to the post-marketing clinical study, whichever was earlier). Subjects were followed for safety for 30 days after the last dose of study drug. An Independent Data Monitoring Committee (IDMC) was formed to evaluate safety data at regular intervals to ensure the continuing safety of the subjects in the study. The first IDMC met after the first 25% of target subjects (approximately 10 subjects) had completed Cycle 2 in the study. The second IDMC met after at least 50% of target subjects had completed Cycle 2. Additional IDMC meetings were to be convened as appropriate until approval from the Ministry of Health, Labour and Welfare (MHLW) or the end of the study.

After the INT-3 amendment of the protocol on 2 April 2014, once abiraterone acetate was approved with the proposed indication by the MHLW, and the market product of abiraterone acetate was delivered to the study site, the investigator was to request subjects to visit the site immediately to perform all applicable procedures scheduled for the end-of-study visit before they were switched from the study drug of abiraterone acetate to the market product. During the period between the approval and the switch to the market product, subjects could continue to receive abiraterone acetate in the post-marketing study, in which the dosage regimen was the same as during the clinical study.

Number of Subjects (pl anned and analyzed): A total of 38 subjects were planned to be analyzed for efficacy. Of 64 subjects who signed informed consent, 47 completed screening and were treated. The number of subjects included in each analysis set was as follows: safety analysis set: 47; full analysis set (FAS): 46; evaluable set: 42; pharmacokinetic analysis set: 47; pharmacodynamic analysis set: 46.

Diagnosis and Main Criteria for Inclusion: Men with mCRPC aged 20 years or older, who had a PSA level of ≥5 ng/mL and ECOG PS score of 0 to 2 and who had received at least 1 but not more than 2 cytotoxic chemotherapy (at least 1 regimen had to be docetaxel) for prostate cancer, were eligible for the study. Diagnosis of mCRPC was based on the following conditions: histologically or cytologically confirmed adenocarcinoma of the prostate; surgical or medical castration with testosterone levels of <50 ng/dL; an evidence of progression (PSA progression in accordance with PSAWG criteria or objective progression by RECIST Version 1.0 criteria); and target or non-target metastatic abnormalities. Hematology and liver transaminase test results at screening had to meet predefined criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] values <2.5×upper limit of normal [ULN]).

Subjects were excluded if they had received other hormonal therapy, systemic corticosteroid therapy, radiotherapy, chemotherapy, or immunotherapy within 4 weeks before Cycle 1 Day 1; prior therapy with ketoconazole for prostate cancer, 17α-hydroxylase/$C_{17, 20}$ lyase (CYP17) inhibitor(s), or investigational agent(s) targeting the AR. Subjects were excluded if they had uncontrolled hypertension, clinically significant heart disease, viral hepatitis or chronic liver disease, brain metastasis, serious or uncontrolled co-existent disease including active and uncontrolled infection; history of pituitary or adrenal insufficiency or hyperaldosteronism; medical condition or comorbidity that could have interfered with their participation in the study.

Test P roduct, Dose and Mode of A dministration, Batch No .: Abiraterone acetate, 1,000 mg/day (4×250 mg tablets) given orally; lot numbers: DTXM, HFZX

Duration of Treatment: Subjects were to receive treatment until disease progression or unacceptable toxicity was observed. Subjects were to discontinue the study drug at disease progression unless the investigator deemed that they continued to derive benefit from abiraterone acetate. If the study treatment was continued after the approval of abiraterone acetate, it was continued up to the switch from the study drug to the market product upon the delivery of the market product to the study site.

Criteria for Evaluation:

***Efficacy Evaluations*:** The primary endpoint was the proportion of subjects achieving PSA response (ie, the first occurrence of PSA decline of ≥50% from baseline which was subsequently confirmed by a measurement obtained at least 4 or more weeks after initial documentation) by 12 weeks of therapy in accordance with PSAWG criteria. The secondary endpoints included the following: PSA response rate (confirmed or unconfirmed) during the treatment period; the duration of a PSA response; serum PSA decline evaluated in accordance with PCWG2 criteria; RAD-ORR in subjects with measurable lesions using RECIST Version 1.0; clinical benefit, as determined by disease stabilization and change in ECOG PS; overall survival; PSA-PFS based on progression defined in accordance with PSAWG criteria; RAD-PFS based on progression defined by RECIST Version 1.0; and modified-PFS. Other endpoints included pain palliation rate using Brief Pain Inventory-Short Form (BPI-SF); change from baseline over time in BPI-SF; time to pain progression evaluated with BPI-SF; and CTC conversion rate.

Pharmacokinetic and Pharmacodynamic Evaluations: Blood samples were collected for determination of plasma concentrations of abiraterone (and if required, selected metabolites) and serum concentrations of testosterone and dehydroepiandrosterone sulfate (DHEA-S).

***Safety Evaluations*:** Safety assessments included AEs and SAEs; clinical laboratory tests for hematology, serum chemistry, urinalysis, and drug lymphocyte stimulation test (DLST); electrocardiogram (ECG) findings; vital signs (blood pressure, pulse rate, and body temperature); and physical examinations (weight). A drug-related AE was defined as an AE that had a relationship to the drug assessed as possible, probable, or very likely (ie, related to abiraterone acetate, prednisolone, or both).

Statistical Methods:

***Sample Size Determination*:** In an overseas Phase 2 study (COU-AA-003) with docetaxel-failure mCRPC subjects, the confirmed PSA response rate by Week 12 was 36% (17 of 47). In another overseas Phase 2 study (COU-AA-004) with docetaxel-failure mCRPC subjects, the confirmed PSA response rate was 48% (15 of 31) for the subjects with no prior ketoconazole use. On the other hand, the PSA response rates in studies of docetaxel were between 12% and 15% in the mitoxantrone and prednisone group, and 21% to 22% in prednisone monotherapy. On the basis of these results, a threshold response rate of 20% was established, and an expected response rate of 40%, 20% higher than the threshold response rate, was assumed. Thirty-eight subjects were required in the efficacy analysis to demonstrate that the lower limit of the two-sided 90% CI of the response rate would exceed the threshold response rate with a power of 80%.

***Efficacy Analyses*:** The primary analysis population for efficacy was the FAS, which was defined as the subjects who received treatment with the study drug at least once and had any posttreatment PSA assessment data. Sensitivity analysis was performed on the evaluable set. For the primary endpoint, the PSA response rate by 12 weeks of therapy in accordance with PSAWG criteria and its two-sided exact 90% CI were calculated. For the secondary endpoints, all continuous variables were summarized using descriptive statistics. Categorical variables were summarized using frequencies and percentages. The Kaplan-Meier product-limit method was used to estimate the median event-free time for the time-to-event data. The corresponding 90% CIs for the median time estimates were calculated. Kaplan-Meier curves were also graphed.

***Pharmacokinetic and Pharmacodynamic Analyses*:** Subjects who received treatment with the study drug at least once and had measurements of plasma drug concentrations were defined as the pharmacokinetic

analysis set. Descriptive statistics were calculated for predose and certain postdose plasma concentrations of abiraterone or its metabolite at each visit, and by dose levels (if applicable) at each visit.

Subjects who received treatment with the study drug at least once and had measurements of pharmacodynamic assessments were defined as the pharmacodynamic analysis set. Using serum concentrations of testosterone and DHEA-S measured for each subject, descriptive statistics of the serum concentrations and the changes from predose of the study drug were calculated at each sampling time.

***Safety Analyses*:** Safety analyses were performed on the safety analysis set, which included the subjects who received treatment with the study drug at least once. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0 and graded in accordance with Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. All reported AEs with onset during the treatment period (ie, treatment-emergent AEs including AEs that worsened postbaseline) were included in the analysis. For each AE, the proportion of subjects who experienced at least 1 occurrence of the given event was calculated. Other safety data (eg, laboratory tests, vital signs, and ECG) were summarized at each scheduled time point using descriptive statistics and frequency tables.

RESULTS:

STUDY POPULATION:

Of the 47 treated subjects, treatment with the study drug was discontinued for all subjects, mainly because of progressive disease (PD) or prohibited medicine use (29.8%, each).

The demographic and baseline disease characteristics of subjects were generally consistent with those of the planned study population. All subjects had a diagnosis of prostate cancer with evidence of disease progression. For the 47 subjects in the safety analysis set, the median age was 72.0 years (range: 51, 83), with 13 (27.7%) subjects being 75 years of age or older. The median baseline PSA concentration was 143.00 ng/mL. All 47 subjects had received prior hormone therapy and docetaxel-based chemotherapy for mCRPC, and 45 subjects were being treated with a luteinizing hormone-releasing hormone (LH-RH) agonist or antagonist.

Major protocol deviations were reported for 17 (36.2%) subjects during the study. The most common deviation was the use of prohibited concomitant medications or therapies (16 subjects), followed by entering the study without meeting the entry criteria (3 subjects). Although one additional event (not withdrawing from the study after meeting the withdrawal criteria) was mentioned in the first interim report, it is not handled as a protocol deviation in this report.

The median duration of abiraterone acetate treatment was 8.34 months (range: 0.2, 25.8). The median number of treatment cycles was 10.0 cycles (range: 1, 28), with 35 (74.5%) subjects having started 6 or more cycles.

EFFICACY RESULTS:

- The primary efficacy endpoint was the proportion of subjects achieving a PSA decline of ≥50% from baseline by 12 weeks of therapy in accordance with PSAWG criteria; ie, the PSA response rate by Week 12. The confirmed PSA response rate by Week 12 for the FAS was 28.3% (90% CI: 17.6%, 41.1%). The lower limit of the two-sided 90% CI (17.6%) was lower than the threshold response rate of 20%. Sensitivity analysis of the primary efficacy endpoint was also performed for the evaluable set, in which the confirmed PSA response rate was 31.0% (90% CI: 19.4%, 44.6%).
- Exploratory analysis of the PSA response rate showed a confirmed ≥30% decline in PSA from baseline in 32.6% (90% CI: 21.3%, 45.7%) of subjects by Week 12 for the FAS, a confirmed ≥75% decline in PSA in 19.6% (90% CI: 10.6%, 31.7%), and a confirmed ≥90% decline in PSA in 4.3% (90% CI: 0.8%, 13.1%).

- In some subgroups, apparent differences in the proportion of subjects with a confirmed PSA response were observed. These subgroups included those categorized by the baseline ECOG PS score, number of prior chemotherapy regimens, baseline PSA category, baseline alkaline phosphatase (ALP) category, and baseline BPI-SF. In the subgroup categorized by the baseline ECOG PS score, the proportion of subjects with a confirmed PSA response decreased with increases in the baseline ECOG PS score (score of 0: 33.3%; score of 1: 25.0%; score of 2: 16.7%).
- The confirmed PSA response rate during the treatment period (28.3% [90% CI: 17.6%, 41.1%]) was the same as that achieved by Week 12, indicating that all subjects with a PSA response achieved the response by Week 12.
- The median PSA response duration was estimated to be 142.0 days (90% CI: 85.0, 394.0). Of 13 subjects with a confirmed PSA response during the treatment period, 12 (92.3%) had PSA progression
- Based on the best overall response, an objective radiographic response of partial response (PR) was observed in 1 (4.5%) of 22 subjects with measurable lesions at baseline. No subjects achieved complete response (CR). Stable disease (SD) was reported for 9 (40.9%) subjects.
- Clinical benefit, determined by disease stabilization and change in ECOG PS, was documented for 16 (34.8%) of 46 subjects. Among these 16 subjects, 81.3% (13 of 16) showed a PSA response.
- The median overall survival was 550.0 days (90% CI: 405.0, 658.0). Of the 46 subjects, 28 (60.9%) had died. The 6-month survival rate was estimated to be 0.891 (90% CI: 0.786, 0.946).
- The median PSA-PFS was 108.5 days (90% CI: 85.0, 114.0). Of the 46 subjects, 45 (97.8%) met the criteria for PSA-based progression. The 6-month PSA-based progression-free rate was estimated to be 0.217 (90% CI: 0.127, 0.323).
- The median RAD-PFS was 106.0 days (90% CI: 85.0, 169.0). All 45 subjects with the evaluable data for RAD-PFS met the criteria for radiographic progression. The 6-month radiographic progression-free rate was estimated to be 0.378 (90% CI: 0.261, 0.494).
- The median modified-PFS was 273.0 days (90% CI: 239.0, 337.0). Of the 46 subjects, 45 (97.8%) met the criteria for modified progression. The 6-month modified progression-free rate was estimated to be 0.674 (90% CI: 0.546, 0.773).
- The pain palliation response, evaluated using the BPI-SF, was observed in 9 (56.3%) of 16 subjects with a baseline pain score of ≥4. The median time to pain progression, on the basis of BPI-SF, was not reached. Of the 16 subjects with a baseline pain score of ≥4, 4 (25.0%) had pain progression. The 6-month pain progression-free rate was estimated to be 0.795 (90% CI: 0.548, 0.916).
- CTC conversion was observed in 9 (36.0%) of 25 subjects whose baseline CTC count was ≥5.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Plasma abiraterone concentrations were maintained during treatment with abiraterone acetate in combination with prednisolone. Serum concentrations of testosterone and DHEA-S declined to below quantification limit levels during treatment with abiraterone acetate in combination with prednisolone.

SAFETY RESULTS:

Treatment with abiraterone acetate in combination with prednisolone was generally safe and well tolerated in Japanese subjects with mCRPC who had previously received docetaxel-based chemotherapy.

Treatment-emergent AEs were reported for 44 (93.6%) of 47 subjects. The most common (reported for ≥10% of subjects) AEs were upper respiratory tract infection (17 subjects, 36.2%), hepatic function abnormal (12 subjects, 25.5%), constipation (11 subjects, 23.4%), weight decreased (8 subjects, 17.0%), hypokalemia, nausea (7 subjects each, 14.9%), diabetes mellitus, hypophosphatemia, disease progression

(6 subjects each, 12.8%), urinary tract infection, hypercholesterolemia, and vomiting (5 subjects each, 10.6%).

The most severe AE reported for each subject was mainly Grade 2 (15 of 47 subjects, 31.9%) or Grade 3 (21 subjects, 44.7%). The Grade 5 AEs were disease (prostate cancer) progression leading to death, reported for 3 (6.4%) subjects. Grade 4 AEs were reported for 2 (4.3%) subjects, which included cerebral infarction and subarachnoid hemorrhage for 1 subject, and disease (prostate cancer) progression and hypocalcemia for another subject. The most common (reported for ≥2 subjects) Grade 3 AEs were hepatic function abnormal, hypophosphatemia (4 subjects each, 8.5%), hypermagnesemia, pneumonia, urinary tract infection (3 subjects each, 6.4%), anemia, osteonecrosis of jaw, and disease progression (2 subjects each, 4.3%).

Twenty-eight (59.6%) of 47 subjects experienced at least 1 AE considered by the investigator to be drug related (abiraterone acetate or prednisolone). The most common (reported for ≥5% of subjects) drug-related AEs were hepatic function abnormal (6 subjects, 12.8%), diabetes mellitus, hypokalemia (5 subjects each, 10.6%), hypercholesterolemia, hypertension (4 subjects each, 8.5%), and weight increased (3 subjects, 6.4%). No Grade 4 or 5 drug-related AEs were reported in the study. Eleven (23.4%) subjects had Grade 3 drug-related AEs. Pneumonia and hepatic function abnormal were the most common Grade 3 drug-related AEs, reported for 2 (4.3%) subjects each.

Eight subjects died within 30 days after the last study drug treatment. Of these, 6 subjects died of AEs within 30 days after the last study drug treatment. One subject died of Grade 4 cerebral infarction and Grade 4 subarachnoid hemorrhage. The other 5 died of Grade 5 (3 subjects) or Grade 3 (2 subjects) disease (prostate cancer) progression. None of these events that led to death were considered to be related to the study drug by the investigator.

SAEs were reported for 21 (44.7%) of 47 subjects in the study. The most common (reported for ≥2 subjects) SAEs were disease (prostate cancer) progression for 6 (12.8%) subjects, pneumonia and urinary tract infection for 3 (6.4%) subjects each, and anemia and dehydration for 2 (4.3%) subjects each. Drug (abiraterone acetate or prednisolone)-related SAEs were reported for 7 (14.9%) subjects, all of which were Grade 3 (pneumonia in 2 subjects, cataract, dehydration, sepsis, and epididymitis) or Grade 2 (gastroenteritis and pancreatitis) in severity. Among the 8 drug-related SAEs, pancreatitis resulted in study drug discontinuation, and gastroenteritis, dehydration, and epididymitis led to study drug interruption.

Treatment with the study drug was discontinued because of AEs for 8 (17.0%) of 47 subjects. These events included 4 disease (prostate cancer) progressions (2 events of Grade 5 and 1 event each of Grade 4 and Grade 3), Grade 4 cerebral infarction, Grade 3 urinary bladder hemorrhage, and Grade 2 pancreatitis and depression (1 event each). Among the AEs that led to discontinuation, pancreatitis was the only event considered to be related to the study drug.

AEs of special interest (hepatotoxicity, anemia, hypokalemia, fluid retention/edema, hypertension, osteoporosis, cardiac disorders, and cataract) were reported for 30 (63.8%) of 47 subjects. The most common (reported for ≥5% of subjects) AEs of special interest were hepatic function abnormal (12 subjects, 25.5%), hypokalemia (7 subjects, 14.9%), hypertension (4 subjects, 8.5%), anemia, and edema (3 subjects each, 6.4%). Most AEs of special interest were Grade 1 or 2 in severity. Grade 3 AEs of special interest included hepatic function abnormal (4 subjects, 8.5%), anemia (2 subjects, 4.3%), hyperbilirubinemia, hypokalemia, hypertension, and cataract (1 subject, 2.1%), none of which led to study drug discontinuation. No Grade 4 or 5 AEs of special interest were reported. Among the AEs of special interest, a number of mineralocorticoid-related toxicities were reported: hypokalemia (14.9%), fluid retention/edema (8.5%), and hypertension (8.5%). All such events, except for Grade 3 hypokalemia and Grade 3 hypertension, were Grade 1 or 2 in severity, and none led to study drug discontinuation.

Most laboratory abnormalities for hematology, serum chemistry, and urinalysis were Grade 2 or lower in severity. Grade 4 hematologic abnormality was reported for 1 (2.1%) subject, and Grade 4 serum

chemistry abnormalities for 5 (10.6%) subjects. The parameters with Grade 4 abnormalities were ALP (2 subjects), lymphocytes, urate, amylase, and calcium (1 subject each). The only Grade 4 laboratory-related AE was 1 event of hypocalcemia.

Mean changes from baseline in vital signs were considered to be not clinically relevant. Postbaseline QTcB (Bazett) and QTcF (Fridericia) values of ≥500 msec were reported for 1 (2.1%) subject each. However, no subjects had QTcB or QTcF prolongation of >30 msec from baseline. Three ECG-related AEs were reported. These events were Grade 2 electrocardiogram QT prolonged, Grade 1 atrial fibrillation, and Grade 1 bundle branch block right, reported for 1 (2.1%) subject each. All 3 events were non-serious, and none of them led to study drug discontinuation.

Most subjects started the study with an ECOG PS score of 0 or 1, and none had a score of 3 or 4 at baseline. During the postbaseline treatment period, 7 (14.9%) subjects had a worst ECOG PS score of 3, and 3 (6.4%) had a score of 4.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

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