**Janssen Research & Development**

# Clinical Study Report: Synopsis [Protocol JNJ-212082-JPN-201; Phase 2]

## 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. Names of companies other than Janssen Research & Development or Johnson & Johnson affiliates have been redacted, unless a contractual agreement is in place with those companies to disclose their names.
- Information has been removed or redacted to protect commercially confidential information.
- Aggregate data have been included, with any direct reference to an individual patient or study subject excluded.
- To disclose as much scientifically useful data as possible, no information other than that outlined above has been removed or redacted.

## SYNOPSIS

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

**Status:** Approved

**Date:** 23 March 2015

**Prepared by:** Janssen Pharmaceutical K.K.

**Protocol No.:** JNJ-212082-JPN-201

**Title of Study:** A Phase 2 Study of JNJ-212082 (abiraterone acetate) in Metastatic Castration-Resistant Prostate Cancer Patients Who Are Chemotherapy-Naïve

**NCT No.:** NCT01756638

**Clinical Registry No.:** CR017059

**Coordinating Investigator:** No coordinating investigator

**Study Centers:** 21 sites in Japan

**Publication (Reference):** Matsubara N, Uemura H, Satoh T, et al. A phase 2 trial of abiraterone acetate in Japanese men with metastatic castration-resistant prostate cancer and without prior chemotherapy (JPN-201 Study). Jpn J Clin Oncol; 2014; 44(12): 1216-26.

**Study Period:** 1 June 2012 (first subject enrolled) to 8 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 chemotherapy-naïve subjects with metastatic castration-resistant prostate cancer (mCRPC).

The primary hypothesis of the study was that the lower limit of the two-sided 90% confidence interval (CI) of the primary endpoint (ie, the proportion of study-drug-treated subjects achieving PSA response by 12 weeks of therapy in accordance with PSAWG criteria) would be higher than 35%.

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

The exploratory objectives were to explore the correlations among CTC enumeration, 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 21 sites in Japan to evaluate the safety and efficacy of abiraterone acetate in subjects with mCRPC who had not received prior cytotoxic chemotherapy. A target sample of 45 subjects was to be analyzed. The study consisted of a screening period (within 14 days before Cycle 1 Day 1), a treatment period (from Cycle 1 Day 1 until disease progression or occurrence of 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). Each cycle of treatment was 28 days. Eligible subjects were orally given abiraterone acetate 1,000 mg once daily at least 1 hour before a meal and 2 hours after a meal any time up to 10 PM every day. Oral prednisolone (5 mg) was concomitantly administered twice daily. Subjects were to be followed for safety for 30 days after the last dose of study drug. An Independent Data Monitoring Committee was formed to evaluate safety data on an ongoing basis to ensure the continuing safety of the subjects enrolled in 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 Ministry of Health, Labour and Welfare (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 (planned and analyzed):** A total of 45 subjects were planned to be analyzed for efficacy. Of the 56 screened subjects, 48 were treated. The number of subjects included in each analysis set was as follows: safety analysis set: 48; full analysis set (FAS): 48; evaluable set: 44; pharmacokinetic analysis set: 48; pharmacodynamic analysis set: 48.

**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 or 1 and who had not received cytotoxic chemotherapy 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; 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, CYP17 (17α-hydroxylase/$C_{17, 20}$ lyase) inhibitor(s), or investigational agent(s) targeting the AR. Subjects were excluded if they had uncontrolled hypertension, clinically significant heart disease, 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 Product, Dose and Mode of Administration, Batch No.:** Abiraterone acetate, 1,000 mg/day (4×250 mg tablets) given orally; lot numbers: DTXM and 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, a PSA decline of ≥50% from baseline) by 12 weeks of therapy in accordance with PSAWG criteria. The secondary endpoints included 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 Pharm acodynamic 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 assessment was based on reported AEs, SAEs, clinical laboratory tests (hematology, serum chemistry, urinalysis, and drug lymphocyte stimulation test [DLST]), vital sign measurements (blood pressure, pulse rate, and body temperature), physical examinations (weight), and electrocardiogram (ECG) findings. 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 1/2 study (Study COU-AA-001) conducted in chemotherapy-naïve castration-resistant prostate cancer (CRPC) subjects, the confirmed PSA response rate by Week 12 was 60% (25 of 42) in the 1,000 mg dose group. In another overseas Phase 1/2 study (Study COU-AA-002) conducted in chemotherapy-naïve CRPC subjects, the response rates were 55% (18 of 33) and 67% (22 of 33) in Phase 1 part and Phase 2 part, respectively. On the other hand, the threshold response rate of 35% was established based on the result from a study of docetaxel, where the PSA response rates were 45% and 32% in the docetaxel every 3 weeks + prednisone group and the mitoxantrone + prednisone group, respectively. Thus, we assumed an expected response rate as 55%, 20% higher than the threshold response rate (35%). A total of 45 subjects were required for 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 post-treatment 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 and other endpoints, all continuous variables were summarized using descriptive statistics. Categorical variables were summarized using frequencies and percentages. Kaplan-Meier product-limit method was used to estimate the median event-free time for the time-to-event data. The corresponding 90% CI for the median time estimate was calculated. Kaplan-Meier curve was 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 pre-dose and certain post-dose 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 pre-dose of the study drug were calculated for 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 post baseline) 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 48 treated subjects, all subjects had discontinued study treatment, mainly because of progressive disease (PD) (54.2%), other reasons (8 subjects, 16.7%), and safety reasons (4 subjects, 8.3%).

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 48 subjects in the safety analysis set, the median age was 70.0 years (range: 46, 89), with 15 (31.3%) subjects being 75 years of age or older. The median baseline PSA level was 31.40 ng/mL (range: 6.0, 469.0). All 48 subjects had received hormonal therapy for prostate cancer prior to study entry, and 46 subjects were being treated with a luteinizing hormone-releasing hormone (LH-RH) agonist or antagonist.

Major protocol deviations were reported for 9 (18.8%) subjects. Five subjects had a violation of conditionally permitted medications (ie, initiation or adjustment of bisphosphonate or anti-RANKL monoclonal antibody therapies). Two subjects entered the study without meeting the entry criteria: 1 subject had been treated with docetaxel hydrate, even though the target population for this study was chemotherapy-naïve subjects, and the other subject had received Chinese herbal medicines until 5 days prior to Cycle 1 Day 1. The remaining 2 subjects received incorrect dose of abiraterone acetate.

The median duration of abiraterone acetate treatment was 14.14 months (range: 1.1, 25.8). The median number of treatment cycles was 16.0 (range: 2, 28), with 42 (87.5%) 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 60.4% (90% CI: 47.5%, 72.3%). The lower limit of the two-sided 90% CI was higher than the threshold response rate of 35%, providing evidence of the efficacy of abiraterone acetate. The result of this primary analysis was supported by a sensitivity analysis performed for the evaluable set, in which the confirmed response rate was 61.4% (90% CI: 47.9%, 73.7%).
- Exploratory analysis of the PSA response rate showed that the proportions of subjects achieving confirmed PSA declines of ≥30%, ≥75%, and ≥90% by Week 12 were 72.9% (90% CI: 60.4%, 83.2%), 39.6% (90% CI: 27.7%, 52.5%), and 18.8% (90% CI: 10.1%, 30.4%), respectively.
- The confirmed PSA response rate during the treatment period was 62.5% (90% CI: 49.6%, 74.2%). The result was similar to that by Week 12, which indicates that most subjects with a PSA response achieved the response by Week 12.

- The median PSA response duration was 448.0 days (90% CI: 282.0, 559.0). Of the 30 subjects with a confirmed PSA response during the treatment period, 19 (63.3%) had PSA progression.
- The median percent change in PSA level from baseline at Week 12, determined in accordance with PCWG2 criteria, was -66.62%, with the majority of subjects experiencing a decline in PSA level.
- Of the 18 subjects with measurable lesions, 4 (22.2%) achieved partial response (PR) and met the criteria for objective radiographic response, based on the best overall response. No subjects achieved complete response (CR). Stable disease (SD) was reported for 11 (61.1%) subjects.
- Clinical benefit, determined by disease stabilization and change in ECOG PS, was documented for 37 of 48 subjects (77.1%).
- The median overall survival was not reached. Of the 48 subjects, 16 (33.3%) died. The 6-month survival rate was estimated to be 0.979 (90% CI: 0.897, 0.996).
- The median PSA-PFS was 335.0 days (90% CI: 255.0, 393.0). Of the 48 subjects, 47 (97.9%) met the criteria for PSA-based progression. The 6-month PSA-based progression-free rate was estimated to be 0.703 (90% CI: 0.578, 0.797).
- The median RAD-PFS was 332.0 days (90% CI: 246.0, 449.0). Of the 48 subjects, 47 (97.9%) met the criteria for radiographic progression. The 6-month radiographic progression-free rate was estimated to be 0.638 (90% CI: 0.511, 0.741).
- The median modified-PFS was 351.0 days (90% CI: 246.0, 475.0). Of the 48 subjects, 47 (97.9%) met the criteria for modified progression. The 6-month modified progression-free rate was estimated to be 0.646 (90% CI: 0.520, 0.746).
- The pain palliation rate, evaluated using the BPI-SF, was 69.2% (9 of 13 subjects with a baseline worst pain score of ≥4). The median BPI-SF worst pain score decreased from 1.0 at baseline to 0.0 and was maintained at 0.0 throughout the treatment period. The median time to pain progression, on the basis of BPI-SF, was not reached. Of the 13 subjects with a baseline worst pain score of ≥4, 2 (15.4%) had pain progression. The 6-month pain progression-free rate was estimated to be 0.833 (90% CI: 0.557, 0.945).
- The CTC conversion rate was 55.6% (10 of 18 subjects with baseline CTC count ≥5). The median CTC count decreased from 3.0 at baseline to 0.0 on Day 1 of Cycle 2 and was maintained at 0.0 up to Cycle 4.

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 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 not received prior cytotoxic chemotherapy.

Of the 48 subjects in the safety analysis set, 47 (97.9%) had at least 1 AE. The most commonly reported AEs (ie, those reported for ≥10% of subjects) were hepatic function abnormal (41.7%), upper respiratory tract infection (31.3%), hypokalemia (18.8%), constipation (16.7%), hypercholesterolemia (14.6%), diabetes mellitus (12.5%), hyperglycemia (12.5%), hypertension (12.5%), hyperbilirubinemia (12.5%), back pain (12.5%), cataract (10.4%), and spinal compression fracture (10.4%).

Most AEs were Grade 1 or 2 in severity. Twenty three (47.9%) subjects had at least 1 Grade 3 AE, and 3 (6.3%) subjects had at least 1 Grade 4 AEs. The most commonly reported Grade 3 AE was hepatic function abnormal (10.4%). Grade 3 drug (abiraterone acetate or prednisolone)-related AEs were reported for 11 (22.9%) subjects. These AEs included hepatic function abnormal (8.3%), hypermagnesemia (4.2%), cellulitis, pneumonia, hypophosphatemia, acute myeloid leukemia, diabetes mellitus, hyperglycemia, cataract, hypertension, and pleurisy (2.1% each). Grade 4 drug-related AEs were pneumonia and septic shock (2.1% each).

Three subjects died within 30 days after receiving the last dose of study drug. The investigator considered 1 death (MedDRA PT: death) to be possibly related to abiraterone acetate and 2 deaths (MedDRA PTs: myocardial infarction and cerebrovascular accident) to be of doubtful relationship to abiraterone acetate. Fourteen (29.2%) subjects had SAEs, which consisted of cellulitis, gastroenteritis, herpes zoster, osteomyelitis, pneumonia, septic shock, acute myeloid leukemia, coagulopathy, dehydration, diabetes mellitus, cerebrovascular accident, cataract, myocardial infarction, hypotension, colonic polyp, ileus, death, disease progression, and compression fracture. Apart from the deaths described above, all SAEs were considered to be not related to abiraterone acetate, except that acute myeloid leukemia was considered possibly related and cellulitis was considered to have doubtful relationship.

Seven (14.6%) subjects discontinued abiraterone acetate because of AEs, including Grade 4 pneumonia, Grade 3 hepatic function abnormal, disease progression, and compression fracture, and Grade 2 ventricular tachycardia. Five (10.4%) subjects required dose reduction or interruption of abiraterone acetate because of Grade 4 septic shock, Grade 3 hepatic function abnormal, hypertension, or pleurisy, or Grade 2 ileus. One (2.1%) subject each required dose reduction of prednisolone because of Grade 4 septic shock, Grade 3 cellulitis or pneumonia, or Grade 2 hyperglycemia or diabetes mellitus.

Thirty-six (75.0%) subjects had AEs of special interest in the following categories: hepatotoxicity, hypokalemia, hypertension, osteoporosis, cardiac disorders, anemia, cataract, and fluid retention/edema. Among these, hepatotoxicity-related AEs were most frequent and were reported for 23 (47.9%) subjects. These AEs included hepatic function abnormal (41.7%), hyperbilirubinemia (12.5%), and hypoalbuminemia (4.2%). Most were Grade 1 or 2 in severity, but Grade 3 hepatic function abnormal occurred in 5 (10.4%) subjects. Of these 5 subjects, 3 discontinued abiraterone acetate and 1 required dose reduction of abiraterone acetate.

As mineralocorticoid-related toxicities that are known to be associated with abiraterone acetate, hypokalemia and hypertension were reported for 9 (18.8%) and 6 (12.5%) subjects, respectively. AEs categorized in fluid retention/edema (Grade 1 edema peripheral and edema and Grade 2 joint swelling) were also reported for 3 (6.3%) subjects. Among these subjects with mineralocorticoid-related AEs, 1 subject required dose interruption of abiraterone acetate because of Grade 3 hypertension that was possibly related to abiraterone acetate. All other mineralocorticoid-related AEs were Grade 1 or 2 in severity, except for Grade 3 and Grade 4 hypokalemia.

Other common (reported for ≥5 subjects) AEs of special interest were spinal compression fracture (5 subjects, 10.4%) and cataract (5 subjects, 10.4%). Most were Grade 1 or 2 in severity, but Grade 3 cataract occurred in 2 (4.2%) subjects. None of these events required dose reduction, treatment

interruption, or treatment discontinuation. The remaining AEs of special interest were infrequent and reported for <5 subjects each. There were no AEs reported in the category sexual dysfunction.

Most laboratory abnormalities were Grade 1 or 2 during the treatment period. One (2.1%) subject had Grade 4 abnormality for neutrophils/leukocytes. Although Grade 3 abnormalities were observed for some hematologic and serum chemistry parameters, shifts from baseline by 2 or more grades were infrequent, apart from a Grade 4 abnormality for neutrophils/leukocytes.

Mean changes from baseline in vital signs and ECG parameters were not considered to be clinically relevant. No subjects had QTcB (Bazett) or QTcF (Fridericia) values of ≥500 msec, and no QTcB or QTcF increases of >60 msec from baseline were observed.

All subjects entered the study with an ECOG PS score of 0 or 1, in accordance with the protocol. The ECOG PS scores for most subjects were maintained at 0 or 1 throughout the treatment period.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

**Disclaimer**

*Information in this posting shall not be considered to be a claim for any marketed product. Some 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.*