SYNOPSIS

Name of Sponsor/Company	Janssen Pharmaceutical K.K.*
Name of Investigational Product	Abiraterone acetate (ZYTIGA ®)

* This study is being conducted by Janssen Pharmaceutical K.K. in Japan. The term "sponsor" is used throughout the clinical study report to represent Janssen Pharmaceutical K.K.

Status: Approved

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Prepared by: Janssen Pharmaceutical K.K.

Protocol No.: ABI-C-14-JP-001-V03

Title of Study: A Phase 4 Study of Abiraterone Acetate in Metastatic Castration-Resistant Prostate Cancer Patients Who Poorly Responded to the First-line Combined Androgen Blockade Therapy

NCT No.: NCT02405858

Clinical Registry No.: Not applicable

Coordinating Investigator(s): No coordinating investigator

Study Center(s): 15 study sites enrolled subjects in this study. The number of contracted sites was 17.

Publication (Reference): None

Study Period: 27 May 2015 (Date first subject signed informed consent) to 31 December 2017 (Date of last observation for last subject recorded as part of the database)

Phase of Development: 4

Objectives: The primary objective was to evaluate the response rate of ≥50% decline of prostate-specific antigen (PSA) from baseline (PSA response) by 12 weeks of therapy according to Prostate Cancer Clinical Trials Working Group (PCWG2) criteria in patients with metastatic castration-resistant prostate cancer (mCRPC) who had failed the first-line combined androgen blockade (CAB) therapy.

The secondary objectives were to evaluate the following: the safety of abiraterone acetate, with concurrent prednisolone (10 mg/day); PSA response by 24 weeks of therapy according to PCWG2 criteria; the duration of PSA response and time to PSA response; PSA-based progression-free survival (PSA-PFS); serum PSA decline evaluation according to PCWG2 criteria; the radiographic objective response rate (RAD-ORR) in patients with measurable lesions at baseline using response evaluation criteria in solid tumors (RECIST) version 1.1; radiographic progression-free survival (RAD-PFS) in patients with measurable lesions at baseline (progression defined by RECIST version 1.1); time to next treatment; overall survival (OS); and pain palliation using Brief Pain Inventory – Short Form (BPI-SF).

Methodology: This was a Phase 4, non-randomized, multi-center, open label, single arm study of abiraterone acetate with prednisolone to investigate its efficacy and safety in patients with mCRPC who had failed the first-line CAB therapy. Considering approximately 10% possible exclusion rate, a target of 54 subjects was to be analyzed in this study. If subjects met eligibility and screening requirements, subjects were orally given abiraterone acetate 1,000 mg q.d., concomitantly with oral prednisolone 10 mg/day. No food were to be consumed for at least 2 hours before the dose of abiraterone acetate was taken and for at least one hour after the dose of abiraterone acetate was taken. A 28-daily dosing cycle continued until disease progression or unacceptable toxicity was observed.

Prostate-specific antigen was measured as a key efficacy endpoint. The serum PSA decline was evaluated according to PCWG2 criteria and primary efficacy endpoint was measured by assessing the proportion of subjects achieving a ≥50% PSA decline by 12 weeks of abiraterone acetate therapy. A PSA response is defined as the first occurrence of ≥50% decrease from baseline by 12 weeks after the first dose of study drug, which would be subsequently confirmed by a measurement that is at least 4 or more weeks after the initial documentation. Other endpoints included PSA response rate by 24 weeks, RADORR, PSA-PFS, RAD-PFS, time to PSA response, and OS. After treatment was stopped, subjects were followed for survival until clinical data cutoff of this study unless the subject died, was lost to follow-up, or had withdrawn consent.

We planned the 2 stage design, and an interim analysis was to be performed when 27 subjects were enrolled and treated. In this study, database lock for interim analysis as well as database lock for the final analysis were planned. If the number of responder was 4 subjects or less, further patient enrollment were to be discontinued. If 5 or more responders were identified prior to the interim analysis, the registration was to be continued at the time of interim analysis. Actually, 5 responders were confirmed prior to the interim analysis and the interim analysis was performed to evaluate the data for primary endpoint. The final database lock occurred at clinical data cutoff of this study for generating this Clinical Study Report (CSR) after all subjects had completed assessments for both the final safety and efficacy endpoints including survival assessment.

The schedule for the various study procedures and evaluations is described in detail in the Time and Events Schedule.

During the course of study, an independent data monitoring committee (IDMC) reviewed the efficacy and safety (as needed) information. The committee was composed of urologists with experience in treating patients; none of whom were involved in the study as investigators.

Number of Subjects (planned and analyzed): A minimum of 48 subjects were required for efficacy analyses and the target sample size was set at 54 subjects, considering approximately 10% possible exclusion rate.

A total of 53 subjects were enrolled in the study. Of these, 3 subjects were considered as screen failures and 50 subjects received the study drug. All 50 subjects were included in the safety analysis set (SAF), which was defined as subjects who received at least 1 dose of study drug. Of the 50 subjects, 49 subjects were included in the full analysis set (FAS), which was defined as subjects who received treatment with the study drug at least once and had any post-treatment PSA assessment data. One subject was excluded from the FAS because the subject withdrew the consent before having any post-treatment PSA assessment data.

Diagnosis and Main Criteria for Inclusion: The target population consisted of adult men with mCRPC aged 20 years or older, who did not respond sufficiently to initial CAB therapy: subjects who had PSA progression according to PCWG2 criteria within a year after the start of first-line CAB therapy, or who had PSA progression (PCWG2) without having a normal PSA level (<4.0 ng/mL) in the first-line CAB therapy, and then, subjects who were under PSA progression (PCWG2) after antiandrogen withdrawal. Subjects must have been surgically or medically castrated, with testosterone levels of <50 ng/dL. Subjects must not have been treated with cytotoxic chemotherapy (including estramustine) for the treatment of prostate cancer.

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate 1,000 mg (four 250 mg tablets) were taken orally once daily. Based on the Japanese regulations, marketed products were used for the study; therefore, no batch numbers were provided.

Reference Therapy, Dose and Mode of Administration, Batch No.: Not applicable.

Duration of Treatment: Each cycle of treatment was 28 days. Study windows were calculated from Cycle 1 Day 1 date and every effort was made for the subject to remain on schedule. Discontinuation of a study drug did not result in automatic withdrawal from the study. A subject had ordinarily to be maintained on study treatment until radiographic progression and clinical progression. If a subject had radiographic progression without clinical progression and alternate therapy was not initiated, treatment could continue at the discretion of the investigator. A subject's study treatment had to be discontinued when the subject met predefined conditions including safety reasons. A subject was to be followed for safety for 30 days after the last dose of study drug (if a subject was decided to study off) or until clinical data cutoff of this study as long as a subject continued to take study drug.

Criteria for Evaluation:

EFFICACY EVALUATIONS

The proportion of subjects achieving a ≥50% PSA decline by 12 weeks of study drug administration according to PCWG2 criteria was evaluated. Tumor burden was evaluated with physical examination and imaging in accordance with RECIST Version 1.0 criteria. Overall survival was evaluated until the clinical data cutoff. Pain was evaluated using BPI-SF instrument.

SAFETY EVALUATIONS

Safety was evaluated based on adverse events (AEs), clinical laboratory tests (hematology and serum chemistry), vital sign measurements, and physical examinations. The evaluation period for safety was from the time a signed and dated informed consent form (ICF) was obtained to at least 30 days after the last dose of study drug or recovery from all acute toxicities associated with the study drug administration. Adverse events were to be reported by the subject for the duration of the study. Adverse events including laboratory AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) and were graded and summarized according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0.

Statistical Methods:

SAMPLE SIZE DETERMINATION

In patients who had PSA progression within a year after the start of androgen deprivation therapy or who had PSA progression without having a normal PSA level (<4.0 ng/mL) in androgen deprivation therapy, PSA response rate of secondary hormonal therapy were quite limited (10% to 14%). These data were based on results from small numbers of patients, not robust, but the data suggested that patients who did not respond sufficiently to the initial CAB therapy had a markedly lower PSA response rate against secondary hormonal therapy as compared with good responders to the initial CAB therapy. Abiraterone acetate, a potent 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor, has different mechanism of action from conventional antiandrogens and is expected to improve the prognosis of disease.

Therefore, we assumed an expected PSA response rate of 35%: clinically meaningful 20% higher than the threshold response rate (15%; conventional antiandrogen replacement therapy). A total of 48 subjects were required for efficacy analysis (α=0.025, and 1-β=0.9) and the sample size was calculated according to Simon's minimax design. Considering approximately 10% possible exclusion rate; therefore, the sample size was set at 54 subjects.

EFFICACY

The primary endpoint was the proportion of subjects achieving PSA response (PSA response rate) by 12 weeks of therapy from baseline according to PCWG2 criteria. A PSA response was defined as the first occurrence of ≥50% decrease from baseline by 12 weeks after the first dose of study drug, which would be

subsequently confirmed by a measurement obtained at least 4 or more weeks after the initial documentation. The proportion and its two-sided exact 95% confidence interval (CI) were calculated.

The secondary endpoints were the following: the duration of PSA response and time to PSA response, PSA response by 24 weeks according to PCWG2 criteria, PSA-PFS with progression defined according to PCWG2 criteria, serum PSA decline evaluation according to PCWG2 criteria, RAD-ORR in subjects with measurable lesions at baseline using RECIST version 1.1, RAD-PFS in subjects with measurable lesions at baseline (progression defined by RECIST version 1.1), time to next treatment, OS, and pain palliation using BPI-SF. For the secondary endpoints, all continuous variables were summarized using descriptive statistics, which included the number of subjects (N), mean, standard deviation (SD), median, minimum, and maximum. 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 95% CI for the median time estimate was calculated. The graph of Kaplan-Meier curve was also presented.

SAFETY

Subjects who received at least 1 dose of study drug were analyzed for safety. The safety parameters evaluated were the incidence, intensity, and type of AEs, clinically significant changes in the subject's physical examination findings, vital sign measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment were tabulated.

RESULTS:

STUDY POPULATION:

A total of 50 subjects were eligible for this study (in this CSR, these subjects are called as subjects enrolled and received the first dose of study drug) and all 50 subjects were treated with the study drug. Of these, 41 subjects (82.0%) discontinued the study drug and 9 subjects (18.0%) were treated with study drug at the time of data cutoff. The most common reason for discontinuation was physician's decision in (22 subjects, 44.0% of subjects enrolled and received the first dose of study drug), followed by progressive disease (15 subjects, 30.0%), withdrawal of consent (3 subjects, 6.0%), and AEs (1 subjects, 2.0%).

The median age of 50 subjects in the SAF was 73.0 years (range, 55-86 years). All 50 subjects were Asian male. The median weight was 64.80 kg (range, 45.0-114.1 kg). The interpretation of electrocardiogram (ECG) was "within normal limits" for 36 subjects (72.0%) and "abnormal, clinically insignificant" for 14 subjects (28.0%).

All 50 subjects had mCRPC with evidence of progression: 1 subject had disease progression as defined by RECIST 1.1 and all subjects had PSA progression as defined by PCWG2 criteria. At initial diagnosis, the median PSA level was 433.3500 ng/mL (range, 7.360-13740.122 ng/mL) and the total Gleason score of 9 was most common (31 subjects, 62.0%). Most subjects (49 subjects, 98.0%) were in Stage IV and 44 subjects (88.0%) had bone metastases.

Major protocol deviations were reported in 9 subjects (18.0%). The reported major deviations were as follows: use of an inappropriate version of ICF (3 subjects, 6.0%), noncompliance with the guidelines of abnormal liver function test (2 subjects, 4.0%), delay in reporting SAE (2 subjects, 4.0%), missing posttreatment follow-up visit (2 subjects, 4.0%), missing imaging assessment at the scheduled visit (1 subject, 2.0%).

The duration of exposure to abiraterone acetate was consistent with the duration of exposure to prednisolone, with the median cycles of 8.86 (range, 0.5-27.9 cycles) and the median weeks of 35.43 (range, 2.1-111.7 weeks). About half of the subjects (26 subjects, 52.0%) received 9-cycle treatment with the study drug.

Dose reduction and dose interruption of abiraterone acetate were required in 8 subjects (with 1 to 2 times of dose reduction) and 6 subjects (with 1 to 3 times of dose interruption), respectively. Dose reduction and dose interruption of prednisolone were required in 5 subjects (with 1 to 3 times of dose reduction) and 2 subjects (with 1 to 2 times of dose interruption), respectively.

EFFICACY RESULTS:

The following results of this study demonstrated the clinical efficacy of abiraterone acetate plus prednisolone in treatment of subjects with mCRPC who poorly responded to the first-line CAB therapy:

- Of 49 subjects in the FAS, 27 subjects achieved PSA response by 12 weeks; the response rate was 55.1% (95% CI: 40.2%-69.3%). The lower limit of the two-sided 95% CI (40.2%) exceeded the predefined threshold value of 15%.
- The result of PSA response by 24 weeks was consistent with the result by 12 weeks: 27 of 49 subjects in the FAS achieved PSA response by 24 weeks and the response rate was 55.1% (95% CI: 40.2%-69.3%).
- The median duration of PSA response for 28 subjects with PSA response was estimated to be 24.1 weeks (95% CI: 12.14-64.00). The median time to PSA response from the first dose of study drug for the 28 subjects was 28.5 days (95% CI: 28.00-56.00).
- The median PSA-PFS from the first dose of study drug for 49 subjects was 24.1 weeks (95% CI: 16.14-28.29).
- The median percent change from baseline in PSA level by 12 weeks and whole period were -59.30 (range, -99.9%-146.0%) and -61.90% (range, -100.0%-146.0%). The majority of subjects had a decline in PSA level during the treatment period.
- Of 49 subjects in the FAS, 9 subjects had measurable lesions at baseline. Of these, no subject achieved CR and 2 subject (22.2%) achieved PR; thus, the RAD-ORR was calculated to be 22.2% (95% CI: 2.8%-60.0%).
- The median RAD-PFS from the first dose of study drug for 49 subjects was 47.1 weeks (95% CI: 35.00-95.00). The median RAD-PFS from the first dose of study drug for 9 subjects with measurable lesions at baseline was 24.1 weeks (95% CI: 12.14-47.14).
- The median time to next treatment was 36.6 weeks (95% CI: 30.00-49.14). Thirty-four subjects (68.0%) received any subsequent therapies. The most common medication was docetaxel (23 subjects, 46.0%).
- The median OS from the first dose of study drug was 102.9 weeks (95% CI: 64.86, NE).
- Of 9 subjects with a worst pain score of ≥4 at baseline, 2 subjects (22.2%) had pain palliation. The median time to pain progression was not estimated.

SAFETY RESULTS:

Safety data from the 50 subjects in the SAF indicated that abiraterone acetate plus prednisolone was generally well tolerated in subjects with mCRPC who poorly responded to the first-line CAB therapy.

- Of 50 subjects in the SAF, 42 subjects (84.0%) had at least 1 TEAE. Three subjects (6.0%) had a TEAE leading to death and 7 subjects (14.0%) had serious TEAEs. Two subjects (4.0%) had a TEAE leading to study drug discontinuation. Abiraterone acetate related TEAE and prednisolone related TEAE were reported for 25 (50.0%) and 18 (36.0%) subjects, respectively. Thirty-one subjects (62.0%) had at least 1 drug-related TEAEs.

- The most common TEAE by preferred term was nasopharyngitis (15 subjects, 30.0%), followed by ALT increased (14 subjects, 28.0%) and AST increased (13 subjects, 26.0%). Other common TEAEs included blood ALP increased (10 subjects, 20.0%), blood lactate dehydrogenase increased (9 subjects, 18.0%), hyperglycemia, constipation, and back pain (6 subjects, 12.0% each), and malaise and weight decreased (5 subjects, 10.0% each). No other TEAEs were reported in more than 10% of subjects.
- Overall, 3 (6.0%) of 50 subjects experienced Grade 5 TEAEs of worst severity. Three subjects (6.0%) experienced Grade 4 TEAEs and 16 subjects (32.0%) experienced at least 1 TEAE of Grade 3. The reported Grade 4 TEAEs were cancer pain, bone marrow failure, chronic obstructive pulmonary disease, and gastric ulcer (1 subject, 2.0% each). The most common Grade 3 TEAE was ALT increased (6 subjects, 12.0%), followed by hyperglycemia and AST increased (5 subjects, 10%), blood ALP increased (3 subjects, 6.0%), and hypertension (2 subjects, 4.0%). All other Grade 3 TEAEs were reported in 1 subject (2.0%) each.
- Drug-related TEAEs were reported in 31 subjects (62.0%). The most common drug-related TEAE was ALT increased (13 subjects, 26.0%), following by AST increased (11 subjects, 22.0%), blood lactate dehydrogenase increased (8 subjects, 16.0%), hyperglycaemia and blood ALP increased (6 subjects each, 12.0%), diabetes mellitus and gamma-glutamyltransferase increased (4 subjects each, 8.0%). All other drug-related TEAEs were reported in 1 subject (2.0%) each, except for malaise (3 subjects, 6.0%) and hot flush and weight increased (2 subjects each, 4.0%). Twenty-five (50.0%) subjects had at least 1 TEAE considered by the investigator to be related abiraterone acetate. The most common abiraterone acetate-related TEAE was ALT increased (13 subjects, 26.0%), followed by AST increased (11 subjects, 22.0%), blood lactate dehydrogenase increased (8 subjects, 16.0%), blood ALT increased (6 subjects, 12.0%), and gamma-glutamyltransferase increased (4 subjects, 8.0%). All other abiraterone acetate-related TEAEs were reported in 1 subject (2.0%) each, except for malaise (3 subjects, 6.0%). Eighteen (36.0%) subjects had at least 1 TEAE considered by the investigator to be related prednisolone. The most common prednisolone-related TEAE was hyperglycaemia (6 subjects, 12.0%), followed by diabetes mellitus (4 subjects, 8.0%), and hot flush and weight increased (2 subjects, 4.0%). All other prednisolone-related TEAEs were reported in 1 subject (2.0%) each.
- The TEAEs leading to death reported in 3 subjects were aortic dissection, dyspnea, and pulmonary hypertension (1 subject, 2.0% each). All 3 TEAEs leading to death were considered unrelated to the study drug.
- Serious TEAEs other than TEAEs leading to death reported in 7 subjects were as follows: 1 subject had atrial flutter and hypercalcemia, 1 subject had cancer pain, 1 subject had chronic obstructive pulmonary disease, 1 subject had bone marrow failure, and 1 subject had gastric ulcer and lung neoplasm malignant. Of these, atrial flutter and hypercalcemia were considered related to abiraterone acetate, and atrial flutter and gastric ulcer ware considered related to prednisolone.
- Two subjects (4.0%) had a TEAE leading to study drug discontinuation. Each subject experienced 1 TEAE: cancer pain (Grade 4) and vomiting (Grade 1). The cancer pain event was considered unrelated to the study drug. The vomiting event was considered related to abiraterone acetate and prednisolone.
- With regard to hematology values, no subjects experienced the worst grade of Grade 3 or higher during the study for any hematology parameters. For shifts in grade showing worsening between the baseline grade and the worst grade, 1 subject showed 2 grade worsening (Grade 0 to Grade 2) in hemoglobin. Other shifts observed in hematology were 1 grade worsening.
- Most of reported worst grades in chemistry values were Grade 2 or lower. Worst grade of Grade 3 was reported for the following parameters: fasting glucose (8 subjects), ALP and ALT (6 subjects each), AST (5 subjects), and sodium, potassium, and albumin (1 subject each). Of these, 3 grade worsening

from baseline (Grade 0 to Grade 3) was observed in ALT (6 subjects), AST (3 subjects), and potassium increase and fasting glucose increase (1 subject each). Two grade worsening (Grade 0 to Grade 2) was observed in ALT (4 subjects), fasting glucose increase and AST (3 subjects), and potassium increase, creatinine, albumin and total bilirubin (1 subject each). Two grade worsening (Grade 1 to Grade 3) was observed in fasting glucose increase (5 subjects), ALP and AST (2 subjects each), and sodium decrease and albumin (1 subject each). Other reported worst grades of Grade 3 were 1 grade worsening or unchanged grade (Grade 2 or Grade 3 at baseline).

- Mean changes from baseline in vital signs and physical examinations were generally minor.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The results of the study indicate that abiraterone acetate at a dose of 1,000 mg/day plus prednisolone 10 mg/day showed favorable efficacy and safety profiles in subjects with mCRPC who poorly responded to the first-line CAB therapy.

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