Janssen Research & Development

Clinical Study Report Synopsis
[JNJ-212082; Phase 1]

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: 16 March 2015

Prepared by: Janssen Pharmaceutical, K.K.

Protocol No.: JNJ-212082-JPN-102

Title of Study: Phase 1 study of JNJ-212082 (abiraterone acetate) in Chemotherapy-Naïve Patients With Castration-Resistant Prostate Cancer

NCT No.: NCT01186484

Clinical Registry No.: CR017137

Coordinating Investigator(s): No coordinating investigator (multicenter)

Study Centers: 5 sites in Japan

Publication (Reference): Matsubara N, Uemura H, Fukui I, et al. Phase-1 study of abiraterone acetate in chemotherapy-naïve Japanese patients with castration-resistant prostate cancer. Cancer Sci. 2014 Oct;105(10):1313-20.

Study Period: 28-June-2010 (date of first subject enrolled) to 2-October-2014 (date of last subject's last visit)

Phase of Development: Phase 1

Objectives:

Primary objective:

The primary objective of this study was to assess the pharmacodynamics and safety of JNJ-212082 (abiraterone acetate) for determining the recommended dose of abiraterone acetate in Japanese patients with castration-resistant prostate cancer (CRPC).

Secondary objectives:

The secondary objectives were as follows:

- To evaluate the pharmacokinetics (single dose monotherapy, multiple dose monotherapy, and multiple dose with prednisolone).
- To evaluate the efficacy of abiraterone acetate for preliminary purposes.

Hypothesis:

The hypothesis of this study was that abiraterone acetate (up to 1,000 mg once daily for 28 days) would be tolerable in patients with CRPC and a 1,000 mg dose would be confirmed as the recommended dose for the Phase 2 study in Japan based on the drug's pharmacodynamics.

Methodology:

This study was a multicenter, open-label, nonrandomized, dose-escalation study in chemotherapy-naïve patients with CRPC. The objectives were to evaluate the pharmacodynamics, safety, pharmacokinetics, and preliminary efficacy of abiraterone acetate.

The initial dose of abiraterone acetate was 250 mg, 500 mg, or 1,000 mg. Each treatment cycle was 28 days. The administration of abiraterone acetate was continued up to discontinuation for any reason including progression of disease and unacceptable toxicity. Each subject received abiraterone acetate orally once daily at least 1 hour before a meal or at least 2 hours after a meal. From Day 8 in Cycle 1, subjects additionally received 5 mg of prednisolone orally twice daily.

After the 6th amendment of the protocol on 13 May 2011, the dose (up to 1,000 mg) of abiraterone acetate in the subsequent cohort was to be determined by the Study Evaluation Team (SET) on the basis of the safety data, pharmacokinetic data, and other relevant data. Because results in the 250 mg (Cohort 1) and 500 mg (Cohort 2) cohorts suggested the possibility that the pharmacokinetics of abiraterone acetate may be affected by food intake, SET determined the dose and dose timing in Cohort 3 to be 1,000 mg and at least 1 hour before breakfast, respectively (ie, 1,000 [−1 hr] mg). After the 7th amendment of the protocol on 13 December 2011, additional cohorts were to be established to explore the relationship of timing of meals to pharmacodynamics and pharmacokinetics of abiraterone acetate. SET set Cohort 4, in which the dose was 1,000 mg and the dose timing was at least 2 hours after a meal (ie, 1,000 [+2 hr] mg).

Dose limiting toxicity (DLT) was defined as any drug related adverse event (AE) of Grade 3 or higher (except for nausea, vomiting, or diarrhea that was controllable by standard therapy).

In each cohort, 6 subjects were to be enrolled initially. Transition to the subsequent cohort or enrollment of additional subjects in the preceding cohort was determined on the basis of the number of subjects who experienced DLT during the recommended dose assessment period (from Day 1 in Cycle 1 to before study drug administration on Day 1 in Cycle 2). Three additional subjects could be enrolled into each cohort; however, this could be done no more than twice (6 subjects in total). The decision to proceed to the next cohort or to enroll additional subjects in the preceding cohort was made after completion of the safety review by the Study Responsible Physician in Cohort 1 and by SET in Cohort 2 or subsequent cohorts.

Once the safety of 500 mg of abiraterone acetate was confirmed, the dose in subjects receiving 250 mg of abiraterone acetate could be increased to 500 mg from the subsequent cycle. Similarly, once the safety of the 1,000 mg dose was confirmed, the dose in subjects receiving abiraterone acetate at a dose lower than 1,000 mg could be increased up to 1,000 mg from the subsequent cycle. If any of the dose increases were not appropriate for the subject due to safety-related reasons, the subject was to receive abiraterone acetate at the original dose. If the dose in the subject was increased, administration was continued at a dose timing at which the safety had been confirmed. Subjects receiving abiraterone acetate at doses of 250 mg, 500 mg, or 1,000 (−1 hr) mg could receive abiraterone acetate at 1,000 mg at least 2 hours after a meal (1,000 [+2 hr] mg), provided the prostate-specific antigen (PSA) levels of these subjects increased and the investigator deemed it appropriate.

After the 9th 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. If the investigator considered necessary, however, abiraterone acetate could be administered with the approved dosage regimen.

Number of Subjects (Planned and Analyzed):

Planned sample size: 6 to 12 subjects per cohort (however, the total number of subjects was not to exceed 63).

A total of 27 subjects were enrolled in this study: 9 subjects in Cohort 1 (250 mg), 6 subjects in Cohort 2 (500 mg), 6 subjects in Cohort 3 (1,000 [−1 hr] mg), and 6 subjects in Cohort 4 (1,000 [+2 hr] mg).

All 27 subjects were included in the efficacy, safety, pharmacokinetic, and pharmacodynamic analysis sets.

Diagnosis and Main Criteria for Inclusion:

Surgically or medically castrated male patients with CRPC whose testosterone level was <0.5 ng/mL (<2.0 nM) and PSA level was ≥2 ng/mL, who had received no prior chemotherapy, and who had PSA progression in accordance with the Prostate Cancer Clinical Trials Working Group (PCWG2) criteria or disease progression by Response Evaluation Criteria in Solid Tumors (RECIST) criteria (for patients with measurable lesions) after the start of androgen deprivation therapy were enrolled in this study. Patients who had undergone surgery or local prostatic intervention within 4 weeks before the initial administration of the study drug, who had uncontrolled hypertension (systolic blood pressure >160 mm Hg and diastolic blood pressure >95 mm Hg), who had a history of pituitary or adrenal insufficiency or hyperaldosteronism, or who had viral hepatitis or chronic liver disease, or liver metastasis were not enrolled in this study.

Test Product, Dose and Mode of Administration, Batch No.:

JNJ-212082 (abiraterone acetate) was orally administered as a tablet containing 250 mg of abiraterone acetate. The doses were 250 mg (1 tablet of abiraterone acetate) in Cohort 1, 500 mg (2 tablets of abiraterone acetate) in Cohort 2, and 1,000 mg (4 tablets of abiraterone acetate) in Cohort 3 and Cohort 4. During the post-marketing study, subjects received the same dose as during the clinical study. If the investigator considered necessary, abiraterone acetate was administered with the approved dosage regimen. The lot numbers of the abiraterone acetate tablets were TKM and HFZX.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not applicable

Duration of Treatment:

Each treatment cycle was 28 days. The administration of abiraterone acetate was continued up to discontinuation for any reason, including progression of disease and unacceptable toxicity. 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:

Primary endpoints

- Pharmacodynamic endpoints: serum concentrations of corticosterone, testosterone, dehydroepiandrosterone sulfate (DHEA-S), and 11-deoxycorticosterone.
- Safety endpoints: AEs, laboratory measurements (hematology, coagulant factors, blood chemistry, and urinalysis), electrocardiogram (ECG), vital signs, and body weight.

Secondary endpoints

- Pharmacokinetic endpoints: plasma concentrations of abiraterone acetate and abiraterone (and selected metabolites, if required).

Plasma concentrations of abiraterone acetate and abiraterone (and selected metabolites, if required) were determined after a single oral administration of abiraterone acetate as monotherapy (from Days 1 to 2 in Cycle 1), after multiple oral administration of abiraterone acetate as monotherapy (from Days 6 to 8 in Cycle 1), and after multiple oral administration of abiraterone acetate with prednisolone (from Days 14 to 16 in Cycle 1 and Day 1 in Cycle 2).

- PSA evaluation: PSA response rate and criteria of PCWG2.

A PSA response was defined as ≥50% reduction in PSA levels from baseline, which was confirmed to have been maintained for at least 4 weeks.

- Objective tumor response in subjects with measurable lesions based on RECIST.

Statistical Methods:

For pharmacodynamics, descriptive statistics of serum concentrations and their changes or percentage changes from baseline were calculated by cohort. In addition, the relationships between serum concentrations of pharmacodynamic parameters and plasma concentrations of abiraterone were investigated. For safety, AEs and laboratory measurements were graded using *National Cancer Institute-Common Terminology Criteria for Adv erse Ev ents (NCI-CTCAE)* where applicable and summarized in frequency tables. For continuous safety data, including laboratory measurements and vital signs, descriptive statistics of absolute values and changes from baseline were calculated. For pharmacokinetics, pharmacokinetic parameters (eg, C_{max}, t_{max}, and AUC_{24}) were estimated using plasma abiraterone concentrations and the actual time of blood sampling, and descriptive statistics of pharmacokinetic parameters were calculated by cohort. Because most plasma abiraterone acetate concentrations were below quantification limit (BQL) at all cohorts, pharmacokinetic parameters of abiraterone acetate were not estimated. For efficacy, descriptive statistics of PSA levels at each evaluation timepoint and their percentage changes from baseline were calculated. The PSA response rate and its 90% confidence interval were calculated. The best overall response based on RECIST was summarized in a frequency table.

RESULTS:

STUDY POPULATION:

A total of 34 subjects provided informed consent, and 27 subjects (9 in the 250 mg, 6 in the 500 mg, 6 in the 1,000 [−1 hr] mg, and 6 in the 1,000 [+2 hr] mg cohorts) were enrolled in this study.

All of 27 subjects were permanently discontinued from the study. The reasons for discontinuation were disease progression in 18 subjects, switch to market products in 5 subjects, and safety-related reasons in 4 subjects.

The median age was 72.0 years (range, 51-80 years). At screening, almost all subjects (25 subjects, 92.6%) had metastases from prostate cancer. The frequently reported distant metastatic sites were the bone (19 subjects, 70.4%) and lung (6 subjects, 22.2%). The median baseline PSA level was 20.900 ng/mL (range, 2.20-1272.00 ng/mL). The Eastern Cooperative Oncology Group Performance Status (ECOG PS) was 0 in 24 subjects (88.9%) and 1 in 3 subjects (11.1%).

DOSE AND FOOD TIMING:

The median treatment duration of abiraterone acetate was 28.1 weeks (range, 3.1-216.1 weeks), and the median number of cycles of treatment was 7.0 (range, 1-54).

In the 250 mg and 500 mg cohorts, abiraterone acetate was to be administered either at least 1 hour before a meal or at least 2 hours after a meal; however, all subjects whose data were available for the timings of food intake and study drug administration received abiraterone acetate at least 2 hours after a meal on pharmacokinetic measurement days. In the 1,000 mg cohorts, subjects received abiraterone acetate at the

specified timing (at least 1 hour before a meal in the 1,000 [−1 hr] mg cohort and at least 2 hours after a meal in the 1,000 [+2 hr] mg cohort), and the dose timing in relation to mealtime was almost consistent during the treatment period.

SAFETY RESULTS:

DLTs occurred in 1 subject each in the 250 mg, 500 mg, and 1,000 (+2 hr) mg cohorts: Grade 3 hepatic function abnormal, Grade 3 hepatic function abnormal, and Grade 3 hyperamylasemia, respectively. The frequency of DLTs was not dose- or exposure-dependent. Oral administration of abiraterone acetate is tolerable at a dose of up to 1,000 mg once daily at both dose timings (at least 1 hour before a meal and at least 2 hours after a meal) in patients with CRPC.

No deaths, due to any reason, including progression of disease, were reported. Serious adverse events (SAEs) were reported in 10 subjects. The most frequently reported SAE was hepatic function abnormal (5/27 subjects, 18.5%). Four subjects were permanently discontinued from the study due to AEs.

During the entire treatment period, AEs were reported in all 27 subjects (100%); drug related AEs were reported in 26 subjects (96.3%). The majority of AEs were Grade 1 or 2 in severity. Frequently reported AEs (incidence ≥20%) included hypoalbuminemia, hypokalemia, hepatic function abnormal, hyponatremia, enzyme abnormality, anemia, hypercholesterolemia, hyperkalemia, hypertriglyceridemia, proteinuria, upper respiratory tract infection, lymphopenia, hypertension, hyperglycemia, hypermagnesemia, hypernatremia, hypophosphatemia, and blood urine present.

AEs of hypokalemia, fluid retention/edema, and hypertension, events related to the pharmacodynamic effects of abiraterone acetate, occurred in 14 subjects (51.9%), 5 subjects (18.5%), and 7 subjects (25.9%), respectively. All these events were Grade 1 or 2 in severity, except for 2 events of Grade 3 hypokalemia, and none of these events required dose reduction, treatment interruption, or treatment discontinuation, except for 1 event of edema peripheral and 1 event of hypokalemia, which required treatment interruption.

Grade 3 or 4 hepatic function abnormal occurred in 6 subjects (2 in the 250 mg, 1 in the 500 mg, 2 in the 1,000 [−1 hr] mg, and 1 in the 1,000 [+2 hr] mg cohorts); however, its frequency and incidence were not dose- or exposure-dependent. In all these subjects, liver function test (LFT) values decreased to their baseline levels or Grade 1 or lower after dose reduction or discontinuation of study treatment. All these events were clinically manageable. All these events were confirmed to have resolved during the study.

No clinically significant changes were observed in systolic blood pressure, diastolic blood pressure, and pulse rate. No notable change from baseline was found in body weight or body temperature except for body weight increase reported in 1,000 (−1 hr) mg cohort.

PHARMACODYNAMIC RESULTS:

The mean serum corticosterone and 11-deoxycorticosterone concentrations rapidly increased with dose following repeated dose of abiraterone acetate at each dose level. The mean changes from baseline on Day 8 in Cycle 1 in the 1,000 mg cohorts were higher than those in the 250 mg and 500 mg cohorts. For the 1,000 mg cohorts, the mean change from baseline on Day 8 in Cycle 1 in the 1,000 (+2 hr) mg cohort was slightly higher than that in the 1,000 (−1 hr) mg cohort. Meanwhile, the mean serum testosterone and DHEA-S concentrations rapidly decreased to near the BQL level on Day 8 in Cycle 1, regardless of the dose level.

Based on the relationships between C_{max} and AUC_{24} of plasma abiraterone and percentage changes from baseline in serum corticosterone and 11-deoxycorticosterone, percentage changes from baseline are not changed largely with increasing C_{max} and AUC_{24}, regardless of multiple oral administrations of abiraterone acetate.

PHARMACOKINETIC RESULTS:

Because most of the plasma abiraterone acetate concentrations were BQL at all cohorts (250 mg, 500 mg, 1,000 [−1 hr] mg, and 1,000 [+2 hr] mg), pharmacokinetic parameters of abiraterone acetate in plasma were not estimated.

Regardless of the dose and dose frequency, the mean plasma abiraterone concentrations rapidly increased and reached maximum concentrations with median t_{max} ranging from 2 to 3 hours.

When abiraterone acetate was repeatedly administrated once daily, the mean plasma abiraterone concentrations reached a steady state by 7-day, regardless of the dose, and accumulation indexes are 1.31 to 1.74 for C_{max}, and 1.40 to 1.69 for AUC_{24} values. The C_{max} and AUC_{24} values are not largely different between coadministration with and without prednisolone.

The C_{max} and AUC_{24} values of abiraterone are affected by the timing between dosing and food. The mean C_{max} and AUC_{24} values in the 1,000 (+2 hr) mg cohort are 3.1 to 6.0 times higher than those in the 1,000 (−1 hr) mg cohort. Meanwhile, from plots on C_{max} and AUC_{24} of abiraterone in plasma versus dose (dose-normalized to 1,000 mg) by visit, C_{max} and AUC_{24} values increased with increasing doses of 250 mg, 500 mg, and 1,000 (+2 hr) mg.

EFFICACY RESULTS:

The PSA response rate was 66.7% (18/27 subjects), and two-third of the subjects exhibited PSA response. The PSA response rate was 66.7% (6/9 subjects), 50.0% (3/6 subjects), 66.7% (4/6 subjects), and 83.3% (5/6 subjects) in the 250 mg, 500 mg, 1,000 (−1 hr) mg, and 1,000 (+2 hr) mg cohorts, respectively.

Based on the objective tumor response according to RECIST, of 20 evaluable subjects, 2 subjects (1 each in the 500 mg and 1,000 [−1 hr] mg cohorts) achieved Partial Response.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

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