SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development, LLC
Name of Finished Product	ZYTIGA®
Name of Active Ingredient(s)	JNJ-212082 (abiraterone acetate)

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Status: Approved

Date: 15 December 2014

Prepared by: Janssen Research & Development, LLC

Protocol No.: 212082PCR3001

Title of Study: An Open-Label Study of Abiraterone Acetate in Subjects with Metastatic Castration-Resistant Prostate Cancer Who Have Progressed After Taxane-Based Chemotherapy

Study Name: Early Access Protocol

EudraCT Number: 2010-021425-13

NCT No.: NCT01217697

Clinical Registry No.: CR017479

Coordinating Investigator(s): Not applicable

Study Center(s): Australia, Brazil, Canada, Colombia, Croatia, Czech Republic, Denmark, Greece, Hong Kong, Hungary, Indonesia, Italy, Korea, Malaysia, Mexico, Poland, Romania, Russian Federation, Singapore, Spain, Thailand, Taiwan, and US

Publication (Reference): None

Study Period: 17 November 2010 to 30 September 2013 (clinical cutoff date). Date of database lock for the clinical cutoff: 04 December 2013. The study is ongoing; 215 subjects remain on study as of the clinical cutoff.

Phase of Development: Early Access Protocol (EAP)

Objectives: The objective of this study was to collect additional safety data during treatment with abiraterone acetate plus prednisone or prednisolone (AA/P) among subjects with metastatic castration-resistant prostate cancer (mCRPC) who had failed 1 of 2 chemotherapy regimens, 1 of which contained a taxane base such as docetaxel, who resided in areas in which abiraterone acetate was not yet available through local healthcare providers, and who were not eligible for enrollment into an available ongoing clinical study of abiraterone acetate.

Methodology: This study was an open-label EAP. Subjects received abiraterone acetate 1,000 mg once daily (administered as four 250-mg tablets) and prednisone or prednisolone 5 mg orally twice daily. Subjects were treated until disease progression or until the subject otherwise discontinued study treatment (eg, to receive marketed drug or due to an adverse event). This study was to be considered completed with the last assessment of the last subject participating in the study (eg, the last assessment before market authorization or reimbursement had been granted by the relevant authority for the country where that

subject was treated or until abiraterone acetate was available by a doctor's prescription or was accessed from another source).

Number of Subjects (planned and analyzed): At the time of the final clinical cutoff, 30 September 2013, 2,314 subjects had been enrolled, treated with AA/P, and met the criteria for analysis.

Diagnosis and Main Criteria for Inclusion: Male subjects with mCRPC who were medically or surgically castrated, had failed 1 or 2 chemotherapy regimens (1 of which contained a taxane such as docetaxel), who resided in areas in which abiraterone acetate was not yet available through local healthcare providers, and who were not eligible for enrollment into an available ongoing clinical study of abiraterone acetate.

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate was administered as oral doses of 1,000 mg once daily (given as four 250 mg tablets). Bulk lot numbers: TKN, WBB, CSTP, CFSS, CXSZ, CXVS, CTTT, CTTY, CXPT, CXSD, CSXG, CXSH, FFTK, FFTM, FFTS, FFTT, FGYB, FGYC, FGYD, FFFH, FFFG, DTXK, HGGT, and KVGX. Prednisone/prednisolone was dosed orally at 5 mg twice daily. Lot number 152119 was provided in Russia; in all other countries, prednisone/prednisolone was provided through physician's prescription.

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

Duration of Treatment: Abiraterone acetate was administered continuously on a 28-day cycle with prednisone or prednisolone until disease progression or until the subject otherwise discontinued study treatment (eg, to receive marketed drug or due to an adverse event).

Criteria for Evaluation: All serious adverse events (SAEs) and all Grade 3 and higher adverse events (AEs) that occurred during treatment and within 30 days after discontinuation of treatment, including laboratory AEs (serum chemistry, hematology), were graded and reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Grade 1 and 2 AEs were reported only if they were considered medically significant by the investigator (eg, required medical intervention, resulted in dose reduction, or led to discontinuation of study treatment).

Statistical Methods:
The sample size for this study was not powered according to statistical calculation. The number of subjects enrolled was determined by medical need and the date of commercialization and reimbursement of abiraterone acetate in the country in which the subject was to be treated. A total of 2,314 subjects were enrolled, treated, and met the criteria for analysis.

The objective of this study was to collect additional safety data during treatment with AA/P among subjects with mCRPC who had failed 1 or 2 chemotherapy regimens, 1 of which contained a taxane base such as docetaxel. The main focus of this analysis and report is therefore to summarize safety parameters collected. Adverse events that are of NCI-CTCAE Grade 3 or 4, are serious, or led to death or treatment discontinuation constituted the majority of the safety analysis.

Adverse events of special interest for abiraterone acetate included cardiac disorders, fluid retention/edema, hypertension, hypokalemia, liver related investigations, osteoporosis and osteoporosis related fractures, and were summarized similarly to treatment-emergent adverse events.

RESULTS:

STUDY POPULATION:

Included in this final analysis, as of the date of the clinical cutoff (30 September 2013), are 2,314 subjects from 23 countries across the world (50.6% in Europe, 23.0% in North America, 20.4% in Asia Pacific, and 6.0% in Latin America). Of the 2,314 subjects enrolled, 2,099 (90.7%) had discontinued study treatment, thereby completing the study, while 215 (9.3%) remained on study. The most frequent reasons for discontinuation of study treatment were disease progression (45.4%) and discontinuation from the study following market authorization and availability of drug reimbursement (17.9%). Discontinuations due to an adverse event (7.4%), death (7.4%), or withdrawal of consent (5.7%) were also reported.

Subjects were aged 44 to 98 years inclusive, with a median age of 70 years. The majority of subjects were white (86.6%). Demographics and baseline characteristics were consistent with the inclusion and exclusion criteria of the protocol.

The median time from initial diagnosis of prostate cancer to first dose of abiraterone acetate in this EAP was approximately 5 years. At baseline, 90.7% of subjects had metastatic disease in bone, while 38.4% had soft tissue or nodal involvement. The median time from initiation of luteinizing hormone-releasing hormone (LHRH) therapy to the first dose of abiraterone acetate in this EAP was approximately 47 months. Prior to receiving abiraterone acetate and other chemotherapy, subjects were primarily treated with hormonal therapy (92.2%), radiotherapy (63.5%), and surgery (54.5%), while 12.6% of subjects received prior immunotherapy.

Concomitant medications were collected only when associated with an SAE. Of the 782 subjects who reported any SAE (including those occurring prior to the first dose on Day 1), 644 (82.4%) received concomitant medication. The most common type of concomitant medication prescribed was analgesics (399 subjects, 51%), of which natural opium alkaloids were taken by 304 subjects (38.9%).

EXTENT OF EXPOSURE:

At the time of the clinical cutoff, the median extent of exposure to abiraterone acetate was approximately 5 months and the maximum extent of exposure was 28.5 months. Study treatment was continued for at least 12 months in 370 subjects (16%) and 116 subjects (5%) received treatment for 18 months or more within the study. At least 6 cycles had been initiated by 1226 subjects (53%), while 134 subjects (5.8%) began 20 or more cycles. Most subjects achieved greater than 95% of planned exposure to abiraterone acetate (2031 subjects [87.8%]) and prednisone (2077 subjects [89.8%]).

One hundred and seventeen subjects (5.1%) had at least 1 dose reduction of abiraterone acetate. The most commonly reported reasons for dose reduction were “adverse event” and “other” event (1.8% and 3.4%, respectively). Of all enrolled subjects, 26.5% had at least 1 dose interruption of abiraterone acetate, the most common reasons for which were “adverse event” and “other” (10% and 19.1%, respectively).

Eight-five subjects (3.7%) had at least 1 dose reduction of prednisone, the most common reasons for which were “adverse event” and “other” (1.5% and 2.2%, respectively). Sixty-three (2.7%) subjects had at least 1 dose increase of prednisone.

SAFETY RESULTS:

The population evaluable for safety included all subjects who received at least 1 dose of abiraterone acetate and prednisone or prednisolone. In this final data analysis, all 2,314 subjects were evaluable for safety.

This study did not collect all AEs, rather only serious or clinically important events were to be reported by the investigator. Clinically important events included those events meeting NCI-CTCAE criteria of

Grade 3 or higher as well as other events considered by the investigator to be medically significant (eg, required medical intervention, resulted in dose reduction, or led to treatment discontinuation). The main focus of this analysis and report are events that are Grade 3 or 4, serious, and those leading to death or treatment discontinuation. Only treatment-emergent adverse events (TEAEs; adverse events that occurred or worsened on or after the first dose of study drug through 30 days after the last dose) are summarized herein.

Serious and other clinically important AEs (excluding Grade 5 events) were reported in 49.2% of subjects and were considered to be drug related by the investigator (ie, considered to have at least a doubtful relationship to administration of abiraterone acetate, prednisone or both) in 21.0% of subjects. The most frequently reported serious or clinically important AEs were increased blood alkaline phosphatase levels (6.3%) and anemia (5.9%). Grade 3 or 4 AEs were reported in 41.1% of subjects, most of which were of Grade 3 severity. The most frequently reported Grade 3 or 4 AE was increased blood alkaline phosphatase levels (6.1%).

As of the clinical cutoff date, 223 subjects (9.6%) died within 30 days of the last dose. Based on the sponsor's evaluation of deaths, the cause of death was disease progression in 123 (5.3%) subjects, an unrelated AE in 85 (3.7%) subjects, and was unknown in 15 (0.6%) subjects. Through the clinical cutoff date, 234 subjects (10.1%) had an AE with an outcome of death at any time during the study or during follow-up. The most common AEs that led to death were general physical health deterioration (1.2%) and disease progression (0.9%). Fifteen subjects (0.6%) experienced AEs which led to death and were considered drug related by the investigator; based on the sponsor's evaluation, of the 15 events considered possibly or probably drug related by the investigator, 4 were considered by the sponsor to be due to progressive disease, 8 were considered due to an unrelated adverse event, and 3 were of unknown cause.

Serious AEs were reported in 28.3% of subjects, most of which (21.6%) were of Grade 3 toxicity. The most common SAEs were back pain (2.2%), anaemia (2.0%), pneumonia (1.4%), urinary tract infection (1.2%), spinal cord compression (1.1%), and haematuria (1.1%). Serious AEs were considered drug related by the investigator in 7.2% of subjects.

Adverse events leading to discontinuation of either abiraterone acetate or prednisone were reported in 15.6% of subjects and were considered drug related by the investigator in 4.6% of subjects. The most frequently reported AEs leading to discontinuation of study medication were general physical health deterioration (1.2%), spinal cord compression (0.6%), back pain (0.6%), and disease progression (0.5%). Adverse events leading to dose modifications or dose interruption of abiraterone acetate were reported in 17.2% of subjects, of which hypertension (1.9%), anemia (1.3%), fatigue (0.9%), and hypokalemia (0.8%) were the most common. Adverse events leading to dose modifications or dose interruption of prednisone occurred in 10.6% of subjects.

Adverse events of special interest for abiraterone acetate included cardiac disorders, fluid retention/edema, hypertension, hypokalemia, hepatotoxicity, and osteoporosis and osteoporosis related fractures. Grade 3 and 4 AEs of special interest were reported in 15.4% and 1.2% of subjects, respectively. The most common Grade 3 or 4 AEs of special interest were blood alkaline phosphatase increased (6.1%), hypertension (4.3%), and hypokalemia (1.2%). Serious AEs of special interest occurred in <6% of subjects and included cardiac disorders, osteoporosis/osteoporosis-related fractures, fluid retention/edema, hepatotoxicity, and hypokalemia. Adverse events of special interest which led to discontinuation of study medication were reported in 2.8% subjects.

Two identified cases of hepatotoxicity meeting the criteria for Hy's law were identified. In both cases, the serious adverse events (hepatic function abnormal and [drug-induced] hepatitis) resolved after discontinuation of abiraterone acetate. Application of eDISH methodology to further investigate the potential for hepatotoxicity identified no further cases other than those identified per Hy's law.

There were no clinically meaningful differences in the AE profile by age subgroup. The overall safety profile for abiraterone acetate was generally similar across the geographical regions in this EAP, taking into account the relatively small number of subjects in some regions and the differing therapy options and practice patterns for mCRPC treatment across and within regions.

STUDY LIMITATIONS:

- No control.
- Subjects were removed from the study and placed on commercial drug once the drug became available.
- Not all adverse events were collected; rather only serious or other clinically important events were collected (ie, events of Grade 3 or higher and other events considered by the investigator to be medically significant, eg, required medical intervention, resulted in dose reduction, or led to treatment discontinuation).
- Investigator decision on the reporting of AEs, ie, when considered clinically important by the investigator.

CONCLUSIONS:

The safety profile of abiraterone acetate in this EAP was similar to that in Study COU-AA-301, the pivotal randomized, double-blind, placebo-controlled study which demonstrated abiraterone acetate treatment improved survival among men with mCRPC whose disease has progressed on or after a docetaxel-based chemotherapy regimen. No new safety signals were detected in conjunction with treatment with abiraterone acetate and prednisone/prednisolone in this EAP.

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