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

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Prepared by: Janssen Research & Development, LLC

Protocol No.: 212082PCR1004

Title of Study: An Open-Label Pharmacokinetic Study of Abiraterone Acetate Suspension in Subjects with Severe Hepatic Impairment Compared to Matched Control Subjects with Normal Hepatic Function.

NCT No.: NCT01516047

Clinical Registry No.: CR100779

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Study Centers: Alamo Medical Research (San Antonio, TX); Orlando Clinical Research Center (Orlando, FL)

Publication (Reference): None

Study Period: 16 January 2012 to 09 November 2012

Phase of Development: 1

Objectives: The primary objective of this study was to characterize the pharmacokinetics (PK) of abiraterone after administration of a single dose of the abiraterone acetate suspension in subjects with severe hepatic impairment and in matched control subjects with normal hepatic function. The secondary objective of this study was to assess the safety of abiraterone acetate suspension in these subject populations.

Methodology: This was an open-label, single dose, 2-cohort, non-randomized study of abiraterone acetate in subjects who had either severe hepatic impairment or qualified for the control cohort. The study consisted of a screening phase (within 21 days before the first study drug administration), followed by a 4-day treatment phase, and subsequently a 28-day follow-up (up to Study Day 29) after the dose of abiraterone acetate suspension.

Eligible subjects were to be admitted to the study center on Day -1 and were assigned to a treatment cohort according to their hepatic function. The details of study cohorts and the abiraterone acetate suspension doses are provided in the table below.

Study Cohorts for Abiraterone Acetate Suspension Doses

Cohort	N[a]	Child-Pugh Class and Score	Description	Suspension Dose (mg)[b]	Volume (mL)
1	1	C (10-15)	Severe Hepatic Impairment	125	5
1	2	C (10-15)	Severe Hepatic Impairment	125[c]	5
1	5-9[d]	C (10-15)	Severe Hepatic Impairment	125[c]	5
2	8	Not Applicable	Normal Hepatic Function	2000	80

[a] Enrollment for the Cohort 1 was staggered. The Study Evaluation Team (SET) met to review data from the first subject enrolled in Cohort 1. If deemed appropriate, enrollment of the next 2 subjects was to begin. The SET was to meet to review the results of the first 3 subjects enrolled in Cohort 1. If deemed appropriate, enrollment of the remainder of the subjects in Cohort 1 was to occur.

[b] The exposure from the suspension was approximately 50% lower compared to the exposure from the tablet. These suspension doses were expected to provide an exposure equivalent to tablet doses 62.5 mg and 1000 mg, respectively.

[c] A dose adjustment might occur based on review of data during SET. The aim was to treat the remaining subjects in Cohort 1 at a suspension dose yielding an exposure equivalent to 1000 mg tablet in healthy subjects

[d] Additional subjects were to be enrolled if dose was adjusted after SET review to ensure at least 8 subjects in Cohort 1 complete at final dose.

On Day 1, subjects received abiraterone acetate after an overnight fast of at least 10 hours. No food was to be consumed for 4 hours after dosing.

Number of Subjects (planned and analyzed): Planned: A total of 16 male subjects (8 subjects for each cohort) were planned to be enrolled. Additional subjects were to be enrolled if at least 8 subjects in each cohort did not complete the required assessments, including the PK blood sample collections. Analyzed: Sixteen treated subjects were included in safety analysis.

Diagnosis and Main Criteria for Inclusion:

Men between 35 and 80 years of age, inclusive, with a body mass index (BMI) 18 kg/m^2 to 40 kg/m^2 (inclusive), who did not have cancer and who had severe hepatic impairment (as described by the Child-Pugh Classification C) and matched control healthy subjects with normal hepatic function were enrolled. Control subjects were age matched ±10 years and BMI matched within 20% of the means of the severe hepatic impairment cohort.

Control subjects were in good health, with no clinically significant findings from medical history, physical examination, laboratory evaluations, 12-lead electrocardiogram (ECG) and vital signs. Subjects with hepatic impairment had to be on a stable dose of medication and/or treatment regimen for at least 2 weeks before dosing as well as during the study if medications to treat underlying hepatic impairment states or medical conditions related to hepatic impairment were necessary.

Diagnosis and Main Criteria for Exclusion:

Subjects in the control cohort who tested positive for hepatitis B surface antigen (HBsAg) or hepatitis C antibodies were not permitted to enroll in the study. Subjects with hepatic impairment who had acute or exacerbating hepatitis, fluctuating or rapidly deteriorating hepatic function as indicated by widely varying or worsening of clinical and/or laboratory signs of hepatic impairment in the judgment of either the investigator or the sponsor's medical monitor were excluded from participating in the study. Subjects with hepatic impairment taking antiviral therapy for treatment of active hepatitis infection at the time of screening, previously diagnosed with hepatocellular carcinoma, or who had a history of biliary sepsis within the past 2 years, were excluded from participating in the study.

Test Product, Dose and Mode of Administration, Batch No.: Impaired subjects received 5 mL of 25 mg/mL suspension which equated to a dose of 125 mg abiraterone acetate. Healthy subjects received 80 mL of 25 mg/mL suspension which equated to a dose of 2000 mg abiraterone acetate.

Reference Therapy, Dose and Mode of Administration, Batch No.:
SC: 365689 – Lot No.11K03/G008A
365690 – Lot No.11K03/G008B

Duration of Treatment: The study included a screening phase (within 21 days before the first study drug administration) followed by a 4-day treatment phase, and subsequently a 28-day follow-up (Study Day 29) after the dose of abiraterone acetate suspension.

Criteria for Evaluation: Serial blood samples (2 mL each) for determination of abiraterone plasma concentrations were collected predose and over 72 hours after the administration of abiraterone acetate. The following key plasma PK parameters were to be calculated using the actual time of blood sampling: C_{max}, t_{max}, AUC_{last}, AUC_{∞}, $t_{1/2}$, CL/F, and V_d/F. Dose-normalized (DN) parameters such as DN C_{max}, DN AUC_{last}, and DN AUC_{∞} were also calculated.

On Day -2, a 6 mL venous blood sample was taken for the determination of the plasma protein binding of abiraterone acetate. Total protein, albumin and α1-acid glycoprotein levels were also determined. The following PK parameters corrected for unbound fraction were calculated: C_{max_unb}, AUC_{last_unb}, AUC_{∞_unb}, and $CL/F_{\_unb}$.

Pharmacodynamics

Serum samples for total testosterone and luteinizing hormone (LH) were collected between 07:00 and 10:00 a.m. Serum total testosterone and LH were to be monitored as part of the clinical laboratory assessments and the data could be utilized for exploratory analyses, if needed.

Safety

Safety was to be evaluated throughout the study, and included assessment of adverse events, clinical laboratory evaluations (hematology and serum chemistry), ECG evaluations, vital sign measurements, and physical examinations.

Statistical Methods:

Analysis Population

The PK population was to include all subjects who have sufficient and interpretable PK assessments to calculate PK parameters of abiraterone. The safety population was to include all subjects who received at least one dose of study drug and will be used for all safety evaluations.

Sample Size Determination

Based on clinical considerations, a sample size of 16 subjects (8 subjects in each cohort) was selected. Additional subjects were to be enrolled to ensure that at least 8 subjects in each cohort completed the required assessments. If the dose was adjusted after SET review, additional subjects were to be enrolled to ensure 8 subjects in the hepatic impairment cohort completed the required assessments at the final dose.

Pharmacokinetics

Descriptive statistics for abiraterone PK parameters were to be presented for each treatment cohort and for the abiraterone concentrations at each sampling time point. PK parameters were evaluated graphically using scatter plots. Plasma concentration-time profiles of abiraterone were to be plotted for each subject and by treatment cohort. Mean plasma concentration-time profiles were to be graphically presented for each treatment cohort. Additional plots or tabulations were to be included if deemed appropriate.

The primary parameters of interest for the statistical analysis were the dose-normalized AUCs and C_{max} (dose-normalized to 2000 mg). Statistical analysis was to be performed by using an analysis of variance (ANOVA) model on the log-transformed data. The geometric mean ratios and the associated 90% confidence intervals (CI) for AUCs and C_{max} of the test cohort (severe hepatic impairment) with respect to the control cohort (normal hepatic function) were to be constructed.

Safety

All subjects receiving study medication were to be included in the safety population. Adverse events were to be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15 and the severity was to be graded according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.0 grading system. Laboratory data were to be descriptively summarized. All serious adverse events (SAEs) and deaths were to be listed. No formal statistical analyses were planned.

RESULTS:

STUDY POPULATION:

Sixteen subjects were treated and completed the study. The median age was 55.5 and 54 years in the severe hepatic impairment and normal hepatic function cohorts, respectively. The classification of hepatic impairment was based on the Child-Pugh Classification System. All subjects in severe hepatic impairment cohort had a Child-Pugh score from 10 to 15.

PHARMACOKINETIC RESULTS:

The median time to reach t_{max} was comparable between both cohorts, with median t_{max} of 1.5 hours (range: 1 to 2 hours) in normal hepatic function and 2 hours (range: 1 to 6 hours) in subjects with severe hepatic impairment. Systemic exposure to abiraterone, as measured by arithmetic mean C_{max}, AUC_{last}, and AUC_{∞}, after administration of abiraterone acetate suspension in subjects with severe hepatic impairment, was approximately 80.6%, 53.0% and 61.5% lower than the systemic exposure measured in subjects with normal hepatic function. Both CL/F and Vd/F were approximately 87.0% and 84.5% lower, respectively, for subjects with severe hepatic impairment compared to subjects with normal hepatic function.

The mean concentration-time profiles revealed that the initial rate of decline of abiraterone in plasma after t_{max} was apparently slower in subjects with severe hepatic impairment. However, the terminal phase of the concentration-time profile seemed to be similar between both cohorts with mean $t_{1/2,\lambda}$ being slightly prolonged in subjects with severe hepatic impairment compared to subjects with normal hepatic function by approximately 18%.

The ratio of the geometric mean estimates for the severe hepatic impairment function cohort after a 125 mg abiraterone acetate suspension dose compared with the normal hepatic function cohort after a 2000 mg abiraterone acetate suspension dose was 22.39% (90% CI: 10.34 to 48.50) for C_{max}, 47.27% (90% CI: 24.01 to 93.06) for AUC_{last}, and 43.59% (90% CI: 18.35 to 103.53) for AUC_{∞}. When exposure parameters are dose-normalized to 2000 mg, the ratio of the geometric mean estimates for the severe hepatic impairment function cohort compared with the normal hepatic function cohort was 358.22% (90%

CI: 165.38 to 775.94) for C_{max}, 756.32% (90% CI: 384.16 to 1489.0) for AUC_{last}, and 697.37% (90% CI: 293.58 to 1656.5) for AUC_{∞}.

SAFETY RESULTS:

No deaths, serious adverse events (SAEs), or TEAEs leading to discontinuation of abiraterone acetate were reported during this study.

One subject in the severe hepatic impairment cohort was reported to have a TEAE of rash (mild, unrelated to study drug) during the study. No TEAEs were reported for subjects in the normal hepatic function cohort. No clinically significant values for liver function tests or any other laboratory parameter were reported for any of the subjects during the study.

STUDY LIMITATIONS:

No notable study limitations were identified by the sponsor.

CONCLUSION(S):

- Systemic exposure to abiraterone after administration of 125 mg abiraterone acetate suspension (62.5 mg tablet equivalent) in subjects with severe hepatic impairment was 22.39% for C_{max}, 47.27% for AUC_{last}, and 43.59% for AUC_{∞}, compared to subjects with normal hepatic function after administration of 2000 mg abiraterone acetate suspension (1000 mg tablet equivalent).
- Overall, a single 125 mg or 2000 mg oral dose of abiraterone acetate suspension appeared to be tolerated equally well by subjects with severe hepatic impairment or subjects with normal hepatic function, respectively.

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