SYNOPSIS

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

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Status: Approved

Date: 8 October 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: 212082HPL1002

Title of Study: An Open-Label, Multiple-Dose, Dose-Finding Study of Abiraterone Acetate in Adult Women With 21-Hydroxylase Deficiency

NCT No.: NCT01495910

Clinical Registry No.: CR100007

Principal Investigator: Richard Auchus, MD, PhD, University of Michigan, 1150 West Medical Center Drive, 5560 MSRB II, Ann Arbor, MI 48109-5678, USA

Study Center(s): The study was conducted at 3 sites in the United States (US).

Publication (Reference) None

Study Period: The first subject was screened (signed informed consent) on 04 January 2012. The last subject last visit was on 26 March 2013. The database was locked for clinical and pharmacokinetic (PK) data on 22 April 2013 and for pharmacological parameters on 22 July 2013.

Phase of Development: 1

Objectives:

The primary objective was to determine the minimal dose of abiraterone acetate required to decrease serum androstenedione to the age-appropriate range for adult women with 21-hydroxylase deficiency.

The secondary objectives were:

- To assess the effect of abiraterone acetate on concentrations of hormones in the steroid synthesis pathway
- To evaluate the PK profile of abiraterone following the administration of the suspension formulation of abiraterone acetate
- To explore potential relationships between the PK of abiraterone and the concentrations of androstenedione and other hormones in the steroid synthesis pathways

- To explore the association between plasma androstenedione and urine androsterone and etiocholanolone
- To assess the safety of abiraterone acetate in this subject population.

Methodology: This was a non-randomized, open-label, multiple-dose, intra-subject sequential dose-escalation study with a planned enrollment of at least 4 but not more than 10 adult women with 21-hydroxylase deficiency. The study consisted of a screening period (within 40 days before the first study drug administration), a qualifying period as part of the screening period for up to 25 days, and a treatment period from Study Days 1 to 8. Due to the intra-subject dose escalation there were multiple treatment periods of 8 days. A rest period of at least 7 days separated each treatment period. Eligible subjects were to be administered study-defined replacement doses of hydrocortisone and fludrocortisone during the qualifying period for at least 6 days prior to qualifying androstenedione draw, and through all treatment periods and rest periods until Study Day 8 of the last treatment period. Abiraterone acetate was administered on Study Days 1 to 6 of each treatment period. Subjects were to proceed to the next higher dose level, after a rest period of at least 7 days, if androstenedione did not normalize in at least 80% of subjects with pharmacodynamic (PD) assessments. Androstenedione normalization was determined based on the mean of the morning androstenedione concentrations on Day 6 and Day 7.

Samples for assessment of PD markers were collected on Study Days 1, 6, 7, and 8 of each treatment period. Serial blood samples for measurement of abiraterone concentrations were collected after the last dose of abiraterone (Day 6) in each treatment period at predose and postdose. An End-of-Study visit occurred on Study Day 8 of the last treatment period.

Number of Subjects (planned and analyzed): Planned: At least 4 but not more than 10 adult women were planned to be enrolled. Analyzed: All the 6 subjects were included in the safety analysis data set.

Diagnosis and Main Criteria for Inclusion: Premenopausal women ≥18 years of age who were receiving a hormonal contraceptive agent containing both estrogen and progesterone and who had confirmed 21-hydroxylase deficiency by CYP21A2 genotype. This genotype is the most common form associated with classic congenital adrenal hyperplasia.

Test Product, Dose and Mode of Administration, Batch No.: Abiraterone acetate suspension was provided as 25 mg/mL suspension in a 10 mL or 20 mL vial (Lot no. 12D03/G008).

Duration of Treatment: The study consisted of a screening period (within 40 days before the first study drug administration), a qualifying period within the screening period for up to 25 days, and a treatment period from Study Days 1 to 8. Due to multiple dose-escalating treatment periods, a rest period of at least 7 days separated each treatment period.

Criteria for Evaluation:

Pharmacodynamic Evaluations

Blood samples were analyzed for androstenedione, 17-hydroxyprogesterone, and testosterone. Urine samples were to be analyzed for measurement of androsterone and etiocholanolone glucuronides.

Pharmacokinetic Evaluations

Serial blood samples for determination of abiraterone plasma concentrations were collected.

Safety Evaluations:

Safety was evaluated throughout the study and included assessment of adverse events (AE), vital sign measurements, physical examinations, clinical laboratory tests (hematology, serum chemistry and urinalysis), and electrocardiograms (ECGs).

Statistical Methods:

Analysis population

The safety population included all subjects who were assigned to treatment and received at least 1 dose of abiraterone acetate suspension. The PK population included all subjects who had sufficient and interpretable PK assessments to calculate the noncompartmental PK parameters. The PK-PD population included all subjects who had at least 1 PK and 1 PD parameter (androstenedione, other hormones in the steroid synthesis pathway) assessment and this population was considered as the population for the determination of the primary objective.

Sample Size Determination

The sample size of at least 4 but no more than 10 subjects was based on feasibility.

Pharmacodynamics

The counts and percentages of subjects with serum androstenedione normalization on Study Days 6 and 7 were to be summarized for each dose level and the associated exact 2-sided 95% binomial confidence intervals for the percentages were to be provided. Mean and mean change from baseline (Day 1 predose value) in androstenedione, 17-hydroxyprogesterone, and testosterone were to be summarized overall and by dose level with subject number, mean, standard deviation, median, and range.

Pharmacokinetics

For each subject, plasma concentration of abiraterone versus time profiles was to be plotted. Mean plasma concentration-time profiles were to be plotted. Plasma concentration data at each timepoint were to be summarized with mean, standard deviation, and coefficient of variation. All estimated PK plasma parameters were to be summarized with mean, median, geometric mean, minimum, maximum, standard deviation, and coefficient of variation. Additional plots or tabulations were to be included, if deemed appropriate.

Pharmacokinetic-Pharmacodynamic Relationship

Different structural PK-PD models were to be explored; assuming either a direct or indirect relationship between abiraterone plasma concentrations and serum hormone levels. Data were to be analyzed using nonlinear mixed-effects modeling.

Safety

All subjects who were assigned to treatment and received at least 1 dose of abiraterone acetate were analyzed for safety. Safety variables were summarized descriptively for AEs, clinical laboratory parameters, ECG, and vital signs. Serious adverse events (SAEs), AEs, and discontinuations from study treatment were provided in listings. Shift tables were also presented for laboratory parameters, as appropriate.

RESULTS:

STUDY POPULATION:

Six (6) adult white women between 19 years to 46 years of age, inclusive, who had confirmed 21-hydroxylase deficiency were treated in this study. All 6 subjects completed the study. The median age was 36 years and the mean body mass index was 39.08 kg/m^2. Subject 200111 had a major protocol deviation in violating inclusion #2 (Must be receiving a hormonal contraceptive agent [any route of administration consistent with product labeling is allowed] containing both estrogen and progesterone from the time of entry).

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Pharmacodynamic:

The 250 mg per day dose of abiraterone acetate administered for 6 days normalized the serum androstenedione concentration with replacement doses of hydrocortisone. This was observed in 83.3% (5/6) of the subjects at this dose level. The primary objective was met.

Number and Percentage of Subjects With Normalized Androstenedione; PD Evaluable Population With 6 Consecutive Doses of AA Administered

(Study 212082HPL1002)

	n(%)[a]	
	Treatment Period 1 (AA 100 mg)	**Treatment Period 2 (AA 250 mg)**
Number of subjects PD evaluable with 6 consecutive doses of AA administered	6	6
Day 6 predose	3 (50.0)	4 (66.7)
Day 7	3 (50.0)	6 (100.0)
Based on Mean of Day 6 predose and Day 7	3 (50.0)	5 (83.3)
95% CI for percentages[b]	(11.8,88.2)	(35.9,99.6)

a: Percentage is based on the number of subjects PD evaluable with 6 consecutive doses of AA administered as denominator.

b: Exact 2-sided 95% binomial confidence intervals for the percentages of normalized subjects.

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Pharmacokinetic:

Systemic exposure to abiraterone at steady state, as measured by maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 24 hours postdose (AUC_{24h}), after administration of 100 mg abiraterone acetate suspension, showed C_{max} values ranging from 0.920 ng/mL to 8.26 ng/mL and AUC_{24h} values ranging from 5.96 ng*h/mL to 37.0 ng*h/mL across the 6 subjects.

Systemic exposure to abiraterone at steady state, as measured by C_{max} and AUC_{24h}, after administration of 250 mg abiraterone acetate suspension, showed C_{max} values ranging from 2.64 ng/mL to 26.0 ng/mL and AUC_{24h} values ranging from 18.9 ng*h/mL to 141 ng*h/mL across the 6 subjects.

Pharmacokinetic/Pharmacodynamic:

The PK/PD analysis indicated that average morning concentrations of androstenedione and testosterone on Days 6 and 7 were highly correlated with daily exposure (ie, AUC_{24h}) to abiraterone, suggesting a positive drug effect in CAH patients. The population PK and indirect response PK/PD models well described the observed PK and PD (androstenedione and testosterone) concentration data. The estimated concentration for 50% of the maximum inhibition of the production rate of androstenedione was

statistically significant, further confirming the drug effect. The model-based simulation indicated that the normalization of serum androstenedione may be dependent on both drug exposure and baseline levels of androstenedione.

SAFETY RESULTS:

No clinically significant abnormalities in vital signs or ECG parameters were reported during this study. No deaths, SAEs, or AEs leading to discontinuation of abiraterone acetate were reported during this study. Fatigue (3 subjects [50.0%]) was the most commonly reported AE. There were no clinically relevant changes in hematology, chemistry, and urinalysis parameters from baseline. No laboratory abnormalities were reported as treatment-emergent adverse events. No subject had a shift from normal at baseline to high or low at the end of the study in any laboratory parameter.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

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