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Research Article

An Open Label, Balanced, Randomized, Two Treatments, Two Sequences, Four Periods, Fully Replicate, Crossover, Bioequivalence Study of Abiraterone Acetate 250 mg Tablets of Abbott Laboratories De Colombia Versus ZYTIGA® (Abiraterone Acetate) 250 mg Tablets of Janssen Biotech, Inc. Under Fasting Condition in Healthy Subjects

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ABSTRACT

Abiraterone acetate is an androgen biosynthesis inhibitor, that inhibits 17 a-hydroxylase/C17,20-lyase (CYP17) the treatment of newly diagnosed high risk metastatic Hormone Sensitive Prostate Cancer (mHSPC) in adult men in combination with Androgen Deprivation Therapy (ADT). The purpose of this study was to evaluate the bioequivalence between Abiraterone acetate 250 mg tablet of Abbott laboratories de Colombia versus marketed Abiraterone acetate 250 mg tablet of Janssen Biotech, Inc. under fasting condition in healthy subjects. An open label, balanced, randomized, two treatments, two sequences, four periods, fully replicate, cross-over single dose study with washout period of 02 days under fasting condition was carried out in 48 male subjects in the age group of 21 to 45 years who met the study eligibility criteria, participated in the study and 47 subjects completed all four periods of the study. The pharmacokinetic samples collected from subjects who completed the study were analysed to determine the plasma concentration of Abiraterone acetate using bio-analytical method.

The 90% confidence interval of AUC_{0-t} and C_{max} were 87.27%-104.58% and 79.10%-99.68% respectively which were within the pre-defined acceptable limits and the test product is bioequivalent to the reference product.

Keywords: Abiraterone acetate; Bioavailability; Bioequivalence; Pharmacokinetic

Abbreviations: AE: Adverse Event; AUC: Area Under the Concentration versus Time Curve; AUC_{0-t}: Area Under the Plasma Concentration versus Time Curve from Zero to Time t; BMI: Body Mass Index; ECG: Electrocardiogram; EMA: European Medicine Agency; FDA: United States Food and Drug Administration; ICMR: Indian Council of Medical Research; K3EDTA: Tripotassium Ethylene Diamine Tetra Acetic Acid; C_{max}: Concentration Maximum; CV: Coefficient of Variation; IEC: Independent Ethics Committee; LCMS/MS: Liquid Chromatography Tandem Mass Spectrometry; mg: Milligram; ml: Millilitre; mM: Milli Molar; ng/ml: Nano Gram per Milliliter; PK: Pharmacokinetic; Tmax: Time Taken to Reach Maximum Concentration.

INTRODUCTION

Many drug patents have recently expired or are scheduled to expire in the near future. In response, many drug manufacturers have expanded their generic drug profile, which requires them to conduct clinical trials that demonstrate that their generic equivalents perform similarly to the innovator drug product. Regulations introduced by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) over the last thirty-five years have strengthened measures to ensure the bioequivalence of drug products, which may be simultaneously manufactured by multiple drug makers [1]. Bioequivalence and bioavailability testing standards have also emerged following recognition that bioequivalence and

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variations in the bioavailability of drug products can result in therapeutic failure and/or toxicity. ZYTIGA® (Abiraterone acetate) is an androgen biosynthesis inhibitor [2]. Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17 α-hydroxylase/C17, 20-lyase). Each ZYTIGA® tablet contains either 250 mg or 500 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5, 16-dien-3-yl acetate. Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55 [2].

The pharmacokinetics of Abiraterone is reported to be variable with a very high intra and inter subject variability [1,3-5]. The following pharmacokinetic values were reported in the studies published earlier (Table 1) [1,3-8].

This study was designed to evaluate the relative bioequivalence of the test Abiraterone acetate 250 mg tablets of Abbott Laboratories de Colombia versus ZYTIGA® (Abiraterone acetate) 250 mg tablets of Janssen Biotech, Inc. under fasting condition in healthy subjects [1,3-5].

MATERIALS AND METHODS

Test product, dose and mode of administration, batch

Abiraterone acetate 250 mg tablets, 01 × 250 mg, Oral with 200 mL of water in sitting posture under fasting condition, 20H696.

Reference product, dose and mode of administration, Lot

ZYTIGA® (Abiraterone acetate) 250 mg tablets, 01 × 250 mg, Oral with 200 mL of water in sitting posture under fasting condition, CFMXY.

Methodology

The study protocol with annexes was prepared and IEC approval was obtained before initiation of the study. Study subjects were screened and enrolled in the study as per the IEC approved protocol [9-11]. Written informed consent was obtained from each volunteer for screening prior to initiation of screening procedure and for the study prior to enrolment. Individual counselling was then given to the willing volunteers by the Investigator in private and any questions and concerns were addressed prior to obtaining consent. The Principal investigator/sub-investigator/physician reviewed all the screening results to assess eligibility of each volunteer. Subjects were enrolled in the study based on the inclusion and exclusion criteria.

This study was designed based on the known pharmacokinetic profile of the investigational product and general accepted standards for the conduct of bio-equivalence study [9,11].

Forty-eight male subjects (Table 2) who met the eligibility criteria were enrolled and 47 subjects completed all the four periods of the study (except one subject, S27, who was withdrawn from the study due to adverse event post dosing of period I). Study drug was administered in sitting posture at fixed time in each period and subjects were instructed to maintain sitting posture for 02 hours post dose.

A washout period of 02 days was maintained between each treatment, in order to minimize any possibility of carryover effect from preceding treatment. The blood samples were collected at pre-defined time intervals for the measurement of concentration and pharmacokinetic parameters of Abiraterone in each period.

Data obtained from 47 study completers was used for the pharmacokinetic analysis (Tables 3 and 4) of Abiraterone.

Table 1: Statistical results of test product-T versus reference product-R for Abiraterone (N=42).

Parameters	Anti-log least square mean		T/R Ratio (%)	90% Confidence interval for test vs. reference	Intra subject V(%) R vs. R	Intra subject CV(%) T vs. R	Power (%)
	Test product (T)	Reference product (R)					
Ln (C_{max})	20573.1496	23168.5398	88.8	79.10%-99.68%	58.19	47.56	93.12
Ln (AUC_{0-t})	116143.685	121573.2473	95.53	87.27%-104.58%	36.43	36.47	98.95

Table 2: Summarized demographic profile of subjects who completed the study for Abiraterone (N=47).

Parameter	Mean	SD	Min	Max
Age (years)	32	6	21	45
Height (m)	1.678	0.07	1.495	1.812
Weight (Kg)	71.4	10.9	52.9	91.3
BMI (Kg/m^2)	25.3	3.05	18.68	29.86

Table 3: Summary of pharmacokinetic parameters for Abiraterone of reference Product – R.

Parameter	N	Reference (R) (Mean ± SD)
C_{max} (pg/mL)	94	31905.486 ± 40016.397
AUC_{0-t} (pg.hr/mL)	94	150387.376 ± 113710.714
$AUC_{0-\infty}$ (pg.hr/mL)	94	167095.418 ± 119892.464
*T_{max} (hr)	94	1.67 (0.75-5.50)
K_{el} (hr^{-1})	94	0.067 ± 0.035
$T_{1/2}$ (hr)	94	12.446 ± 5.709
$AUC_{\%Extrap\_Obs}$	94	11.575 ± 6.249

Note: *Expressed in terms of median (range).

Statistical analysis of Abiraterone was performed using the pharmacokinetic data obtained from 42 subjects; five subjects were excluded for the following reasons:

- S15 reported emesis within two times the reported median T_{max}.
- Four subjects (S11, S21, S29 and S31) exhibited pre-dose concentrations greater than 5% of C_{max} in one of the study periods.

Thus, these subjects were excluded from statistical analysis based on the pre-defined protocol criterion.

Bioequivalence was determined by statistical comparison of Ln-transformed data of C_{max} and AUC_{0-t} of the test and reference formulations using SAS® version 9.4.

Subjects drug administration and blood sampling

After an overnight fasting of 10 hours, subjects were administered with a single oral dose of either test product or reference product with 200 mL of water as per the randomization schedule in sitting posture at ambient temperature in each period.

Compliance to drug administration was assessed by examination of the oral cavity and hands of the subject immediately after dosing.

All the subjects remained in sitting posture for 02 hours after dosing. During this restriction period, the subjects were permitted to walk for reasons such as but not limited to the following: Natural exigencies. Subjects were restricted from consumption of water for 01 hour before and 01 hour after dosing in each period and were allowed to drink water ad libitum thereafter. Washout period of 02 days were maintained between the treatments.

The pharmacokinetic profile (in terms of rate and extent of absorption) of both test and reference products were evaluated based on measured concentration of drug in the human plasma samples collected during the clinical phase. Blood samples for pharmacokinetic analysis were designed appropriately for characterizing the pharmacokinetic profile for the given treatments at the dose administered.

A total of 25 blood samples of 03 mL each at 00.00 (Pre-dose), 00.25, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.33, 03.67, 04.00, 04.33, 04.67, 05.00, 05.50, 06.00, 07.00, 08.00, 12.00, 18.00, 24.00 and 32.00 hours post dose, were collected for measurement of pharmacokinetic parameters in each period.

Tolerability

Subjects were monitored for Adverse Events (AEs) during all four periods of the study. Subjects were instructed to inform clinic personnel of any untoward medical symptoms and/or events that arose during the study. The Principal Investigator/sub-investigator/study physician also evaluated the subjects for subsequent dosing. Each adverse event reported by the subjects during the study was assessed for its seriousness, severity, relationship with the study drug and outcome [9,10].

Subject's Safety was assessed *via* continuous monitoring and scheduled recording of safety measurements throughout the study through clinical examinations, vital assessment, 12 lead Electrocardiogram (ECG), clinical laboratory parameters (e.g., Hematology, Biochemistry, Urine analysis and Serology test) and monitoring subjects' well-being, symptoms and signs for adverse events.

No serious adverse events were reported during the conduct of this study. A total of 18 non-serious adverse events were reported by 13 subjects during the study. Eight adverse events were reported following administration of the reference product and 10 adverse events with test product. All AEs reported in the study resolved without sequelae and were assessed to be either mild or moderate in intensity. The incidence of AEs in the study for reference product was (16.67) and test product was (21.28) [9,10].

The study medications were considered to be relatively well tolerated by the selected study population at the administered dose levels.

Pharmacokinetic and statistical analysis

Pharmacokinetic was performed using the concentration data obtained from 47 subjects in fasting conditions who completed all four periods of the study (Table 2).

Statistical analysis (Table 1 and Figure 1) was performed using the pharmacokinetic data obtained from 42 subjects; five subjects were excluded from statistical analysis for the following reasons:

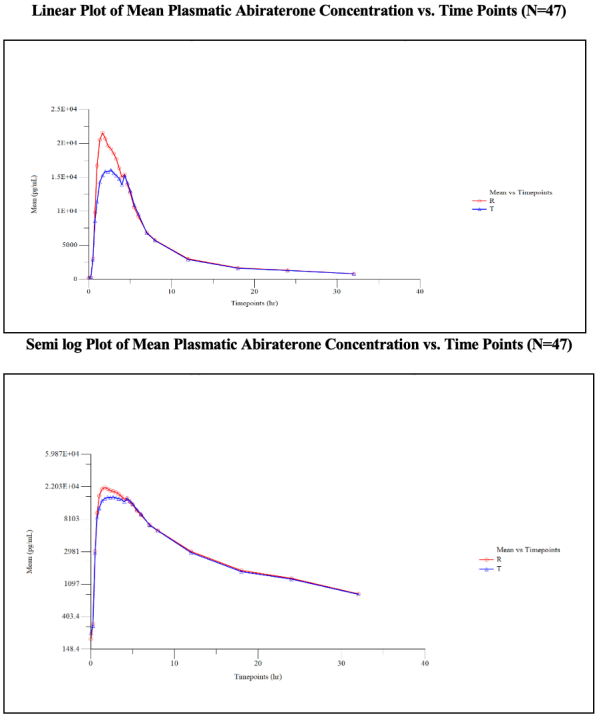

Figure 1: a) Linear plot of mean plasmatic abiraterone co tration vs. time points (N=47); b) Semi log of mean plasmatic abiraterone concentration vs. time points (N=47).

- S15 was excluded as the subject reported emesis within two times the reported median T_{max}, this is based on the pre-defined protocol criterion which states "Data from subjects who experience emesis before two times the median T_{max}, as determined in the pharmacokinetic analysis will be excluded from further statistical analysis".
- Four subjects, S11, S21, S29 and S31 were excluded as these subjects exhibited pre-dose concentrations greater than 5% of C_{max} in one of the study periods, his exclusion is based on the pre-defined protocol criterion which states "If the pre-dose concentration is

more than 5% of C_{max} of the respective subjects, then the subject will be dropped from bioequivalence analysis".

In order to test the two one-sided tests for bioequivalence, ratio analysis, 90% confidence intervals for the difference between treatments' least-square mean was calculated for Ln-transformed C_{max} and AUC_{0-t} of Abiraterone acetate.

Pharmacokinetic parameters were calculated using non-compartmental model of Phoneix® WinNolin® version 8.1 (Tables 3 and 4) and statistical analysis was carried out using the SAS® statistical software, version 9.4 of SAS Institute Inc., USA (Tables 1 and 5).

Table 4: Summary of pharmacokinetic parameters for Abiraterone of test product – T.

Parameter	N	Test (T)
		(Mean ± SD)
C_{max}(pg /mL)	94	24791.083 ± 16043.858
AUC_{0-t} (pg.hr/mL)	94	137032.209 ± 79211.207
$AUC_{0-\infty}$ (pg.hr/mL)	94	154610.824 ± 85782.716
*T_{max} (hr)	94	2.33 (0.75-6.00)
K_{el} (hr^{-1})	94	0.064 ± 0.031
$T_{1/2}$ (hr)	94	13.583 ± 8.705
$AUC_{\%Extrap\_Obs}$	94	12.906 ± 9.178

Table 5: p-Value for C_{max} and AUC of abiraterone.

Parameters	C_{max}	AUC_{0-t}	Significance
Sequence effect	0.4516	0.7126	Insignificant for C_{max} and AUC_{0-t}
Period effect	<.0001	<.0001	Significant for C_{max} and AUC_{0-t}
Treatment (Formulation) effect	0.0911	0.4042	Insignificant for C_{max} and AUC_{0-t}
Subjects nested within sequence	<.0001	<.0001	Significant for C_{max} and AUC_{0-t}

The mean, standard deviation, standard error, geometric mean, coefficient of variation, minimum, median, maximum and range were calculated for C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, T_{max}, $T_{½}$, K_{el} and AUCExtrapolate (Table 3 and 4).

RESULTS AND DISCUSSION

Forty-eight male subjects in the age group of 21 to 45 years, who met the study eligibility criteria, participated in the study and 47 subjects completed all four periods of the study Table 2, except one subject, S27, was withdrawn from the study due to adverse event (fever and headache) in period I post dose.

The clinical phase of the study was conducted over a period of 09 days. Blood sampling was done at pre-defined intervals up to 32.00 hours in all four periods, separated by a washout period of 02 days between each period.

The plasma concentrations of Abiraterone were quantified in samples of 47 study completers using a validated bio-analytical method in LC-MS/MS.

The pharmacokinetic analysis of Abiraterone was performed using the concentration data obtained following analysis of 47 study completers (Tables 3 and 4).

Statistical analysis of Abiraterone was performed using the pharmacokinetic data obtained from 42 subjects Tables 1 and 5; five subjects were excluded for the following reasons:

- S15 reported emesis within two times the reported median T_{max} and
- Four subjects (S11, S21, S29 and S31) exhibited pre-dose concentrations greater than 5% of C_{max} in one of the study periods.

Thus, these subjects were excluded from statistical analysis based on the pre-defined protocol criterion.

The results of the statistical analysis of Abiraterone with the test product were observed to be comparable to that of the reference product.

The C_{max} and AUC of Abiraterone are expected to be highly variable from the articles published earlier and the studies conducted at our site. Hence, the C_{max} obtained also exhibited a high variability. A second peak was observed in the mean plot of test product and this is consistently seen in all the subjects. This could be due to enterohepatic recirculation. However, there are no published articles confirming the same.

The ISCV of C_{max} for reference product was calculated to be 58.19%, hence, 90% confidence interval limit was widened using scaled-average-bioequivalence and the value obtained was found to be within the widened limits of 69.84% to 143.19%. The 90% Confidence interval was 79.10%-99.68%, which was within the widened, limits mentioned (Table 1 and Figure 1).

The 90% confidence interval of AUC_{0-t} was 87.27%-104.58%, which was within the acceptable limits of 80.00% to 125.00% (Table 1 and Figure 1).

CONCLUSION

Bioequivalence was demonstrated between Abiraterone acetate 250 mg tablets of Abbott Laboratories de Colombia versus ZYTIGA® (Abiraterone acetate) 250 mg tablets of Janssen Biotech, Inc under fasting condition in healthy subjects.

All the published studies report a high variability in healthy subjects after single dose administration. The data obtained in the current study also confirm the same and the high variability observed in this study is similar to that already reported.

The adverse events reported in the study were also similar to the reported list of adverse events in the summary of product characteristics. All the adverse events were mild to moderate in intensity and are resolved. This proves that Abiraterone 250 mg tablets are well tolerated in healthy subjects at a given dose after single dose administration.

ACKNOWLEDGEMENTS

Bioequivalence was demonstrated between Abiraterone acetate 250 mg tablet of Abbott laboratories de Colombia versus ZYTIGA® (Abiraterone acetate) 250 mg tablet of Janssen Biotech, Inc. under fasting condition in healthy subjects.

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