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ORIGINAL ARTICLE

Pharmacokinetics and bioequivalence of generic and branded abiraterone acetate tablet: a single-dose, open-label, and replicate designed study in healthy Chinese male volunteers

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Abstract

Purpose Abiraterone acetate is a highly variable drug and has been approved for the treatment of patients with metastatic castration-resistant prostate cancer in many countries. This study was conducted to compare the pharmacokinetic profile between the test product (abiraterone acetate tablet) and reference product ZYTIGA® (250 mg) mainly.

Methods To overcome the high intra-subject variability of abiraterone, a two-sequence and four-period crossover study was designed to assess bioequivalence between the two products in 32 healthy male Chinese subjects under fasting conditions. The plasma concentration of abiraterone was analyzed by a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) assay and the reference-scaled procedure was used to determine bioequivalence for the pharmacokinetics parameters.

Results The point estimate of geometric mean ratios with 90% confidence interval (CI) of maximum observed concentration (C_{max}) and the area under the concentration–time curve (AUC_{0t}) for abiraterone in the test and reference products were 100.19% (90% CI 87.05–115.32%) and 105.99% (90% CI 96.34–116.62%), respectively, and were both within the range of 80.00–125.00%. The 95% confidence upper limit bound for $(\bar{Y}_T - \bar{Y}_R)^2 - \theta S^2_{WR}$ was −0.1079 for C_{max} and was −0.0515 for AUC_{0t}.

Conclusions Bioequivalence was demonstrated between the two abiraterone acetate products. The study also confirmed high intra-subject variability, for abiraterone: coefficient of variation (CV, %) of C_{max} values for the test and reference products were 40.33% and 46.58%, while for AUC_{0t} were 24.02% and 34.16%, respectively.

Trial registration http://www.chinadrugtrials.org.cn/: CTR20170997.

Keywords Abiraterone acetate · Highly variable drug · Intra-subject variability · Bioequivalence · LC-MS/MS

Introduction

Prostate cancer is the most commonly diagnosed cancer in men, and accounting for 15% of all cancers in men worldwide [1, 2]. In China, prostate cancer has become the sixth prevalent cancer in men and the highest incidence of urological tumors, the incidence is increasing rapidly with over

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10% per year [3, 4]. Although in the early phases PCa is highly sensitive to androgen deprivation therapy, it is able to grow regardless of low blood levels of testosterone (castration-resistant prostate cancer [CRPC]). The treatment of metastatic CRPC (mCRPC) has evolved dramatically over the last decade, and several new agents have recently been approved for the clinical use, including docetaxel, enzalutamide, apalutamide, mitoxantrone and abiraterone acetate (AA) [5–9].

Abiraterone is a CYP17 inhibitor indicated to use in combination with prednisone for the treatment of patients with mCRPC and metastatic high-risk castration-sensitive prostate cancer (CSPC) [10]. After oral administration, abiraterone acetate is converted to abiraterone (active metabolite) rapidly and achieves C_{max} at around 2 h post administration [10]. Abiraterone is highly bound (> 99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein, and extensively distributed in the body [10]. There were two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each [10]. The half-life of abiraterone was reported to be close to 15 h in plasma in healthy volunteers [11, 12].

Although the pharmacokinetic properties or bioavailability of AA (250 mg tablet) has been previously investigated in other populations, including patients and healthy volunteers [11, 12], a search of the MEDLINE and ScienceDirect databases for English-language articles, including all publication years, using the search terms of abiraterone, bioequivalence, pharmacokinetics, and Chinese, did not identify published information on the pharmacokinetics of abiraterone in a Chinese population.

Therefore, the aim of the present study was to assess the pharmacokinetics and bioequivalence of the generic test formulation (abiraterone acetate 250 mg tablet, which was the only specification developed by Jiangxi Qingfeng Pharmaceutical Co., Ltd. Jiangxi, China) and the branded reference formulation (abiraterone acetate 250 mg tablet, ZYTIGA®, Janssen-Cilag International N.V.) after administration of a single 250 mg oral dose in fasting healthy Chinese male volunteers. In light of previous data on the large variability of AA, we applied a two-sequence and four-period crossover (2 × 4), replicate study design, such that the true intra-subject variability for the test and reference products can be established independently, and the bioequivalence acceptance limit could be adjusted based on the variability for the reference product and the scaled-average-bioequivalence method, according to European Medicines Agency (EMA) and US Food and Drug Administration (FDA) Guidelines on the investigation of bioequivalence for highly variable drugs [13, 14]. This study was required by Chinese regulatory authorities to provide support for the generic product to obtain marketing authorization in China.

Materials and methods

Ethics

This study was conducted according to the Declaration of Helsinki, the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and Chinese GCP, as well as Guidelines for Human Bioequivalence Studies [15–18]. The study protocol, protocol amendments and all applicable documents including informed consent form were reviewed and approved by the Ethic Committee of Xuanwu Hospital Capital Medical University (2017 No. 14). Informed written consent was obtained from all subjects prior to screening.

Materials

The test formulation abiraterone acetate tablet (250 mg) was produced by the Jiangxi Qingfeng Pharmaceutical Co., Ltd. and the reference formulation ZYTIGA® (abiraterone acetate tablet, 250 mg) was purchased from Janssen-Cadlag International N.V. Both products were shipped and stored between 15 and 30 °C until the study, and were tested by Jiangxi Qingfeng Pharmaceutical Co., Ltd, with demonstrated quality and strength, according to the certificate of analyses. Bioanalytical standard abiraterone and internal standard [$^2H_4$]-abiraterone were both purchased from TLC pharmaceutical standards ltd, Ontario, Canada.

Subjects

Thirty-two healthy Chinese male subjects aged ≥ 18 years with a body mass index (BMI) between 20 and 27.9 kg/m^2 were enrolled in the study. Subjects were in good health conditions, as determined by a detailed medical history, full physical examination, vital signs (body temperature, pulse, respiratory rate, and blood pressure), 12-lead ECGs, and clinical laboratory tests (urinalysis, hematology, blood chemistry, blood coagulation, testosterone and luteinizing hormone) and serologic tests including hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus antibody, and Syphilis antibody with values within the reference range or deemed normal by the clinical investigator. Subjects were excluded if they had history of clinically significant cardiovascular, endocrine, gastrointestinal, hematological, hepatic, neurological, psychiatric, pulmonary, and renal diseases, history of drug abuse or alcohol abuse (more than 28 drinks per week) or heavy smoking (more than five cigarettes per day within 3 months), or if they received any medication within 14 days prior to or during the study period. Anyone who has participated in an investigational drug study within 3 months, who donated or

lost whole blood over 200 mL within 3 months, or who is allergic to the study medications or any other similar compounds, was excluded.

Study design and conducts

This was a randomized, open-label, two-sequence, four-period, single-dose bioequivalence study, conducted in 32 healthy male Chinese subjects under fasting condition, to compare the pharmacokinetic and safety profiles of the test abiraterone acetate tablets (T), manufactured by Jiangxi Qingfeng Pharmaceutical Co., Ltd. and ZYTIGA® (250 mg tablets, R), manufactured by Janssen-Cilag International N.V. The sample size calculation was mainly driven by maximum observed concentration (C_{max}) of abiraterone due to a higher intra-subject coefficient of variation (CV, about 42%) than the area under the concentration–time curve (AUC_{0-t}) [10]. Thirty-two subjects will provide at least 80% power to have 90% confidence interval (CI) of estimated geometric least square mean ratio within the bioequivalence acceptance criteria of 72.15–138.59% according to EMA guideline, assuming intra-subject variability CV of 45% and taking account of the possible dropout of approximately 30%.

Subjects were randomized into two treatment sequence groups: Sequence 1 = TRTR and Sequence 2 = RTRT, and each study period was separated by a 7-day washout period. The study protocol was reviewed and approved by the Ethic Committee of Xuanwu Hospital Capital Medical University. The study was conducted in accordance with Chinese Guideline for Bioequivalence Studies with Pharmacokinetic Endpoints for Generic Chemical Drugs and FDA Guideline on Bioanalytical Method Validation [18, 19].

In the evening before the study, subjects were assigned with randomized numbers into two treatment sequence groups (TRTR and RTRT) and underwent an over-night fast (10 h). The next morning, each subject received either an oral dose of one tablet of the test product abiraterone acetate tablet (250 mg tablet, Batch No. 170401) or one tablet of the reference product ZYTIGA® (250 mg tablet, Batch No. VWMS) according to the randomly assigned treatment sequence. Blood samples (4 mL each) were drawn at 0 (pre-dose) and at 15, 30 min and at 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 60, and 72 h post-dose. No water was consumed between 1 h before and 1 h after drug administration, except the 240 mL water to swallow the study medications. Lunch and dinner, prepared as standardized Chinese low-fat meals, were provided approximately 4- and 10-h post-dose, respectively. Study periods 2, 3, and 4 followed the pre-specified treatment sequence and repeated the above procedures. Each of the four study periods was separated by a 7-day washout period.

Subjects were confined to the Phase I Clinical Trial Unit under clinical monitoring during the whole study period and were required to abstain from engaging in strenuous exercise. Subjects were discharged after the 72-h blood sample was drawn and safety assessments were completed in period 4. Throughout the study, subjects were required to abstain from smoking, taking concomitant medications (including traditional Chinese medicines), consuming food or beverages containing alcohol, caffeine, and/or grapefruit juice.

Blood sampling and drug analysis

Blood sampling and handling procedures were operated under yellow light condition. Whole blood samples were collected in precooled polypropylene tubes containing Na^2-EDTA as an anticoagulant and NaF as a stabilizing agent and were centrifugated at 2–8 °C within 30 min to obtain plasma specimens, which was divided into two parts and stored at − 80 °C low-temperature refrigerator pending for the analysis of abiraterone.

The bioanalytical method validation and clinical sample analyses were conducted in accordance with FDA Guideline on Bioanalytical Method Validation [19]. Throughout this study, the analysts were blinded from the randomized treatment sequence and clinical sample analyses included all subjects who completed two or more study periods.

Concentrations of abiraterone were analyzed in plasma using a validated LC-MS/MS method. Briefly, abiraterone were extracted from human plasma samples using a liquid–liquid extraction method: an aliquot (100 µL) of plasma was spiked with 50 µL of the internal standard working solution ([^{2}H4]- abiraterone in 50% acetonitrile aqueous solution) in 96-well plates, stood for 2 min and then, 500 µL of methyl tert butyl ether solution was added and blew dry with N_2 after 5 min. After repeated for three times, 600 µL solution was added following a vortex process for 5 min after sealing the plate. The resulting mixture was then centrifuged at 4000 rpm for 5 min at 4 °C. Upon centrifugation, the supernatant was transferred to auto-sampler vials and an aliquot (5 µL) was injected onto the LC-MS/MS system for the analysis of abiraterone, in which the LC system employed a reverse phase column (C18, 4.6 × 50 mm), using a 1.8 min gradient with methanol/acetonitrile 50/50 (v/v) and water containing 0.1% formic acid from volume ratio 70/30 to 95/5, and back to the volume ratio of 70/30 at 4.04 min. The analyte was detected by a triple-quadruple mass detector (API4000, AB Sciex) in positive ion mode with electrospray ionization in multiple reaction monitoring mode (*m*/*z* 350.2→150.0 for abiraterone and *m*/*z* 354.3→160.3 for internal standard). For the analysis of abiraterone, the Lower Limit of Quantitation (LLOQ) was 0.2 ng/mL and the assay dynamic range was 0.2–200 ng/mL. Excluded LLOQ, intra-batch accuracy and precision were 94.2–99.2% and ≤ 8.0%,

while inter-batch accuracy and precision were 88.3–107.6% and ≤7.0%, respectively. For LLOQ, intra-batch accuracy and precision were 97.0% and ≤11.0%, while inter-batch accuracy and precision were 85.5–109.0% and ≤8.7%, respectively. Short-term stability on ice bath was unstable (> ± 15% of initial values) beyond 6 h. However, the analyte was stable when stored at 5 °C for at least 46 h and when stored at − 80 °C after 80 days. Calibration curves were constructed by the LC-MS/MS software Analyst 1.6.3 using quadratic regression curve fitting for abiraterone. Calibration curve fitting processes for both analytes included a weighting factor of 1/X. Quantitation of QC and clinical samples were also performed by the Analyst software using the same mathematical algorithm as that in the calibration standard curves.

Safety assessments

Safety data evaluations including the assessment of treatment emergent adverse event (TEAE), physical examinations, vital signs (sitting blood pressure, pulse, breathing rate, and armpit body temperature), clinical laboratory tests (hematology, blood biochemistry, urinalysis, blood coagulation and hormone), and 12-lead ECGs were performed throughout the study. All adverse events (AE) or/and Serious AEs (SAE) were assessed by clinical investigators for the severity and their relationships to the medications under investigation.

Pharmacokinetic and statistical analyses

Pharmacokinetic parameters were derived with the validated computer program Phoenix® WinNonlin 7.0 (Certara, L.P., Princeton, New Jersey, USA). Pharmacokinetic and statistical analyses were performed using SAS software (version 9.4, SAS Institute, Cary, NC, USA). The following pharmacokinetic parameters were calculated from the plasma concentration–time data based on actual blood sampling times: C_{max}, the time of occurrence of C_{max} (T_{max}), AUC_{0-t} and the area under the concentration–time curve from time 0 to infinity ($AUC_{0-\infty}$). AUC_{0-t} was calculated using the linear and logarithmic trapezoidal methods, for increasing and decreasing concentrations, respectively. All PK parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) underwent natural log transformation before statistical analyses, and then the geometric least square mean ratios (test/reference) and the corresponding 90% confidence intervals were calculated using mixed-effects model procedure. Bioequivalence assessment was made based on statistical comparisons of C_{max} and AUC_{0-t} values between the test and reference products for abiraterone. Abiraterone acetate has been reported as a highly variable drug and, therefore, the reference scaled-average-bioequivalence (RSABE) method was to be applied to the acceptance limit of C_{max} and AUC_{0-t} according to EMA guideline [13, 20], based on the intra-subject standard deviation (S_{WR}) of the reference product obtained from this study. If $S_{WR} \geq 0.294$, the method of RSABE will be used, and bioequivalence will be declared if the point estimate of geometric mean ratios of C_{max} and AUC_{0-t} are both within the range of 80.00–125.00% and the 95% confidence upper limit bound for $(\bar{Y}_T - \bar{Y}_R)^2 - \theta S^2_{wR}$ less than zero. If $S_{WR} < 0.294$, the two one-sided t test would be used to test the statistical hypothesis, and bioequivalence will be declared if 90% CI of the geometric mean ratio of C_{max} and AUC_{0-t} is between 80 and 125%. For T_{max}, median (range) values were to be compared between test and reference products.

Results

Subjects disposition and baseline characteristic

Figure 1 shows the disposition of study subjects, a total of 85 subjects were screened within 14 days prior to the study and 33 were enrolled and randomized into treatment sequence of TRTR or RTRT according to the randomization sequence table. One subject discontinued from the study before administration due to personal reason at the beginning of period 1. As a result, another qualified subject was randomized instead and accepted investigational drugs. Finally, a total of 32 subjects completed all four periods of the study and were included in safety analysis set (SAS), pharmacokinetic analysis set (PKAS) and bioequivalence analysis set (BEAS). The mean age (± standard deviations [SD]) of SAS subjects was 31.56 (± 7.74) years (range 21–54), the mean BMI was 24.32 (± 2.07) kg/m^2 (range 20.0–27.6) and the mean body weight (± SD) was 70.54 (± 7.26) kg (range 60.7–89.0) (Table 1). The demographic characteristics between TRTR and RTRT sequences were comparable.

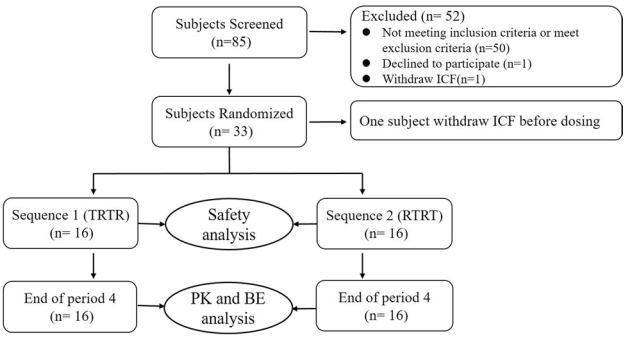

Fig. 1 Study design and subject disposition

Table 1 Demographic characteristics (safety analysis set)

Parameters (units)	TRTR	RTRT	Total
Age (years)			
N (Nmiss)	16(0)	16(0)	32(0)
Mean ± SD	31.56 ± 9.42	31.56 ± 5.92	31.56 ± 7.74
Min–max	21–54	24–47	21–54
Height (m)			
N (Nmiss)	16(0)	16(0)	32(0)
Mean ± SD	1.70 ± 0.05	1.70 ± 0.07	1.70 ± 0.06
Min–max	1.61–1.82	1.57–1.83	1.57–1.83
Weight (kg)			
N (Nmiss)	16 (0)	16 (0)	32 (0)
Mean ± SD	70.03 ± 6.96	71.05 ± 7.73	70.54 ± 7.26
Min–max	61.6–86.1	60.7–89.0	60.7–89.0
BMI (kg/m^2)			
N (Nmiss)	16 (0)	16 (0)	32 (0)
Mean ± SD	24.18 ± 1.97	24.46 ± 2.23	24.32 ± 2.07
Min–max	20.7–26.9	20.0–27.6	20.0–27.6

Pharmacokinetic properties

Mean plasma concentrations and median plasma concentrations of abiraterone for all four study periods are presented in Figs. 2 and 3, relatively. The corresponding pharmacokinetic parameters are summarized in Table 2. All pharmacokinetic data and statistical calculations included 32 subjects who completed the entire study per study protocol (four periods).

Following oral administration of both test and reference products, AA was rapidly absorbed and formed its main active metabolite abiraterone, which peaked at 2 h. Abiraterone was cleared slowly from the systemic circulation with a similar mean half-life between the two treatments at approximately 15 h. Mean abiraterone exposure PK parameters including $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were comparable between test and reference treatments. Mean $t_{1/2}$ was also compatible. Overall, the PK profiles of abiraterone were mostly overlapping between the two treatments.

Bioequivalence

Statistical comparisons of abiraterone between the test and reference products showed that the geometric least square mean ratios of C_{max} and AUC_{0-t} values were 100.19% and 106.00%, respectively, and the corresponding 90% confidence intervals were 87.05–115.32% and 96.49–116.14%, all fell within 80–125% acceptance limits (Table 3). The study demonstrated high intra-subject variability for C_{max} and AUC_{0-t} values for reference product at 46.58% and 34.16%, and for test product at 40.33% and 24.02%, respectively (Table 3). Therefore, we used the reference scaled-average-bioequivalence approach in this particular study to evaluate the bioequivalence between test and reference products. The 95% confidence upper limit bound for $\left(\bar{Y}_T - \bar{Y}_R\right)^2 - \theta S^2_{WR}$ was −0.1079 for C_{max} and was −0.0515 for AUC_{0t}. The statistical results of this study showed that the bioequivalence of test and reference formulations was achieved not only by reference scaled-average-bioequivalence approach, but also by conventional average bioequivalence evaluation.

Safety and tolerability

Safety data were collected for all subjects who administrated at least one dosing ($N = 32$). A total of 18 adverse events (AEs) was reported in this study, of which 9 were deemed by the clinical investigator as probably drug-related. In general, these adverse events are consistent with those reported

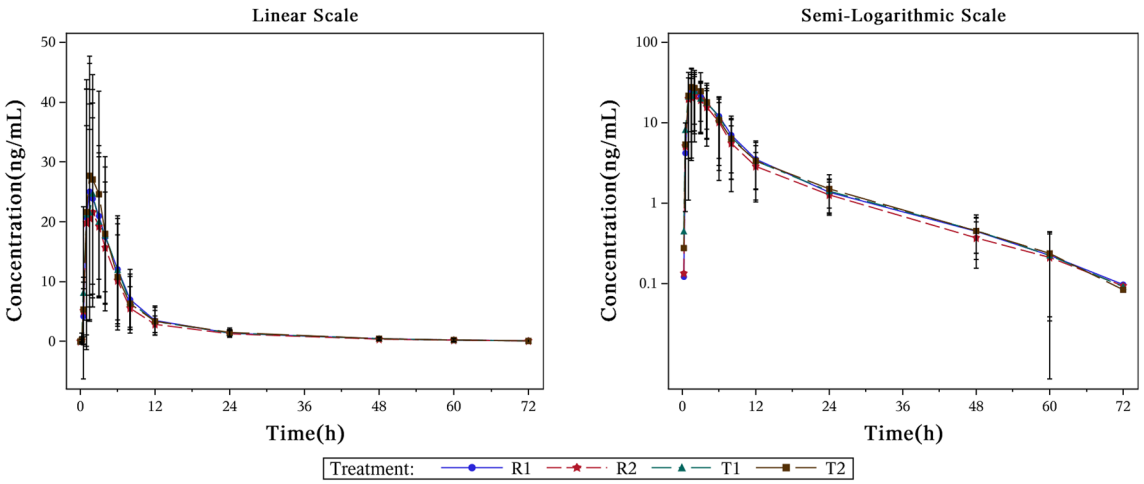

Fig. 2 Mean plasma concentration–time profiles of abiraterone in healthy subjects following single oral dose administration of the test (T1 and T2) and reference (R1 and R2) products (250 mg ZYTIGA®)

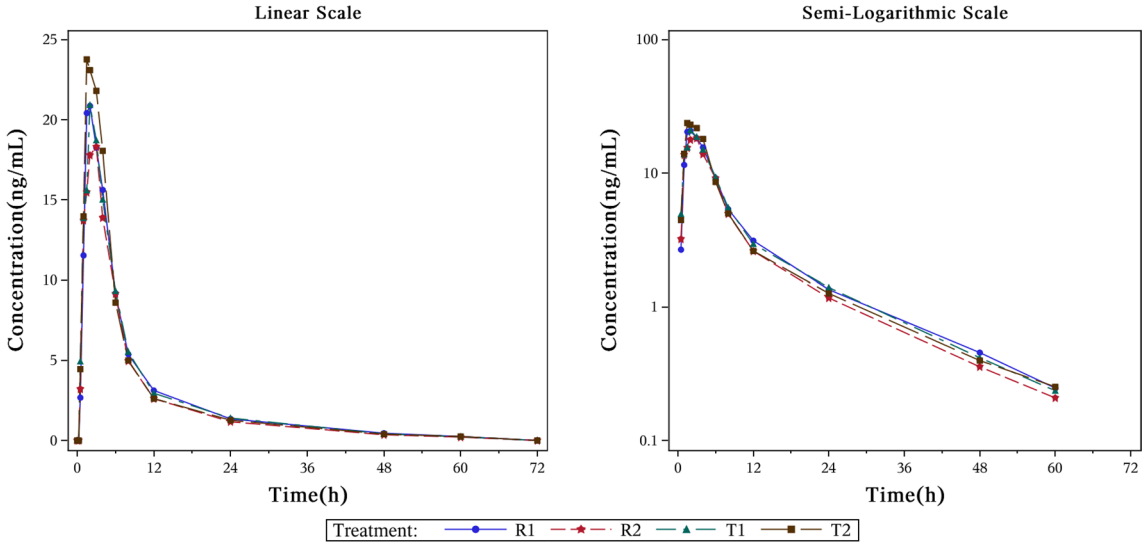

Fig. 3 Median plasma concentration–time profiles of abiraterone in healthy subjects following single oral dose administration of the test (T1 and T2) and reference (R1 and R2) products (250 mg ZYTIGA®)

Table 2 PK Parameters of AA in healthy Chinese male subjects under fasting condition

PK Parameters(units)	Mean ± SD (CV %) ($N = 32$)	
	Test ($n = 64$)	Reference ($n = 64$)
C_{max} (ng/mL)	35.39 ± 21.55 (60.90)	33.04 ± 18.05 (54.64)
AUC_{0-t} (h ng/mL)	192.25 ± 98.00 (50.98)	177.79 ± 84.90 (47.76)
$AUC_{0-\infty}$ (h ng/mL)	198.80 ± 97.34 (48.96)	184.42 ± 84.84 (46.00)
$\%AUC_{ex}$	4.41 ± 3.82 (86.59)	4.53 ± 3.91 (86.12)
λ_z (1/h)	0.0520 ± 0.0177 (34.05)	0.0524 ± 0.0215 (41.04)
$t_{1/2}$ (h)	14.92 ± 6.40 (42.87)	15.37 ± 6.92 (45.03)
V_d/F (L)	36772.65 ± 34900.30 (94.91)	37279.00 ± 31429.94 (84.31)
CL/F (L/h)	1643.02 ± 981.00 (59.71)	1705.96 ± 950.10 (55.69)
T_{max} (h)[a]	2.00 (1.00, 6.00)	2.00 (1.00, 6.00)
F (%)	115.92 ± 53.48 (46.13)	–

[a]Median [Min, Max]; *SD* standard deviation, *CV* Coefficient of variation, *N* subject number, *n* PK parameters number

Table 3 Bioequivalence evaluation

PK parameters (Unit)	Geometric LS mean			Ratio of GLSM (%)	90% CI	S_{WR}	Boundary (≤ 0)	CVw%	Power (%)
	n	T	R						
C_{max} (ng/mL)	32	28.5584	28.5035	100.19	(87.05, 115.32)	0.4431	− 0.1079	40.33 (T) 46.58 (R)	99.47
AUC_{0-t} (h ng/mL)	32	167.4343	157.9693	105.99	(96.34, 116.62)	0.3323	− 0.0515	24.02 (T) 34.16 (R)	98.26
$AUC_{0-\infty}$ (h ng/mL)	32	175.3241	165.6206	105.86	(96.49,116.14)	0.3148	− 0.0454	22.60 (T) 32.27 (R)	98.34

LS least-squares, *GLSM* Geometric LS Mean, *CI* Confidence interval, S_{WR} Standard deviation within individuals of reference product, *CVw%* Coefficient of variation within individuals

for ZYTIGA® [10–12], with most frequent adverse events including gastrointestinal and respiratory system disorders, as well as skin reactions (Table 4). Most of the adverse events were mild to moderate in severity and fully recovered within a few hours to a few days after onset, without requiring medical treatment. No clinically important changes in vital signs, physical examination, or ECG parameters were observed based on the baseline during the study for any treatment group. There were no serious AEs and no death were reported during the study. No AEs led to withdrawal from the study.

Discussion

Considering subjects' safety and referencing EMA Abiraterone tablets 250 mg product-specific bioequivalence guidance, this study only conducted under fasting condition, because ZYTIGA® must be administered on an empty stomach. When exposed to the food, the systemic exposure of the product (AUC) is increased to 10 times. In addition, taking ZYTIGA® with meals has the potential to result in increased and highly variable exposures [10, 20, 21].

This study compared the pharmacokinetic and safety profiles of two AA products and was designed as a full replicate study to overcome the difficulty of the high variability of abiraterone, for which the subjects took both the test and reference products twice. This study design enabled us to obtain the true intra-subject variability for the test and reference products independently, and apply the reference scaled-average-bioequivalence approach, which offers more flexible bioequivalence acceptance criteria for highly-variable drug products, referenced to the current FDA and EMA/CHMP Guidelines on the Investigation of Bioequivalence [13, 14].

As bioanalysis of pre-dose samples for study period 2, 3, and 4 did not show any detectable AA levels and no carryover effect was observed by statistical calculations ($p \geq 0.05$). This 2×4 crossover study demonstrated high intra-subject variability for C_{max} values of AA (40.33% and 46.58% for the test and reference product, respectively). Although the intra-subject variability data from this study qualify AA as a "highly variable drug" and the bioequivalence acceptance criteria could be widened using the scaled-average-bioequivalence approach [13], the actual results of statistical comparisons between the test and reference products for AA (C_{max} and AUC_{0-t}) fell within the conventional acceptance limit for bioequivalence of 80.00–125.00%.

Previous studies have demonstrated inter-individual variability as high as 91.37% in 30 healthy Japanese male [12]. It is noteworthy that the variability for AUC_{0-t} is considerably

Table 4 Summary of TEAEs (safety analysis set)

n (%)/*N*	TRTR (*n* = 16)	RTRT (*n* = 16)	Total (*n* = 32)
At least one TEAE	4 (25.00)	5 (31.25)	9 (28.13)
TEAEs related to study treatment	3 (18.8)	4 (25.00)	7 (21.88)
Serious AEs	0	0	0
TEAEs leading to early withdrawal	0	0	0
Deaths	0	0	0
TEAEs (preferred term, *N*)			
Rash	3[a]	0	3
Pruritus	1[a]	0	1
Skin bruise	0	1	1
Penile erythema	0	1[a]	1
Blood triglyceride increased	1	0	1
Headache	0	1	1
Blood pressure evaluated	0	1[a]	1
Chest tightness	0	1	1
Epistaxis	0	1[a]	1
Dry throat	0	1	1
Sore throat	0	1	1
Cough	0	1	1
Upper respiratory tract infection	1	0	1
Vomit	0	1[a]	1
Abdominal distension	0	2[b]	2

n subject number, *N* TEAE number, *AE* adverse event, *TEAE* treatment-emergent adverse event

[a]Drug related

[b]One AE related to drug and the other one unrelated to drug

lower than that for C_{max}, as oppose to AUC, as C_{max} is more sensitive to subtle changes, even within a subject. When calculating PK parameters, we found that the R^2 of λ_z was lower than 0.8 in three subjects (No. 027 in period 3, No. 011 and No. 029 in period 4), while the percentage of AUC_{ex} was over 20% and occurred in two periods (2 and 3) of subject No. 027 (Supply table). These may result in an inaccurate calculation of $AUC_{0-\infty}$, although the biases were within the acceptance range and there was no impact on C_{max} and AUC_{0-t}. A sensitivity analysis was done by eliminating the three subjects and the results showed that the S_{WR} of $AUC_{0-\infty}$ of the reference was 0.2863, less than 0.294. The ratio of the geometric mean ratio of the test and the reference formulations was 1.0846, and its 90%CI was (98.20, 119.80) and also in the bioequivalence range of 80.00–125.00%. The data of these three subjects has no influence on the bioequivalence evaluation between the two products.

A total of 9/32 subjects experienced at least one TEAE during the study period, except for one case of increased triglyceride (unrelated to the drugs) that was assessed by clinical investigator as a moderate AE, the other AEs were all mild. At the last scheduled visit, 16 AEs recovered and 2 AEs improved without any treatment. No serious adverse events occurred during the trial, and no subjects withdrew due to adverse event. Both the test and reference AA tablets were well tolerated by healthy Chinese male subjects after four single dose periods.

A limitation is that the study was conducted with a small subject population in fasting condition, for ZYTIGA® has just been approved administration under fasting condition, though the fasting and fed conditions were both recommended by the FDA draft guidance on Draft Guidance on Abiraterone Acetate. However, we firmly believe the results are concrete and suggest bioequivalence between the two AA formulations. Additionally, it may contribute to increase the access to AA formulation for prostate cancer patients and decrease the burden of Chinese health care system.

Conclusion

In this replicate designed bioequivalence study, AA tablets were shown to be safe and well tolerated in healthy Chinese male subjects and demonstrated a similar PK profiles between the test and reference products. In conclusion, the current study demonstrated that the test abiraterone acetate tablet is bioequivalent to the reference product ZYTIGA®.

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Compliance with ethical standards

Conflict of interest All the authors have no conflict of interest regarding the sponsor or the content of this article.

Ethical approval The study protocol, protocol amendments and all applicable documents including informed consent form were reviewed and approved by the Ethic Committee of Xuanwu Hospital Capital Medical University (2017 no. 14).

Informed consent Informed consent was obtained from all subjects prior to screening.

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