A Bioequivalence Study of Avanafil in Healthy Chinese Male Subjects Under Fasting and Fed Conditions: Results of a Randomized, Open-Label, Single-Dose, 2-Sequence, 2-Period Crossover Study

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Abstract

This bioequivalence study was conducted to determine the pharmacokinetics and safety profiles of an originator and a generic avanafil formulation in Chinese male subjects under fed and fasting conditions. Each eligible subject was initially randomly given avanafil (200 mg) in a test-reference or reference-test order, before being switched to another study drug sequence after 7 drug-free days. The bioequivalence of test and reference avanafil were determined if the 90%CIs of the geometric mean ratio (GMR) for the area under plasma concentration-time curve (AUC) from time 0 to infinity ($AUC_{0-\infty}$), AUC from time 0 to the last detectable concentration (AUC_{0-t}), and the maximum plasma concentration (C_{max}) fell within the range 80%-125%. Under fasting/fed conditions, the 90%CIs of GMR for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 98.9% to 109.5%/96.0% to 101.2%, 99.6% to 110.3%/96.6% to 102.4%, and 99.3% to 116.8%/94.3% to 106.7%, respectively, which were all within the 80%-125% range. Adverse events (AEs) occurred in 20.8% of subjects under fasting conditions and 20.7% of subjects under fed conditions, with a severity of grade 1. No significant difference was found in the rate of occurrence of AEs and drug-related AEs in the test and reference-avanafil groups (all $P > .05$). We concluded that the test and reference avanafil were bioequivalent in healthy Chinese male subjects under fasting and fed conditions.

Avanafil (Stendra) is an oral, quick-onset, highly selective second-generation type 5 phosphodiesterase (PDE5) inhibitor that is administered to treat erectile dysfunction and to improve vaginal penetration and hence to have successful sexual intercourse. It has been widely marketed in the United States, France, Germany, and the United Kingdom, among other countries.[1–3]

Avanafil is rapidly absorbed after oral administration, with a maximal plasma concentration (C_{max}) achieved at a median time to reach C_{max} of 30-45 minutes under fasting condition.[4–6] When concomitantly taken with a high-fat diet, the avanafil absorption rate decreased, t_{max} was extended by 1.12 to 1.25 hours on average,[6] C_{max} decreased by 24%, and the area under the plasma concentration-time curve (AUC) increased by about 14% compared with the fasting condition.[4] Avanafil is mainly metabolized by the liver, with cytochrome P450 (CYP) 3A4 the major metabolizing enzyme and to a minor extent CYP2C. The active circulating metabolite is M4, which can inhibit PDE5 with

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a pharmacological activity contribution of about 4%. The other metabolite M29 has no effect on PDE5.[7] The terminal elimination half-life time was 5 hours, with the predominant route of elimination being stool and also to a lesser extent urine.[8] There was no significant drug accumulation after multiple dosing, and the pharmacokinetic parameters were similar for single and multiple doses.[5] However, because of metabolism by CYP3A4, avanafil should not be coadministered with strong CYP3A4 inhibitors, and the maximum dosage of avanafil should be 50 mg when coadministered with moderate CYP3A4 inhibitors over a 24-hour period. In addition, avanafil combined with nitrates is contraindicated, and α-adrenergic blockers or other antihypertensives have been reported to increase the likelihood of hypotension. At baseline as well as during therapy, blood pressure monitoring is strongly recommended.[9]

Because of its pharmacokinetic characteristics and high selectivity for PDE5, avanafil induced few incidents of adverse events (AEs) compared with other PDE5 inhibitors.[10] The most commonly reported AEs included headaches, flushing, nasal congestion, nasopharyngitis, and back pain.[2,5,11]

The reference avanafil was developed by Sichuan Haisco Pharmaceutical Co., Ltd., based on an actual clinical need, and its main ingredients, administration route, indications, and dosage were completely consistent with branded avanafil. It is important to confirm the bioequivalence between the generic and branded drugs in accordance with the requirements of consistency in evaluation for generic drugs in China. The initial recommended dose of avanafil in clinical practice is 100 mg, but based on efficacy and safety data, the dose can be increased to 200 mg.[2]

The present trial was carried out on healthy Chinese male subjects who had fasted or been fed to determine the bioequivalence, pharmacokinetic, and AE profiles of 2 formulations of avanafil. Considering the clinical dose of avanafil, safety profiles, the concentration range of plasma samples, and the sensitivity of the detection method, the dose of avanafil in this bioequivalence study was set at 200 mg.

Methods

Design of the Study and the Characteristics of Participating Subjects

The present equivalence study included 2 randomized, open-label, single-dose, 2-sequence, 2-period crossover trials carried out in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology. All subjects orally received the test (T) or reference (R) avanafil (200 mg) under fasting (overnight fasting for 10 hours) or fed (high-fat/high-calorie meals) conditions together with 240 mL of warm water, from March

7, 2018, to June 20, 2018, and from November 12, 2018, to January 17, 2019, respectively. In both trials, each subject was initially given either the TR or RT drug sequence, before being switched to the alternative drug sequence after allowing 7 days for drug elimination.

Subjects enrolled had to meet the following inclusion criteria: aged 18-65 years (inclusive); weight $\geq$ 50 kg, with body mass index of 19-26 kg/m^2; exhibit normal clinical and vital signs, 12-lead electrocardiogram (ECG) recordings and laboratory test results; agree to use effective contraception for at least 1 month after signing the informed consent form until the last drug administration of the trial.

The exclusion criteria were: a clear history of diseases of the central nervous system; cardiovascular, digestive, respiratory, musculoskeletal, or hematologic systems, kidney, liver, metabolism, or any other condition that could have interfered with the study results. Also, those subjects who had a laboratory results of alanine aminotransferase > 1.2 of the upper limit of the normal value (ULN), aspartate aminotransferase > 1.2 ULN, or creatinine (Cr) > 1.0 ULN. Further criteria are listed in more detail in File S1.

The ethics committee of the clinical trial, Huazhong University of Science and Technology, approved the study protocols (approval number 2017 [269]-1), which were conducted according to the ethical principles of the Helsinki Declaration, International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, and Good Clinical Practice. All participants submitted prior informed consent before taking part. The trial was registered with chinadrugtrials.org.cn (registry number CTR20180041).

Pharmacokinetic Evaluations

The test and reference avanafil bioequivalence was determined according to the main pharmacokinetic parameters, including the AUC from time 0 to infinity (AUC$_{0-\infty}$), AUC from time 0 to the last detectable concentration (AUC$_{0-t}$), and C$_{max}$. Secondary pharmacokinetic parameters such as the time to reach C$_{max}$ (t$_{max}$), half-life (t$_{1/2}$), elimination rate constant (λz), and plasma concentrations were also evaluated.

Blood samples in subjects under fasting condition were collected at the following 16 times: predose (within 1 hour), 10, 20, 30, and 45 minutes and 1, 1.25, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, and 24.0 hours postdose. In addition to the above 16 times, blood samples in subjects under fed conditions were collected 2.5, 3.5, and 5.0 hours postdose. The blood samples (4 mL) were directly collected in K$_2$-ethylenediaminetetraacetic acid anticoagulant tubes, immediately separated by centrifugation (1700g for 10 minutes at 4°C), and preserved at

−60°C until the plasma drug concentrations were measured.

Avanafil was extracted from plasma samples using the protein precipitation method and avanafil-^{13}C-d$_3$ (TLC Pharmaceutical Standards, Toronto, Ontario, Canada) was used as the internal standard. Drug concentrations were determined using a validated high-performance liquid chromatography-tandem mass spectrometry method. Chromatography was performed using LC-20AD system (Shimadzu Corporation, Tokyo, Japan) equipped with an Ultimate XB C18 column (2.1 × 50.0 mm, 5.0 μm; Welch Materials, Inc., Shanghai, China). The mobile phase consisted of (A) aqueous solution containing 0.1% formic acid and (B) acetonitrile solution containing 0.1% formic acid, delivered at a flow rate of 1.0 mL/min and a column temperature of 35°C. A QTRAP 4000 mass spectrometer (AB Sciex, Framingham, Massachusetts) equipped with an electrospray ionization source in the positive ionization mode was utilized to optimize the analytical method. Multiple reaction monitoring transitions were at m/z of 484.2 to 154.8 for avanafil and 488.3 to 158.8 for the internal standard. Analyst 1.6.2 (AB Sciex) and Watson LIMS 7.5 software (Thermo Fisher Scientific, Waltham, Massachusetts) were used for data acquisition and the calculation of plasma drug concentrations. The linear range of the analytical methodology was 15.0-6000 ng/mL, with the lower limit of quantitation (LLOQ) set at 15.0 ng/mL on the basis of a signal-to-noise ratio ≥ 5; measured concentrations below the LLOQ were recorded as below the quantification limit (BQL). The within-day accuracy (range, %) and maximum precision (% relative standard deviation [RSD]) of 3 quality controls was −4.6 to 6.3 and 4.2, respectively. The between-day accuracy (range, %) and maximum precision (% RSD) of 3 quality controls was −2.7 to 2.8 and 3.9, respectively.

Safety

Safety evaluations were conducted at screening, during treatment, and at follow-up. In particular, the rate of occurrence and severity of AEs, serious AEs (SAEs), drug-related AEs, treatment-emergent AEs (TEAEs), laboratory test results, physical examination, and vital signs and 12-lead ECG analysis were carefully documented. All AEs were reported according to the Medical Dictionary for Regulatory Activities (version 21.1), based on the systematic organ classification and preferred terms. TEAEs were classified as AEs that occurred after the initiation of first drug administration until the end of the treatment period.

Randomization and Sample Size

The randomization method utilized a randomized block design, with SAS Enterprise Guide (version 7.1) software used to generate the random grouping table. Eligible subjects were allocated a random number that decided whether they were given the test drug or reference avanafil based on the random grouping table.

According to previous studies, the total coefficient of variation (CV) for avanafil varied from 20% to 40%, because of the different study populations, designs, and drug dosages.[3,5] For the trial under fasting conditions, sample size was set at 20, with a 10% drop-off rate predicted, and 24 subjects were eventually enrolled. Assuming the intraindividual CV (intra-CV) for subjects under fed conditions was 22.5%, the estimated sample size was 53, based on the geometric mean ratio (GMR) of the main pharmacokinetic parameters between the test and reference avanafil (0.90 with a two one-sided t-test [TOST] error [α] of 0.05 and a power [$1 - \beta$] of 85%). Allowing for a withdrawal rate of 10%, 60 subjects were enrolled in the trial under fed conditions.

Statistical Analysis

SAS Enterprise Guide (version 7.1) was used for all analyses. Continuous variables are given as mean ± SD and categorical variables as percentages and numbers. All tests were 2-sided, and $P < .05$ was considered a statistically significant finding.

Bioequivalence and pharmacokinetic analyses were conducted in randomized subjects who completed at least 1 period treatment and had at least 1 evaluable pharmacokinetic parameter. Analysis of variance (ANOVA) was performed following logarithmic transformation of the main parameters (AUC$_{0-\infty}$, C$_{max}$, AUC$_{0-t}$), in which the factors inputted into the ANOVA model were the experimental drugs (test/reference), study period (first or second), sequence group (TR or RT), and study subjects. On the basis of ANOVA, the least-squares mean of C$_{max}$, AUC$_{0-t}$, and AUC$_{0-\infty}$ of test and reference avanafil was analyzed using a 1-sided t test. The Hodges-Lehmann test was used for nonparametric analysis of t$_{max}$ to reveal any differences between the test and reference avanafil formulations. The 90% confidence intervals (CI) and intra-CV of the GMR (test/reference) for the main pharmacokinetic parameters were calculated, and if the 90%CI was between 80% and 125%, the test and reference avanafil were considered equivalent. All BQL values were recorded as 0 when calculating the mean values of the plasma concentration. Pharmacokinetic parameters were evaluated using a noncompartmental model available in WinNonlin version 6.3 (Certara L.P., Princeton, New Jersey) to comprehensively reflect the characteristics of drug absorption, distribution, metabolism, and excretion (drug disposition). Demographic and baseline characteristics were analyzed according to the full analysis set that included randomized subjects who were given the experimental drug once and for whom the Wilcoxon

rank sum test was employed to evaluate continuous variables. Fisher's exact test was used to evaluate variables that were categorical. Safety evaluation was conducted in the safety set, including randomized subjects who received either the test or reference avanafil dosage and had at least 1 postadministration safety assessment. The incidence of AEs in the test and reference avanafil groups was analyzed using Fisher's exact test.

Results

Subject Dispositions and Baseline Demographics
For the fasting trial, a total of 70 subjects were screened and 24 were enrolled (12 per group), of whom 18 subjects finally completed the 2-period treatments and 6 subjects were lost to follow-up (Figure S1). For the fed trial, a total of 192 subjects participated in the screening period, and 60 were finally enrolled (30 per group). Of all randomized subjects, 57 received the test avanafil, 55 received the reference avanafil, and 54 completed the 2-period study. Finally, 100% of the 24 subjects (in both the test and reference groups) under fasting conditions and 96.7% of 58 subjects (57 in the test and 55 in the reference groups) after feeding were enrolled for further bioequivalence, pharmacokinetic, and safety analyses.

Regardless of the fasting or feeding state, no differences were found between the demographic characteristics of the TR and RT groups (all $P > .05$). Of the enrolled subjects, those who had fasted had a mean age of 24.5 years (range, 18 to 32 years); likewise subjects under fed conditions had a mean age of 28.7 years (range, 20 to 45 years); see Table S1.

Pharmacokinetics and Bioequivalence
The mean plasma drug concentrations and pharmacokinetic parameters of subjects who fasted or were fed are presented in Figure 1 and Table 1. Under the fasting and fed states, the measured plasma concentrations of the TR and RT avanafil formulations were virtually identical within 0-24 hours. All pharmacokinetic parameters between the test and reference avanafil were similar in the fasting and fed states, without significant differences (all $P > .05$). After food intake, increases in $AUC_{0-\infty}$, AUC_{0-t}, $t_{1/2}$, and t_{max} and a decrease in C_{max} were observed for the TR avanafil dosage.

Table 2 summarizes the bioequivalence evaluation of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for avanafil administered under fasting and fed conditions in healthy subjects. Under fasting conditions, the GMRs of test and reference avanafil for $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 98.9% to 109.5%, 99.6% to 110.3%, and 99.3% to 116.8%, respectively. Under fed conditions, the GMRs

of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} were 96.0% to 101.2%, 96.6% to 102.4%, and 94.3% to 106.7%, respectively. Regardless of the fasting or fed state, the 90%CIs of the main $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} parameters fell within the equivalent range (80.0%-125.0%), proving that test and reference avanafil formulations were equivalence under fasting and fed conditions. Of the factors in the ANOVA model, only study duration had a significant influence on the calculation of $AUC_{0-\infty}$ and AUC_{0-t} after logarithmic transformation ($AUC_{0-\infty}$, $P = .01$; AUC_{0-t}, $P = .041$) in subjects under fasting conditions. No significant differences were found between the TR and RT avanafil doses in the sequence groups for the trial duration or the experimental drug in subjects under fed conditions (all $P > .05$).

Safety
A total of 7 AEs occurred in 5 subjects (20.8%) under fasting conditions, all of which were associated with the administered drug, with 2 (8.3%) in the test avanafil group and 3 (12.5%) in the reference group (Table 3). For subjects under fed conditions, a total of 12 (20.7%) experienced 20 AEs (all TEAEs), of whom 11 (19.0%) experienced 14 drug-related AEs, 6 subjects in the test avanafil group (10.5%) and 5 subjects in the reference avanafil group (10.1%). Urine protein was detected in subjects administered test and reference avanafil under fasting conditions. For subjects under fed conditions, urine protein detection and dizziness were detected in both the test and reference avanafil groups, but a higher incidence of blood pressure decrease was only reported in the reference avanafil group.

During the study period, the severity of AEs for all subjects was grade 1 after oral administration under fasting and fed conditions, and no concomitant medication was required or administered. Except for the unknown outcome of 2 subjects in the fed trial, the remaining subjects were cured or improved without any further treatment. None of the subjects had SAEs or AEs that led to withdrawal from the trial or death. With regard to whether subjects had fasted or been fed, the incidence of AEs or drug-related AEs in the TR and RT groups was virtually identical (all $P > .05$).

Discussion

The present study has confirmed the bioequivalence between test and reference avanafil formulations after a fast or a feed. Regardless of whether subjects had fasted or fed, the 90%CIs of GMR (test/reference) for the parameters ($AUC_{0-\infty}$, AUC_{0-t}, and C_{max}) fell within the prespecified range (80%-125%), which met the requirements of the bioequivalence standard. These
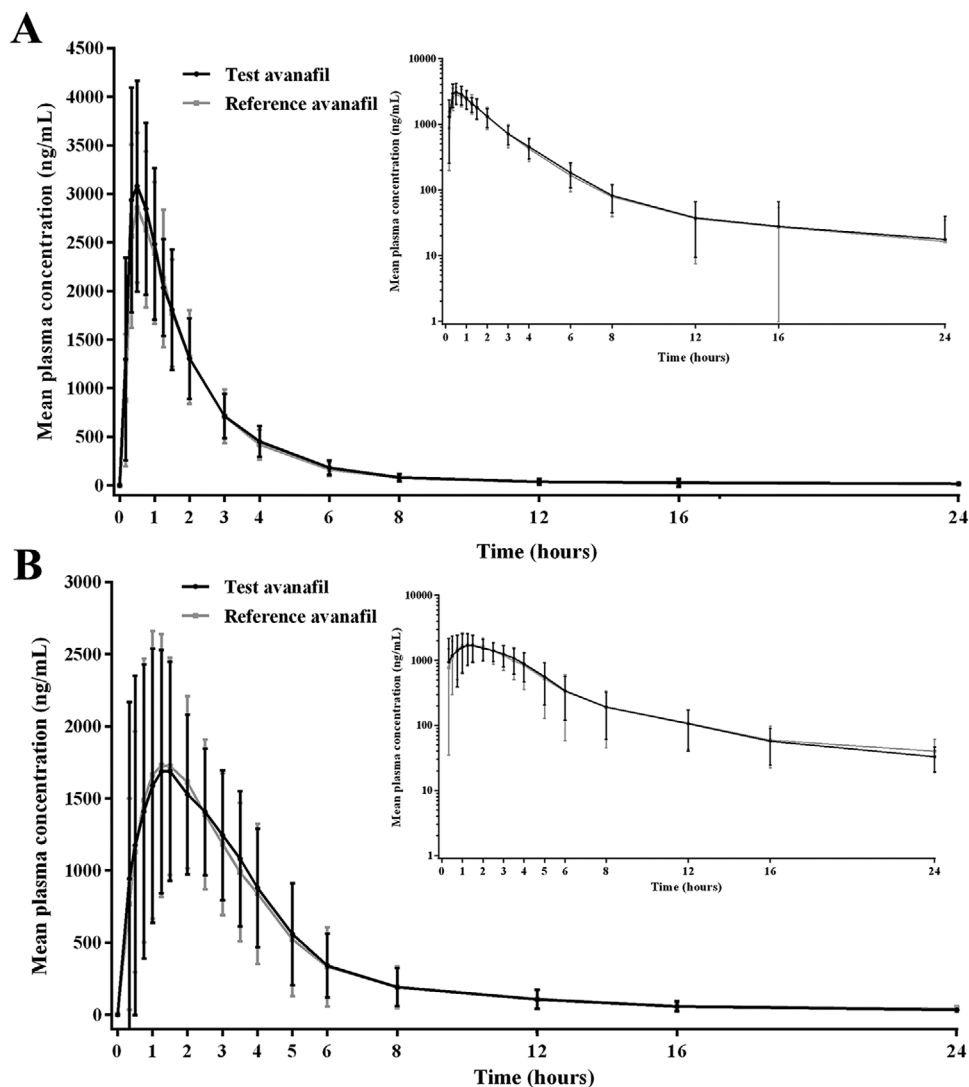
Figure 1. Mean (SD) plasma concentration-time profiles of test and reference avanafil administered to healthy subjects under (A) fasting and (B) fed conditions (on linear and semilogarithmic scales). All below the quantification limit (BQL) values were recorded as 0 when calculating the mean values of plasma concentrations. All data are presented as mean with standard deviation (SD).

findings indicated that the extent and rate of absorption between the TR and RT avanafil formulations were equivalent under fasting or fed conditions. In addition, the main pharmacokinetic parameters of test avanafil in our study showed a lower intra-CV% (<30%), confirming that avanafil was not a highly variable drug[5]; thus, the prespecified equivalence range of 80% to 125% was deemed reasonable.[12]

The study period in the ANOVA model had a significant influence on the calculation of $AUC_{0-\infty}$ and AUC_{0-t} after logarithmic transformation ($AUC_{0-\infty}$, $P = .01$; AUC_{0-t}, $P = .04$) under the fasting condition and the common reason was the presence of drug residues in the second period because of a short washout time.[13] However, the washout period of 7 days was much more than 7 times the mean $t_{1/2}$ for test (4.3

hours) and reference (5.3 hours) avanafil. In addition, the plasma concentration of avanafil in all subjects at the first administration time during the second period was recorded as BQL, so the influence of the study design itself on the equivalence result could be excluded.

The results of plasma concentrations and pharmacokinetic parameters (AUC, C_{max}, t_{max}, and $t_{1/2}$) were similar for test and reference avanafil in healthy Chinese subjects under both fasting and fed conditions, findings consistent with previously reported studies.[5] Similar to branded avanafil, slight increases in the AUC (absorption extent), t_{max}, and $t_{1/2}$ and a decrease in C_{max} (absorption rate) were observed with test avanafil after food intake, which is in agreement with a previous literature report of a 14% AUC increase with concomitant

Table 1. Pharmacokinetics Parameters of Test and Reference Avanafil Administered Under Fasting and Fed Conditions to Healthy Subjects

	Under Fasting Conditions		Under Fed Conditions	
Parameters	Test Avanafil (n = 24)	Reference Avanafil (n = 24)	Test Avanafil (n = 57)	Reference Avanafil (n = 55)
$AUC_{0-\infty}$ (ng·h/mL)[a]	7250 ± 2314	6973 ± 2235	8124 ± 2557	8177 ± 2679
AUC_{0-t} (ng·h/mL)[a]	7073 ± 2246	6731 ± 2043	7864 ± 2521	7835 ± 2579
C_{max} (ng/mL)[a]	3411 ± 1047	3122 ± 798	2301 ± 727	2302 ± 768
T_{max} (h)[b]	0.5 (0.3-0.8)	0.5 (0.3-1.3)	1.5 (0.3-5.0)	1.3 (0.3-5.0)
$t_{1/2}$ (h)[a]	4.3 ± 3.5	5.3 ± 5.3	5.3 ± 3.2	5.7 ± 2.6

AUC, area under the plasma concentration-time curve; $AUC_{0-\infty}$, AUC from time 0 to infinity; AUC_{0-t}, AUC from time 0 to last detectable plasma concentration; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life time; t_{max}, time to reach C_{max}.
[a] Data are presented as the mean ± SD.
[b] Data are presented as the median (range).

Table 2. Bioequivalence Evaluation of $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} for Avanafil Administered Under Fasting and Fed Conditions to Healthy Subjects

Parameters	GMR, %	90%CI	Power, %	Intra-CV, %
Under fasting conditions				
$AUC_{0-\infty}$ (ng·h/mL)	104.0	98.9-109.5	100.0	10.3
AUC_{0-t} (ng·h/mL)	104.8	99.6-110.3	100.0	10.3
C_{max} (ng/mL)	107.7	99.3-116.8	92.05	10.6
Under fed conditions				
$AUC_{0-\infty}$ (ng·h/mL)	98.7	96.1-101.3	100.0	8.3
AUC_{0-t} (ng·h/mL)	99.6	96.7-102.5	100.0	9.1
C_{max} (ng/mL)	100.7	94.7-107.1	100.0	19.3

AUC, area under the plasma concentration-time curve; $AUC_{0-\infty}$, AUC from time 0 to infinity; AUC_{0-t}, AUC from 0 to last detectable drug concentration; C_{max}, maximum plasma concentration; CI, confidence interval; Intra-CV, intraindividual coefficient of variation; GMR, geometric mean ratio.

food intake,[4] but the AUC changes in our study were slightly higher than previously reported (15%-20%; Table 1), a finding that may be attributed to different high-calorie diets, a more sensitive assay, or different subject population responses. Avanafil at doses of 50, 100, or 200 mg without restriction of food and alcohol intake also showed significant improvements in sexual function compared with placebo.[14] However, because of its substrate promiscuity, the metabolizing activity of CYP3A4 for certain drugs is significantly inhibited by grapefruit juice, red wine CYP and St. John's wort, leading to accumulation, which needs dose adjustments.[15] Therefore, avanafil is not recommended for concomitant use with strong CYP3A4-inhibiting drugs and the maximum dose of avanafil should be 50 mg/24 hours with moderate CYP3A4-inhibiting drugs; grapefruit juice within 24 hour of taking avanafil should be avoided.[8] Otherwise, even though concomitant food intake may delay the absorption of avanafil, high-calorie diets do not significantly influence CYP3A4 activity.[16]

The safety results revealed that all AEs were TEAEs in both the fasting and fed trials, with an incidence of 20.8% and 20.7%, respectively. The severity of AEs were both grade 1, and except for the unknown outcome of 2 subjects in the fed trial, all the remaining subjects were cured or had greatly improved symptoms without the need for further therapy. As reported in earlier studies, ECG changes, heart rate increases, and dizziness were also observed in subjects under fasting and fed conditions, whereas other commonly reported AEs such as headaches and flushing[2,17] were not found in the present study. No significant difference was found between the rate of occurrence of AEs or drug-related AEs in the 2 groups (all $P > .05$), indicating good tolerance, a finding consistent with previously published studies.[5,17]

Conclusion

In summary, the pharmacokinetic profiles proved that test and reference avanafil tablets (200 mg) were bioequivalent in healthy Chinese men and that both formulations were well tolerated, regardless of whether a subject had fasted or been fed.

Table 3. Summary of AEs in the Safety Population of Subjects

	Test Avanafil, n (%) (n = 24)	Reference Avanafil, n (%) (n = 24)
Under fasting conditions		
Any AEs	2 (8.3)	3 (12.5)
Drug-related AEs, termed by PT	2 (8.3)	3 (12.5)
Urine protein detection	1 (4.2)	1 (4.2)
Direct bilirubin increase	0	1 (4.2)
Platelet count decrease	0	1 (4.2)
Creatine phosphokinase increase	0	1 (4.2)
Supraventricular extrasystole	1 (4.2)	0
Ventricular extrasystole	1 (4.2)	0
Under fed conditions		
Any AEs	7 (12.3)	6 (10.9)
Drug-related AEs, termed by PT	6 (10.5)	5 (10.1)
Urine protein detection	1 (1.8)	1 (1.8)
Creatine phosphokinase increase	0	1 (1.8)
Aspartate transaminase increase	0	1 (1.8)
Alanine transaminase increase	1 (1.8)	0
Heart rate increase	1 (1.8)	0
Dizziness	1 (1.8)	1 (1.8)
Blood pressure increase	1 (1.8)	0
Blood pressure decrease	0	2 (3.6)
Systolic blood pressure increase	0	1 (1.8)
T-wave abnormalities in the electrocardiograph	1 (1.8)	0
Supraventricular extrasystole	1 (1.8)	0

AEs, adverse events; TEAEs, treatment-emergent AEs.
Note: All data are presented as number of subjects and percentage.

Conflicts of Interest

The authors declare no conflicts of interest.

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Data-Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.