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ORIGINAL RESEARCH

Pharmacokinetics and Bioequivalence of Two Formulations of Valsartan 80 mg Capsules: A Randomized, Single Dose, 4-Period Crossover Study in Healthy Chinese Volunteers Under Fasting and Fed Conditions

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Purpose: To compare the bioequivalence of two formulations of valsartan (80 mg capsules) under fasting and fed conditions in healthy Chinese volunteers using a full-replicate study design.

Methods: A total of 78 Subjects were randomly assigned to fasting cohort (n = 48) or fed cohort (n = 30). Each cohort includes 4 single-dose observation periods and 3-day washout periods. Blood samples were collected at designed time point. Plasma concentration of valsartan was analyzed by a validated LC-MS/MS method. Noncompartmental analysis method was employed to determine the pharmacokinetic parameters. Based on the within-subject standard deviation (S_{WR}) of the reference formulation, either reference-scaled average bioequivalence (RSABE) or average bioequivalence (ABE) method was used to evaluate the bioequivalence of the two formulations.

Results: Under fasting conditions, the RSABE method was used to evaluate the bioequivalence of C_{max} (S_{WR}>0.294), while ABE method was used to evaluate the bioequivalence of AUC_{0-t} and $AUC_{0-\infty}$. The geometric mean ratio (GMR) of the test/reference for C_{max} was 99.52%, and the 95% upper confidence bound was <0. For AUC_{0-t} and $AUC_{0-\infty}$ comparisons, GMRs were 102.07% and 101.92%, and the 90% CIs of the test/reference were 96.28%–108.21%, 96.28%–107.88%, respectively. Under fed conditions, the S_{WR} value of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ all exceeded the cutoff value of 0.294 and therefore, the RSABE method was used. The GMRs for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 98.78%, 103.33% and 103.08%, respectively, while the 95% upper confidence bound values were all <0. These results all met the bioequivalence criteria for highly variable drugs. All adverse events were mild and transient.

Conclusion: In this study, the generic formulation of valsartan 80 mg capsule was considered to be bioequivalent to the reference product under both fasting and fed conditions, and satisfied the requirements for marketing in China.

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Keywords: valsartan, bioequivalence, replicate, pharmacokinetics, safety

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Introduction

Valsartan is an orally active angiotensin II type 1 receptor blocker for the treatment of hypertension alone or in combination with other antihypertensive agents.[1,2] Angiotensin receptor blockers (ARBs) are recommended to both hypertension

treatment and cardiovascular prevention in different settings.[3,4] It was patented in 1990 and came into medical use in 1996 known as Diovan which was initially used for the treatment for hypertension. It became available as a generic medication in 2012 worldwide. Bioequivalence studies comparing generic to innovator products are required for marketing a new generic product by the National Medical Products Administration (NMPA) of China. A systemically active generic drug is considered to be bioequivalent to the reference drug if the rate and extent of absorption of the two products do not show any significant difference, by conducting bioequivalence (BE) studies in human subjects to compare its pharmacokinetic characteristics.[5]

Valsartan is mainly administrated at a dose of 80 mg or 160 mg/d.[6] The absorption of Valsartan is rapid with the T_{max} of 2–4 hours. Intravenous administration showed a double exponential decay of pharmacokinetics with the $T_{1/2}$ of 6 hours. The absolute bioavailability of Diovan is reported to be 25% (range 10% to 35%).[7] The solubility of valsartan is pH dependent and thus may cause subject variability in drug absorption and failure in bioequivalence studies.[8] The within-subject variabilities for valsartan in C_{max} (CV~30%) and AUC (CV~44%) are considerable.[9,10] In light of these findings to indicate the high intra-subject variability of valsartan, we applied a two-sequence and four-period crossover (2 x 4), full replicate study design, such that the true intra-subject variability for the test and reference products can be determined independently, such that the reference scaled average bioequivalence (RSABE) method may be applied to assess bioequivalence with widened acceptance limit, according to NMPA Guideline for human bioavailability and bioequivalence studies for pharmaceuticals.[11]

Orally administered valsartan is excreted mainly in the feces (~83%) and minor portion in the urine (~13%).[10] Valsartan is highly bound to serum proteins (95%), mainly serum albumin. The volume of distribution valsartan after IV (20 mg in 12 volunteers) administration was small (17 L), indicating that valsartan was not widely distributed in tissues.[12,13] After intravenous administration, the plasma clearance was approximately 2 L/h and the renal clearance was approximately 0.62 L/h (approximately 30% of total clearance).[7]

Clinical trials for Valsartan treatment for hypertension versus placebo demonstrated its side effects like viral infection (3% vs 2%), fatigue (2% vs 1%) and abdominal pain (2% vs 1%).[7] Compared with ACEI, the incidence of dry cough is significantly less. A bioequivalence trial (randomized, single-dose, 2-period crossover study) of 2 formulations of valsartan 160-mg tablets was conducted in 60 healthy Korean male volunteers. The results indicated that the test preparation and the reference preparation were bioequivalent and both formulations were well tolerated, with no serious adverse events reported.[14] Although there are reports in the literature regarding the pharmacokinetic (PK) characteristics of valsartan,[15–19] but few have fully addressed its intra-subject variability, especially under fed conditions. Thus, the current study was designed to compare the pharmacokinetic properties and bioequivalence of two formulations of valsartan (80 mg capsules) under fasting and fed conditions in healthy Chinese volunteers, using a full-replicate study design, and seek regulatory approval for the generic formulation to be marketed in China.

Subjects and Methods

Subjects

This study was conducted at the Phase I clinical research center of Shanghai Xuhui Central Hospital from August to October 2018. All subjects had been informed about the study and had provided written informed consent before participating in the study. Also, before starting any screening or research-related procedures, the researcher had explained to the subjects the nature of the study and had answered all questions related to the study. The subject had been asked to provide informed consent. All clinical laboratory tests were performed by masked bio-analysis at the Clinical Laboratory of Shanghai Xuhui Central Hospital, which was accredited by Shanghai Center for Clinical Laboratory of China. All QC samples, which were purchased from the National Center for Clinical Laboratories of China or Shanghai Center for Clinical Laboratory of China, will be detected together with the samples from patients at the laboratory every day. All participants were free to withdraw from the study at any time.

The inclusion criteria comprised healthy Chinese volunteers aged 18 to 45 years, with the body mass index between 19.0 to 28.0 kg/m^2, in good health and physical condition as determined by medical history, vital signs, physical examinations, 12-lead ECG, chest X-ray examination and laboratory tests (blood chemistry, hematology, urinalysis, hepatitis B surface antigen, hepatitis C antibody, HIV antibody and syphilis antibody).

The exclusion criteria included a history of heavy smoking (more than 10 cigarettes per day) and/or drug dependence and/or alcohol abuse. Those who had participated in other clinical trials within 3 months prior to this study, or who had blood loss of >400 mL within 3 months, or who had blood transfusions or donated blood >200 mL within 1 month before this study were also excluded. Subjects must not use any medications, vitamins and/or herbal supplements, within 2-week prior to study drug administration. For female subjects, their weight should be more than 45 kg besides the body mass index between 19.0 to 28.0 kg/$m^{2.}$ Positive pregnancy test or lactation women should be excluded.

Study Design

This study was a single-dose, open-label, randomized, two-sequence, four-Period crossover bioequivalence study. The study was performed in accordance with the ethical standards for studies in humans of the Declaration of Helsinki and its amendments,[20] the International Conference on Harmonisation Guideline for Good Clinical Practice,[21] and the Guideline for Good Clinical Principles recommended by NMPA of China.[22] The study protocol and informed-consent form were approved by the ethic committee of Shanghai Xuhui Central Hospital. The study was also approved by NMPA of China (B201800338-01). According to NMPA guideline on the investigation of bioequivalence,[11] this study was conducted in two cohorts under fasting and fed conditions. The sample size for fasting and fed conditions were calculated based on preliminary studies by using SAS (version 9.4) software.

In cohort 1, 48 subjects were randomly assigned to sequence A (TRTR) and sequence B (RTRT), and received valsartan under fasting conditions; in cohort 2, 30 subjects were randomly assigned to sequence C and (TRTR) sequence D (RTRT), and received valsartan under fed conditions. Two randomization tables were generated for the cohort 1 and 2, by SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) (Supplementary Table 1). The test product (T) was 80 mg valsartan capsule (lot # 201,706,082, expiration date 06/2019) was manufactured by Changzhou Siyao Pharmaceutical Co., Ltd.) and the reference product (R) was DIOVAN 80 mg capsule (lot# X2125, expiration date 12/2019), manufactured by Beijing Novartis Pharmaceutical Co., Ltd.).

All participants were required to undergo an overnight (10-hour) fast prior to dosing. Subjects who participated in the fed study must take a high-calorie, high-fat breakfast (which contains 148 calories of protein, 260 calories of carbohydrate, and 525 calories of fat) 30 minutes before dosing.[11] Investigational drugs were administered with 240 mL of water under supervision of a qualified pharmacist. Subjects were not allowed to drink water 1 hour before and 1 hour after dosing, except the water used for drug administration. Food intake was strictly controlled and standardized lunch and dinner were provided approximately 4 and 10 hours postdose, respectively. Alcoholic beverages, coffee, xanthine-containing drinks, intense physical activity, and smoking were not allowed during the study period.

All participating volunteers were under medical supervision by a physician throughout the study. Blood samples (2 mL) were drawn to K_2-EDTA containing vacuum blood collection tubes at 0 (pre-dosing), 0.5, 1, 1.5, 2, 2.5 3, 3.5, 4, 5, 6, 8, 12, 24, and 36 hours post-dose in the fasting cohort, and at 0 (pre-dosing), 0.5, 1, 2, 3, 3.5, 4.4.5, 5.5.5, 6, 8, 12, 24, and 36 hours post-dose in the fed cohort of the study. After sample collection, plasma was separated by centrifugation (2000 g ×10 minutes, 4°C), transferred into polypropylene tube within 1 hour, and was stored at −80°C until analyzed by liquid chromatography tandem mass spectrometry (LC-MS/MS).

Safety

Safety assessments included physical examinations, vital signs (oral body temperature, pulse rate, and sitting blood pressure), 12-lead ECGs, clinical laboratory tests and adverse event (AE) monitoring.

Determination of Plasma Valsartan Concentrations

In this study, the concentration of valsartan in plasma was determined by a validated LC-MS/MS method.[23,24] A deuterium labeled analytical internal standard (valsartan-d^9) was used for the quantitative determination of valsartan. In order to ensure the reliability of the analytical method for the determination, validation of this analytical method was performed to evaluate its selectivity, linearity, precision, accuracy and stability in solution according to the technical guideline for clinical pharmacokinetics of chemical drugs published by NMPA.[25]

The bioanalytical method and validation results are briefly described as follows: Protein precipitation method was used to extract valsartan from human plasma samples:

An aliquot (10 μL) of valsartan-d^9 (20 μg/mL in 50% [vol/vol] methanol) was added as internal standard to100 μL of plasma and mixed well, then 200 μL of acetonitrile was added into each sample and mixed well (vortex 10 s). After centrifuging the mixture at 15,000 rpm× 3 min at 4°C, the supernatant was transferred into auto-sampler vials and 20 μL was injected into the LC-MS/MS system for analysis.

Chromatographic conditions were as follows: The column was ACQUITY UPLC BEH C18 2.1× 50 mm, 1.7 μm, and the column temperature was 40°C, with a flow rate of 0.600 mL/min. The mobile phase A was 100% water containing 5 mM ammonium acetate and 1.0% formic acid, mobile phase B was 100% acetonitrile containing 0.1% formic acid. The starting gradient was 40% mobile phase B, and increased to 55% mobile phase B at 1 min applying a linear gradient elution program, then increased to 90% at 1.01 min and held until 1.80 min, then return to 40% B at 1.81 min and stop at 2.50 min.

The valsartan and internal standard valsartan-d^9 were detected by a triple-quadruple mass detector (API4000; AB Sciex) in positive-ion mode with electrospray ionization (ESI) in multiple-reaction-monitoring (MRM) mode (m/z 436.2/235.2 for valsartan, m/z 445.2/235.2 for valsartan-d^9).

The lower limit of quantitation (LLOQ) of valsartan was 7.00 ng/mL with dynamic range of 7.00 to 7000 ng/mL. And quality control (QC) samples (low QC, 21 ng/mL; Geometric Mean QC, 210 ng/Ml; medium QC, 3500 ng/mL; high QC, 5250 ng/mL; dilution QC, 14,000 ng/mL) were analyzed to assess the accuracy and precision of the method. All QC samples are evenly distributed among the samples to be analyzed.

Pharmacokinetic and Statistical Analysis

Pharmacokinetic analysis was conducted with noncompartmental model using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). C_{max} and T_{max} values were obtained directly from individual concentration-time curves (C-T) of valsartan. AUC_{0-t} was calculated using the linear trapezoidal rule. $AUC_{0-\infty}$ was calculated as $AUC_{0-t} + C_t/_z$, where C_t was the concentration at the last point and λ_z was the slope of the linear regression of the log-transformed C-T curve. Valsartan plasma $t_{1/2}$ was calculated as $0.693/_z$.[25]

Primary pharmacokinetic parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}) and the secondary pharmacokinetic parameters (T_{max}, $t_{1/2}$, λ_z) were summarized to their mean, median, standard deviation, maximum, minimum values and coefficient of variation, etc.

Statistical analysis was also performed using SAS version 9.4 on Ln-transformed primary pharmacokinetic parameters..

Due to the anticipated high intra-individual variation of valsartan, this study used a full-replicate design based on the within-subject variability of the reference formulation, according to the FDA-recommended reference-scaled average bioequivalence (RSABE) method.[26]

Prior to bioequivalence evaluation, the within-subject standard deviation (S_{WR}) of the reference formulation was calculated and if $S_{WR} < 0.294$ for any primary PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$), which corresponds to within-subject variability (CV_W%) <30%, bioequivalence was evaluated by the standard average bioequivalence (ABE). Bioequivalence was claimed if the 90% confidence interval (CI) for the test/reference GMR of the above pharmacokinetic parameter(s) falls within the range of 80.00% −125.00%.

If $S_{WR} \geq 0.294$ (CV_W% ≥30%) for any primary PK parameter(s), RSABE method was used for bioequivalence evaluation. In this case, the 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta S^2_{WR}$ was calculated based on Howe's Approximation I.[27]

Where Y_T and Y_R are the natural log transformed AUC or C_{max} mean values for test and reference formulation, respectively.

$\theta = \left(\frac{Ln(1.25)}{\sigma_{w2}}\right)^2$ is the BE limit and $\sigma_{w0} = 0.25$ is the regulatory constant set by US FDA and China NMPA.

For any given primary PK parameter(s), bioequivalence was concluded if the 95% upper confidence bound for $(Y_T - Y_R)^2 - \theta S^2_{WR}$ is ≤0 and the test/reference GMR falls within 80.00% −125.00%.

Results

Volunteers Characteristics

A total of 78 healthy Chinese volunteers were enrolled and all completed the study (Figure 1). In the fasting study cohort, 48 (45 males, 3 females) healthy Chinese volunteers were enrolled (Mean ± SD age, 27.0 ± 4.5 years [range, 18–39]; height, 167.2 ± 6.4 cm [range, 148.0 −178.5]; weight, 63.2 ± 7.6 kg [range, 50.2–79.0]; and BMI, 22.6 ± 2.1 kg/m^2 [range, 19.1–27.7]). In the fed study cohort, 30 (24 males, 6 females) healthy Chinese volunteers were enrolled (Mean ± SD age, 27.0 ± 4.9 years [range, 19–39]; height, 166.9 ± 7.3 cm [range, 149.0 −180.0]; weight, 63.5 ± 7.0 kg [range, 50.2–79.3]; and BMI, 22.8 ± 1.8 kg/m^2 [range, 19.5–26.1]).

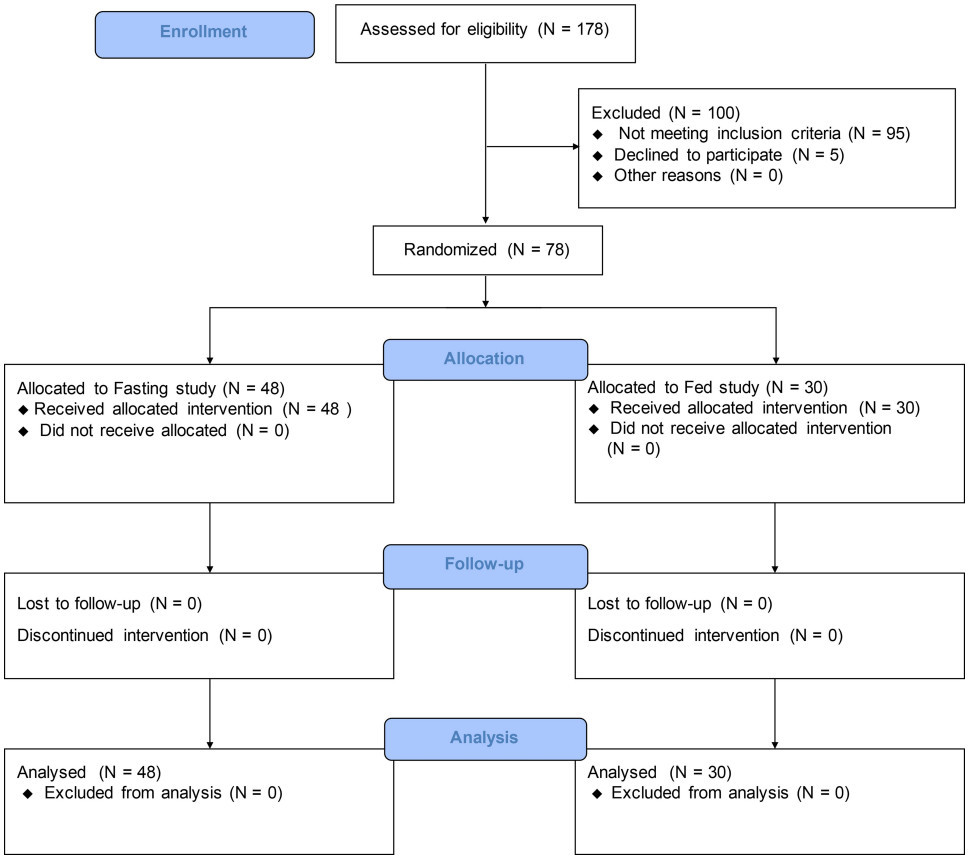

Figure 1 Study flow diagram according to CONSORT recommendations.

Safety

Under fasting conditions, 6 subjects (12.5%) who received test formulation and 7 subjects (14.6%) who received reference formulation were reported to experience drug-related treatment-emergent AEs (TEAEs). Under fed conditions, 4 (13.3%) who received test formulation and 2 subjects (6.7%) who received reference formulation were reported to experience TEAEs (Table 1). The most common TEAEs in test formulation was hypotension, whereas in reference formulation the most common TEAEs were diarrhea. All AEs were considered to be mild intensity by the investigators and were transient as the subjects recovered by the end of the study. No serious AEs were reported and none of the subjects were withdrawn from the study due to AEs.

Pharmacokinetics

The mean (± SD) plasma concentration-time (C-T) curves of valsartan following single-dose oral administration of four individual sequence (T1, T2, R1, R2) under fasting and fed conditions are shown in Figure 2. The primary PK parameters under fasting and fed conditions are summarized in Tables 2 and 3.

Bioequivalence

The bioequivalence evaluation between the test and reference formulations of valsartan 80 mg capsules in healthy volunteers under fasting and fed conditions are presented in Tables 4 and 5.

As shown in Table 4, under fasting conditions, the S_{WR} for C_{max} exceeded the regulatory cutoff of 0.294, and therefore, RSABE method was used for equivalence evaluation. The test/reference GMR for C_{max} was 99.52%, falls within 80.00% −125.00%, and the 95% upper confidence bound was −0.0837<0, which demonstrated that C_{max} comparison has met bioequivalence criteria for highly variable drugs. Since S_{WR} for AUC_{0-t} and $AUC_{0-\infty}$ were less than 0.294, ABE method was used to evaluate the bioequivalence for these PK parameters. The 90% CIs of GMR were 96.28%–108.21%, 96.28%–107.88%, all fell within the range of 80.00% −125.00%, also met the bioequivalence criteria for ABE. In summary, the test and reference formulations of

Table 1 All Drug-Related Treatment-Emergent AEs of Test and Reference Formulations of Valsartan 80-Mg Capsules After Oral Administration Under Fasting and Fed Conditions in Healthy Chinese Volunteers

TEAEs	No. (%)[b]of Subjects with TEAEs			
	Fasting Study (N = 48)		Fed Study (N = 30)	
	Test	Reference	Test	Reference
Hypotension	1 (2.1)	1 (2.1)	2 (6.7)	0 (0.0)
Diarrhea	1 (2.1)	3 (6.3)	1 (3.3)	2 (6.7)
Dizziness	1 (2.1)	1 (2.1)	1 (3.3)	0 (0.0)
Bellyache	0 (0.0)	0 (0.0)	1 (3.3)	2 (6.7)
Hematuria	2 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
Increase in ALT[a]	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)
Chest pain	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Increase in bilirubin	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Weak	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block (I)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Cough	0 (0.0)	1 (2.1)	0 (0.0)	0(0.0)
Total number of TEAEs	9 (18.8)	8 (16.7)	5 (16.7)	4 (13.3)
Total subjects of TEAEs	6 (12.5)	7 (14.6)	4 (13.3)	2 (6.7)

Notes: [a]alanine aminotransferase; [b]Number (%) of subjects reporting drug-related treatment-emergent adverse events.
Abbreviations: TEAE, treatment emergent adverse event; N, number.

valsartan 80 mg capsules were bioequivalent under fasting conditions.

Statistical analysis of pharmacokinetic parameters under fed conditions (Table 5) showed that the S_{WR} of the primary pharmacokinetic parameters (C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$) all exceeded the cutoff value 0.294, which means CV_W% >30%, the bioequivalence evaluation for all three PK parameters were performed using RSABE method.

The results showed that the GMR of the test and the reference formulations for C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ all fell within the range of 80.00% −125.00%, and the 95% upper confidence bound values were less than 0, which met the bioequivalence criteria for highly variable drugs and therefore, the test and reference formulation were concluded to be bioequivalent under fed conditions.

On ANOVA, using logarithmic-transformed data, no sequence or formulation effects were observed for any PK parameters.

Discussion

This study evaluated the bioequivalence of two formulations of valsartan (80 mg capsules) in two study cohorts

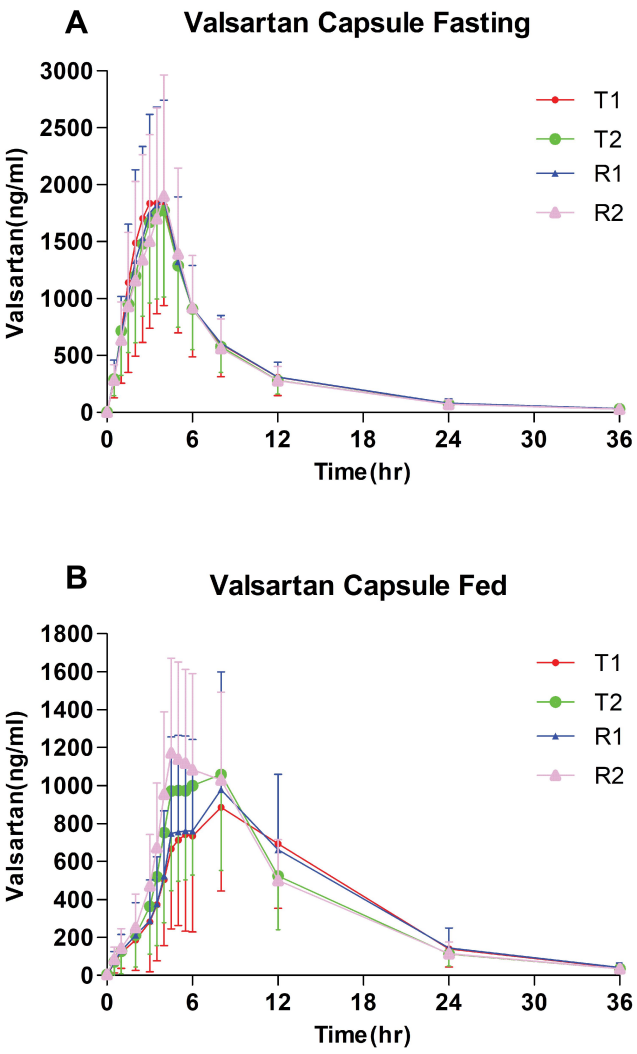

Figure 2 Mean (SD) plasma concentration-time curves of valsartan following single-dose oral administration of four individual sequence (T1, T2, R1, R2) under fasting (**A**, N = 48) and fed (**B**, N = 30) conditions in healthy Chinese volunteers.

under fasting and fed conditions, both cohorts were open label, randomized, single-dose, two sequence, four-period, full replicate crossover study in healthy Chinese volunteers. As Changzhou Siyao Pharmaceuticals Co., Ltd produced two kinds of valsartan, 4080 mg, 80 mg capsules were chosen to be evaluated in our study, which was in consistent with the guideline that recommended to consider highest dose for bioequivalence study. The results of this study provide support for the marketing of the new generic valsartan capsule (80 mg) in China.

A total of 78 healthy subjects were enrolled in this study under fasting and fed conditions and all completed the study. The drug administration and blood collection process were well followed. The subjects and numbers of AEs in the test and reference formulations were similar. In

Table 2 Pharmacokinetic Properties of Test and Reference Formulations of Valsartan 80-Mg Capsules After Single-Dose Administration in Healthy Chinese Volunteers Under Fasting Condition

Parameters	N[a]	Test	Reference
		48	48
C_{max} (ng/mL)	Mean ± SD CV (%) GeoMean	2058.89 ± 929.46 45.14% 1876.29	2123.84 ± 988.04 46.52% 1885.43
AUC_{0-t} (ng*h/mL)	Mean ± SD CV (%) GeoMean	13,515.67 ± 5630.81 41.66% 12,446.25	13,368.94 ± 5578.13 41.72% 12,193.43
$AUC_{0-\infty}$ (ng*h/mL)	Mean ± SD CV (%) GeoMean	13,835.35 ± 5753.65 41.59% 12,750.94	13,703.56 ± 5701.33 41.60% 12,511.29
T_{max} (h) [b]	Median (Min - Max)	3.25 1.00–4.02	3.50 1.00–6.00
λ_z (h^{-1})	Mean ± SD CV (%) GeoMean	0.11 ± 0.02 15.82% 0.11	0.11 ± 0.02 18.16% 0.10
$t_{1/2}$ (h)	Mean ± SD CV (%) GeoMean	6.57 ± 1.12 17.11% 6.48	6.86 ± 1.51 21.94% 6.72
$AUC_{0-t}/AUC_{0-\infty}$ (%)	Mean ± SD CV (%) GeoMean	97.62 ± 1.60 1.64% 97.61	97.47 ± 1.64 1.68% 97.46

Notes: [a]In this study, a total of 48 subjects were enrolled, each subject took the test formulation twice and the reference formulation twice in 4 cycles, so all statistical parameters were from 96 data. [b]Median (min-max).

Abbreviations: C_{max}, the maximal plasma concentration; AUC_{0-t}, the area under the plasma concentration–time curve; $AUC_{0-\infty}$, the area under the plasma concentration–time curve extrapolated to infinity; T_{max}, the time to peak plasma concentration; λ_z, elimination rate constant; $t_{1/2}$, elimination half-life.

the fed study cohort, 2 subjects developed local skin infections, which were considered to be caused by the implanted catheters and successfully treated with topical drugs by clinical investigator. All other subjects who experienced AEs were recovered without any treatment.

We compared the results of pharmacokinetic parameters from our study to those reported in drug product prescribing information and literatures. Under fasting conditions, the T_{max} and $t_{1/2}$ values are close to the range described in the reference drug instructions (T_{max}, 2–4 hours, $t_{1/2}$ 6 hours).[5] The peak plasma concentration (C_{max}) and total exposure (AUC_{0-t}, $AUC_{0-\infty}$) values in our study were also comparable to those reported in the literatures[10,11] after dose adjustment (Supplementary Table 2).

After taking high-calory and high-fat meal, the $t_{1/2}$ value is close to the reported range, whereas the T_{max} was significantly prolonged and peak concentration (C_{max}) was also significantly decreased by ~40%, but the total exposure (AUC_{0-t}, $AUC_{0-\infty}$) did not decrease significantly, which were equivalent to the results under fasting condition after dose adjustment (Supplementary Table 2). According to the drug product prescribing information, food intake with valsartan capsules reduces the exposure (as measured by AUC) of valsartan by about 48% and C_{max} by about 50%.[5] The results of our study partially support the food effects reported for this drug.

For bioequivalence evaluation under fasting conditions, RSABE method was used to evaluate C_{max}, while ABE method was used to evaluate AUC_{0-t} and $AUC_{0-\infty}$, for all three primary PK parameters, the test and reference valsartan capsules were determined to be bioequivalent.

This study clearly demonstrated, under fasting conditions, the reference product valsartan capsule is highly variable only in terms of C_{max} (>30%), but not in terms of AUC_{0-t} and $AUC_{0-\infty}$. Moreover, the full-replicate study

Table 3 Pharmacokinetic Properties of Test and Reference Formulations of Valsartan 80-Mg Capsules After Single-Dose Administration in Healthy Chinese Volunteers Under Fed Condition

Parameters		Test	Reference
	N[a]	30	30
C_{max} (ng/mL)	Mean ± SD CV (%) GeoMean	1235.75 ± 484.60 39.21% 1144.93	1289.40 ± 546.88 42.41% 1159.09
AUC_{0-t} (ng*h/mL)	Mean ± SD CV (%) GeoMean	12,967.47 ± 4515.78 34.82% 12,305.08	13,263.13 ± 5611.31 42.31% 11,908.32
$AUC_{0-\infty}$ (ng*h/mL)	Mean ± SD CV (%) GeoMean	13,300.63 ± 4657.74 35.02% 12,615.51	13,599.84 ± 5759.67 42.35% 12,238.90
T_{max} (h)[b]	Median (Min - Max)	8.00 (4.00–12.00)	5.75 (4.00–12.00)
λ_z (h^{-1})	Mean ± SD CV (%) GeoMean	0.12 ± 0.02 13.82% 0.12	0.12 ± 0.02 17.70% 0.12
$t_{1/2}$ (h)	Mean ± SD CV (%) GeoMean	5.95 ± 0.88 14.79% 5.89	5.94 ± 0.85 14.27% 5.88
$AUC_{0-t}/AUC_{0-\infty}$ (%)	Mean ± SD CV (%) GeoMean	97.54 ± 0.94 0.97% 97.54	97.32 ± 1.98 2.03% 97.30

Notes: [a]In this study, a total of 48 subjects were enrolled, each subject took the test formulation twice and the reference formulation twice in 4 cycles, so all statistical parameters were from 96 data. [b]Median (min-max).

Abbreviations: C_{max}, the maximal plasma concentration; AUC_{0-t}, the area under the plasma concentration–time curve; $AUC_{0-\infty}$, the area under the plasma concentration–time curve extrapolated to infinity; T_{max}, the time to peak plasma concentration; λ_z, elimination rate constant; $t_{1/2}$, elimination half-life.

Table 4 Bioequivalence Evaluation of Test and Reference Formulations of Valsartan 80-Mg Capsules in Healthy Volunteers Under Fasting Condition

Parameters	Fasting Condition		
	C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)
S_{WR}	0.3770	0.2423	0.2381
Evaluation method	RSABE	ABE	ABE
Upper 95% CI	−0.0837	NA	NA
Geometric mean ratio (T/R)	99.52%	102.07%	101.92%
90% CI	NA	96.28%–108.21%	96.28%–107.88%
Results	Bioequivalent	Bioequivalent	Bioequivalent

Abbreviations: C_{max}, the maximal plasma concentration; AUC_{0-t}, the area under the plasma concentration–time curve; $AUC_{0-\infty}$, the area under the plasma concentration–time curve extrapolated to infinity; S_{WR}, within-subject standard deviation; RSABE, reference-scaled average bioequivalence; ABE, average bioequivalence; CIs, confidence intervals.

Table 5 Bioequivalence Evaluation of Test and Reference Formulations of Valsartan 80-Mg Capsules in Healthy Volunteers Under Fed Condition

Parameters	Fed Condition		
	C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)
S_{WR}	0.4992	0.4382	0.4214
Evaluation method	RSABE	RSABE	RSABE
Upper 95% CI	−0.1357	−0.1018	−0.0943
Geometric mean ratio (T/R)	98.78%	103.33%	103.08%
90% CI	NA	NA	NA
Results	Bioequivalent	Bioequivalent	Bioequivalent

Abbreviations: C_{max}, the maximal plasma concentration; AUC_{0-t}, the area under the plasma concentration–time curve; $AUC_{0-\infty}$, the area under the plasma concentration–time curve extrapolated to infinity; S_{WR}, within-subject standard deviation; RSABE, reference-scaled average bioequivalence; ABE, average bioequivalence; CIs, confidence intervals.

design allowed us to obtain within-subject variability for the test and reference product separately, and the results showed the CV_w% for C_{max} for the test formulation was 30.5%, which was significantly less than that for the reference formulation with CV_w% of 39.0%. The CV_w% values for AUC_{0-t} and $AUC_{0-\infty}$ were similar between the test and reference formulations (Supplementary Table 3).

Under fed conditions, bioequivalence evaluation for the test and reference formulations of valsartan were all assessed using RSABE method, since the S_{WR} for all primary PK parameters (C_{max}, AUC_{0-t}, $AUC_{0-\infty}$) exceeded the cutoff value of 0.294 and all met the corresponding bioequivalence criteria for highly variable drugs in terms of 1) the 95% upper confidence bound and 2) GMR falls within 80–125%.

Once again, this study demonstrated, under fed conditions, the reference product valsartan capsule is highly variable in all primary PK parameters. Similar to the observation made under fasting conditions, the CV_w% value of C_{max} for the test formulation was 29.6%, significantly less than that for the reference formulation of 50.0%, and the CV_w% values of AUC_{0-t} and $AUC_{0-\infty}$ were 19.0%, 18.9% for the test formulation, significantly less than those of the reference formulation of 44.5%, 42.6%, respectively (Supplementary Table 3).

Conclusions

The results from this study suggest that the test formulation of valsartan 80 mg capsule was bioequivalent to the reference formulation under both fasting and fed conditions. It meets the requirements of bioequivalence according to NMPA Guidelines for the Study of Bioequivalence of Highly Variable Drugs and the Guiding Principles for the Investigation of Human Bioequivalence for Pharmaceuticals Based on Pharmacokinetic Parameters. Both formulations were generally well tolerated.

Data Sharing Statement

All of the individual participant data collected during the trial, after deidentification, can be shared. Study Protocol, Statistical Analysis Plan, Informed Consent Form, and Clinical Study Report can also be available. All shared and available data besides the information presented in the article can be obtained by contacting the corresponding author. To gain access, data requestors will need to sign a data access agreement. Data are available indefinitely.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

Xiaodong Wang is the employee from Changzhou Siyao Pharmaceutical Co., Ltd. Kanyin E Zhang reports that ViaClinical Ltd received service fees from Changzhou Siyao Pharmaceutical Co. to perform this study. The authors report no other conflicts of interest in this work.

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