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CLINICAL TRIAL REPORT

Pharmacokinetics and Bioequivalence of Two Fixed-Dose Combination Tablets of Valsartan/Amlodipine (80/5 Mg) in Healthy Chinese Subjects

Mengli Tian[1], Jinlong Huang[2], Yingrong Chen[1], Qiuyue Jin[1], Hong Jiang[2], Cunyuan Shi[2], Jue Mei[1], Min Xu[1], Xiang Yu[1], Shuixin Yang[1]

[1]Clinical Trial Center, Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, Huzhou, 313000, People's Republic of China; [2]Zhejiang Jianfeng Pharmaceutical Co Ltd., Jinhua, 321025, People's Republic of China

Correspondence: Shuixin Yang, Clinical Trial Center, Huzhou Central Hospital, Fifth School of Clinical Medicine of Zhejiang Chinese Medical University, 1558, North Third Ring Road, Huzhou, 313000, People's Republic of China, Tel +86-0572-2978254, Email ysx@hzhospital.com

Purpose: The study aimed to investigate the pharmacokinetics and bioequivalence of coformulations of valsartan and amlodipine in healthy Chinese subjects under both fasting and fed conditions.

Methods: The research was conducted under both fasting and fed studies and employed a single-center, randomized, open-label, single-dose, three-period design with partial-repeat and crossover elements. A total of 71 healthy Chinese adult participants were included under fasting (n = 36) and fed (n = 35) conditions. The subjects were orally administered valsartan/amlodipine tablets (80/5 mg) per cycle either as the test (T) or reference (R) formulation. The washout period was 14 days. Plasma concentrations of valsartan and amlodipine were determined using ultrahigh-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS), and the noncompartmental analysis method was used for estimating the pharmacokinetic parameters.

Results: Under fasting conditions, the within-subject standard deviations (S_{wr}) of maximum plasma concentration (C_{max}), area under the concentration–time curve from time 0 to the time of the last-measurable plasma concentration (AUC_{0-t}), and area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$) for valsartan were calculated to be ≥0.294 and evaluated by the reference-scaled average bioequivalence (RSABE) method. The point estimates of the geometric mean ratios (GMRs) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan were 1.0805, 1.0991, and 1.1015 respectively, and the critical bounds were all less than 0. The S_{wr} of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for amlodipine were all <0.294, and the 90% confidence intervals (CIs) of the GMRs fell within the bioequivalence range, as evaluated by the average bioequivalence (ABE) method. Under the fed condition, the S_{wr} of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were all <0.294 for both valsartan and amlodipine; the ABE method was therefore employed for the evaluation of bioequivalence, and the 90% CIs of the GMRs fell within the bioequivalence range. All the observed adverse events were mild and transient.

Conclusion: The two formulations of valsartan/amlodipine (80/5 mg) tablets were bioequivalent and safe.

Keywords: valsartan, amlodipine, bioequivalence, pharmacokinetics, safety

Introduction

The guidelines for the prevention and control of hypertension emphasize that early combination therapy with potent antihypertensive medications is crucial for achieving blood pressure (BP) targets and can significantly reduce the risk of cardiovascular events and mortality. The initiation of combination therapy at an early or intermediate stage of hypertension has been currently recommended.[1] Combination therapy can help patients achieve their BP goals in a shorter time, reduce the need for changes in medication, enhance treatment adherence, and optimize the cost-effectiveness and cost–benefit of hypertension management.[2–4] Valsartan is an angiotensin II receptor blocker while amlodipine is a dihydropyridine calcium channel blocker. The combination medicine valsartan/amlodipine is convenient to take, provides better control of BP than individual drugs, and is well tolerated.[5] In particular, the incidence of peripheral

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edema was significantly lower in patients receiving valsartan/amlodipine combination therapy than in those that received amlodipine monotherapy.[6]

Exforge® (valsartan/amlodipine) from Novartis is the first ever fixed-dose combination, was approved as a first-line treatment for hypertension by the European Medicines Agency and the United States Food and Drug Administration (FDA) in 2007. Further, it was approved in 2009 in China, offering a safe and effective fixed combination medication for the management of hypertension. The valsartan/amlodipine combination is an association of two well-known antihypertensive products with specific targets for cardiovascular protection, namely, calcium channel blockade and antagonism of the renin–angiotensin–aldosterone system.[7] Data available to date has shown that this combination is well tolerated and effective, even for severe hypertension.[3,7,8]

The current study aimed to investigate the bioequivalence and pharmacokinetics (PK) of two formulations of valsartan/amlodipine medication (80/5 mg) in healthy Chinese subjects under fasting and fed conditions and to provide evidence for obtaining marketing approval for the test formulation. The average bioequivalence (ABE) and reference-scaled average bioequivalence (RSABE) methods were employed herein for evaluating the bioequivalence of the drug formulations. The within-subject standard deviation of the reference formulation (S_{wr}) was calculated before the assessment of bioequivalence; standard ABE method was applied if $S_{wr} < 0.294$ for any primary PK parameter, including the maximum plasma concentration (C_{max}), area under the concentration–time curve from time 0 to the time of the last-measurable plasma concentration (AUC_{0-t}), and area under the concentration–time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$). The RSABE method was applied for the evaluation of bioequivalence if $S_{wr} \geq 0.294$ and the within-subject coefficient of variation $CV_{WR}\% \geq 30\%$ for any primary PK parameter. Our study was conducted primarily in accordance with the guidelines established in the "Draft Guidance on Amlodipine Besylate; Valsartan"[9] issued by the FDA in 2008 and the "Guiding Principles for the Investigation of Human Bioequivalence for Pharmaceuticals Based on Pharmacokinetic Parameters"[10] as well as the "Technical Guidelines for Bioequivalence Studies of Highly Variable Drugs"[11] issued by the National Medical Products Administration (NMPA) of China.

Materials and Methods

Study Products

Drug formulations: valsartan/amlodipine tablet, 80/5 mg (each tablet contains valsartan 80 mg and amlodipine 5 mg). Test formulation (T): batch number 2103003 (Jianfeng Pharmaceutical Co. Ltd, China). Reference formulation (R): Exforge®; batch number BUJ44 (manufactured by Novartis Farmaceutica S.A, Switzerland).

Compliance with Ethics Guidelines

The study was approved by the Ethics Committee at Huzhou Central Hospital on June 21, 2021 (Approval No. 2021–018-01), and this trial was registered on the Chinese Clinical Trial website (http://www.chinadrugtrials.org.cn/index.html; Registration number: CTR20211658, Date: July 16, 2021). The bioequivalence clinical trial was retrospectively registered with the Chinese Clinical Trial Registry, which is recognized by the World Health Organization (WHO; https://www.chictr.org.cn/; Registration number: ChiCTR2300075526, Date: September 7, 2023). The study was conducted in accordance with the Guidelines for Good Clinical Practice established by the International Conference on Harmonization as well as the ethical standards established in the Declaration of Helsinki. Written informed consent was obtained from each subject before their participation in this study.

Subjects

The study participants included healthy male or female subjects aged 18 years or older, with a body mass index (BMI) of 19–26 kg/m^2 and body weights of ≥50 and ≥45 kg for men and women, respectively. The subjects did not have any plans for pregnancy within the next 3 months and voluntarily agreed to use effective contraception. Additionally, the women were required to have a negative pregnancy test result at the screening visit. All participants fully understood the trial process and potential adverse reactions before the beginning of the trial and voluntarily signed an informed consent form. All subjects were healthy, as confirmed by a retrospective evaluation of clinical history, physical examination,

measurement of vital signs, clinical laboratory tests (spanning hematology, biochemistry, urinalysis, and serology), and 12-lead electrocardiography, all of which were conducted within a duration of 14 days preceding this study.

Individuals with a documented history of postural hypotension, characterized by a systolic blood pressure (SBP) of <100 mmHg, a diastolic blood pressure (DBP) of <60 mmHg, or with a history of postural hypotension were excluded from the study. Other main exclusion criteria included the following: subjects with a history of a) allergy to valsartan/amlodipine or any component of the drug, b) allergy to two or more drugs or food items, c) and/or any evidence of cardiovascular, hepatobiliary, renal, endocrine, hematological, or gastrointestinal disorders, especially those that significantly affect the absorption, distribution, metabolism, and excretion of the drug, d) medical conditions related to the mode of action of the drug under test, e) surgery within a 3-month duration prior to the screening, f) use of any prescription medication or herbal remedies within a 2-week duration prior to the study, g) smoking, alcoholism, or drug dependence before the screening, h) donation of whole blood or blood components or significant blood loss (≥400 mL) within a 3-month duration prior to the screening, and i) any other conditions that would render them unsuitable for participation in this study, as evaluated by the investigator.

Estimation of Sample Size

Amlodipine exhibits low intraindividual variation while valsartan is a highly-variable drug; the intraindividual variation in valsartan was therefore used as a reference in the current study. The drug description and results from previous research suggest a CV_{WR} of 30%–40% for both C_{max} and AUC in the case of valsartan.[12–14] The current study assumed an intraindividual variability of 40% for valsartan and therefore employed the RSABE assessment method. The desired test power was set at 80% with a significance level of 0.05 and the expected geometric mean ratio (GMR) was 1.1 for the trials under fasting and fed conditions. The sample size was calculated to be 27 subjects. Considering the existence of subject shedding rate, the sample sizes for the trials under both fasting and fed conditions were set at 36 participants each.

Study Procedures

A randomized, open-label, three-period, three-sequence, single oral dose, partial-repeat, and crossover study was conducted herein at the Clinical Trial Center of Huzhou Central Hospital. A total of 71 healthy Chinese adult participants were enrolled for the trials under fasting (n = 36) and fed (n = 35) conditions. The washout period was 14 days; all subjects were hospitalized in the Clinical Trial Center the day before dosing and placed on a uniform diet for the duration of hospitalization.

All subjects were asked to fast overnight for at least 10 h before drug administration. For the trial under fasting conditions, a snack (toasted bread) was provided at 9 pm the day before the administration of the drug. Subjects in the trial under fed conditions consumed an additional high-fat, high-calorie standard meal 30 min before drug administration. Each subject received a single oral dose (80/5 mg) of T or R formulations with 240 mL of water. The hands and mouth of the subjects were inspected, and they were escorted to the bathroom within 2 h of drug administration to prevent drug concealment or vomiting. After 2 h of drug administration, the subjects were provided 200 mL of lukewarm water to replenish the blood volume. The high-fat, high-calorie test meal provided approximately 800–1000 calories, including ~150 calories from protein, 250 calories from carbohydrate, and 500–600 calories from fat. The subjects were reminded by the researchers to completely consume the high-fat meal to reduce any bias. Standardized lunch and dinner was provided at 4 and 10 h after drug administration, respectively. Subjects were prohibited from consuming caffeine-containing beverages, food rich in methylxanthine, fruits that affect drug metabolism (including grapefruit, dragon fruit, or mango), and alcohol from a period 48 h prior to dosing until the completion of blood sampling. To ensure accurate results, the remaining quantity of the drug, empty packaging, and medication delivery apparatus were collected after the administration of the dose.

Safety Assessments

Safety and tolerability variables were assessed during the study, including adverse events (AEs), vital signs (SBP, DBP, pulse rate, and ear temperature), 12-lead electrocardiograms (ECGs), physical examinations, inquiries, and laboratory assessments spanning hematology, clinical chemistry, and urinalysis. Vital signs were assessed at screening, predose, and

postdose (2.0 ± 0.5, 6.0 ± 0.5, 12.0 ± 0.5, 24.0 ± 0.5, 48.0 ± 0.5, and 72.0 ± 1.0 h) periods. The characteristics, clinical features, severity, time of occurrence, end time, management measures, and regression of any AEs that occurred during the study were recorded, and any correlation with the test drug was determined. The subjects were closely supervised by the study physician, and any abnormalities were promptly treated. All participants with AEs, whether considered drug-related or not, were regularly monitored until recovery, stability, or until follow-up was no longer possible. All AEs were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Collection and Pre-Processing of Blood Samples

Blood samples were collected for PK analysis under both fasting and fed conditions. The sampling schedule comprised 23 time points, with samples collected at 0 h (just prior to drug administration) and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 8.0, 9.0, 10.0, 12.0, 15.0, 24.0, 48.0, and 72.0 h after the administration of the drug. Approximately 4 mL of venous blood was drawn at each time point. To maintain sample integrity, all samples were centrifuged (3500 rpm, 4°C, 10 min) within one hour of collection and promptly stored at a temperature of −60°C or below for subsequent analysis.

Bioanalytical Methods

Procedure for Chromatography

The chromatographic separation was carried out using the Shimadzu UPLC-30A liquid chromatograph system. The chromatographic column EC C18 (50 mm × 4.6 mm, 2.7 μm), mobile phase A comprising 0.4% aqueous solution of formic acid (pH 3.2), and mobile phase B consisting of methanol were employed. The following gradient elution was employed: 0–2.0 min, 65% B→95% B; 2.0–3.0 min, 95% B; 3.0–3.1 min, 95% B→65% B; and 3.1–4.0 min, 65% B. The column was run at a flow rate of 0.8 $mL \cdot min^{-1}$, auto injector and column temperatures corresponding to room temperature (20°C–25°C), and an injection volume of 10 μL.

Mass Spectrometry Analysis

The analytes were detected using a Triple Quad 5500 tandem triple quadrupole mass spectrometer (Applied Biosystems/Sciex) with an electrospray ionization source, a spray voltage of 5500 V, temperature of 500°C, collision gas pressure of 9 kPa, atomizing gas of 50 kPa, turbine gas of 50 kPa, curtain gas pressure of 35 kPa, residence time of 150 msec, positive ion detection, and multireaction monitoring scanning mode. The generated ions at m/z 436.3→m/z 235.1 (valsartan), m/z 445.3→m/z 235.2 (valsartan-d9), m/z 409.2→m/z 238.2 (amlodipine), and m/z 413.2→m/z 238.1 (amlodipine-d4) were used for quantitative analysis.

Processing and Analysis of Plasma Samples

The plasma samples were first placed at room temperature and illuminated under yellow light. Once the samples were fully thawed, 100 μL of each sample was pipetted into the wells of a 96-well plate. This was followed by the addition of 10 μL of an internal standard mixture (valsartan-d9: 200 ng/mL, amlodipine-d4: 5.0 ng/mL) followed by 10 μL of formic acid. The contents were thoroughly mixed, followed by the addition of 480 μL of acetonitrile, vortex mixing for 10 min, and centrifugation at 4000 rpm for 5 min at 4°C. The supernatant (300 μL) was transferred to another plate and evaporated to dryness under nitrogen at 40°C. This was followed by the addition of 150 μL of a 50% aqueous solution of acetonitrile, vortex mixing for 5 min, and thorough mixing of the contents to perform ultrahigh-performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS) analysis.

The assay was found to be linear for valsartan and amlodipine over the concentration ranges of 25–5000 and 0.05–10 ng/mL, respectively. The lower limits of quantitation for valsartan and amlodipine were 25 and 0.05 ng/mL, respectively. The intrabatch and interbatch precision of quality control concentrations were less than 3.98% and 5.53% for valsartan, and 3.18% and 6.14% for amlodipine, respectively. An analysis of the matrix effect revealed that the CV of the matrix effect factors normalized with respect to those of the internal standards for valsartan and amlodipine were all below 15%, indicating that the determination of valsartan, amlodipine, and the internal standard compound in human plasma are not affected by the biological matrix. A total of 175 each out of 2390 and 2323 samples from the studies under fasting (7.3%)

and fed (7.5%) conditions, respectively, were chosen for an incurred sample reanalysis. The results confirmed method reproducibility as the percentage changes in the concentration from the original results ranged from −12% to 16%, which is within the acceptance criterion of ±20%.

Statistical Analyses

The PK parameters were calculated using Phoenix WinNonlin Software version 8.2; the PK parameters were estimated by a noncompartmental method, and plasma concentration–time curves were constructed. The intraindividual CVs were computed for the primary evaluation indicators C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$. The secondary evaluation indicators included time to maximum plasma concentration (T_{max}), terminal half-life ($T_{1/2}$), and $AUC\_\%_{Extrap}$. Furthermore, in accordance with the NMPA regulatory guidelines, logarithm-transformed PK parameters were analyzed using multivariate analysis of variance (ANOVA) to assess the effects of sequence, formulation, and period. Statistical analysis was conducted using the SAS statistical analysis software version 9.4. The bioequivalence was evaluated in accordance with both the ABE and RSABE methods.

Results

Demographic Characteristics

A total of 36 and 35 participants of the trials under fasting and fed conditions, respectively, were randomly assigned to the TRR, RTR, and RRT groups (Figure 1). Twenty seven (75.0%) of the participants of the trial under fasting conditions were males while nine (25.0%) were females; the participants had a mean age of 32.06 ± 8.51 years, mean height of 166.38 ± 8.58 cm, mean weight of 61.72 ± 7.04 kg, and mean BMI of 22.30 ± 1.94 $kg{\cdot}m^{-2}$. Thirty of the subjects (83.3%) were Han Chinese while six (16.7%) belonged to other nationalities. Thirty (85.7%) of the participants of the trial under fed conditions were males and five (14.3%) were females, with a mean age of 29.86 ± 6.51 years, a mean height of 167.39 ± 5.80 cm, and mean BMI of 23.10 ± 2.04 $kg{\cdot}m^{-2}$. Thirty-two subjects (91.4%) were Han Chinese while three (8.6%) belonged to other nationalities. All qualified subjects met the inclusion criteria and did not meet the exclusion criteria.

Dataset Segmentation

Figure 1 (A: trial under fasting conditions; B: trial under fed conditions) illustrates the cluster characteristics, trial completion, and dropout of subjects. The participant K023 (RRT sequence) voluntarily withdrew from the study under fasting conditions before the commencement of the first cycle without taking any drugs while the participant K002 (RRT sequence) withdrew from the same study after the collection of the 24-h blood samples during the second cycle due to personal reasons, having taken two doses of the R formulation. A total of 34 subjects completed the trial under fasting conditions. A total of 36 subjects were included in the full analysis set (FAS) while 35 subjects (excluding the unmedicated participant K023) were included in the safety (SS), PK concentration (PKCS), PK parameter analysis (PKPS), and bioequivalence (BES) sets.

In the trial under fed conditions, participants C005 (TRR sequence) and C014 (RTR sequence) completed only the first cycle, withdrawing due to COVID-19 vaccination during the washout period of the first cycle for participant C005 and withdrawal due to personal reasons for C014, respectively. The 33 remaining subjects successfully finished all three cycles of the study. Thirty-five subjects with valsartan components were included in the FAS, SS, PKCS, PKPS, and BES. The amlodipine components of two subjects C010 and C031 were excluded from the BES because their three-cycle predose blood concentrations were greater than 5% of the C_{max} of the corresponding cycle. All 35 subjects were included in the other analysis sets.

PK and Bioequivalence Evaluations

Table 1 summarizes the detailed PK metrics of two oral formulations of valsartan/amlodipine in the trials under fasting and fed conditions. Figure 2 shows the mean ± standard deviation values in the plasma drug concentration–time curves of valsartan and amlodipine in the studies under fasting and fed conditions. The figure reveals similar disposition process of the test and

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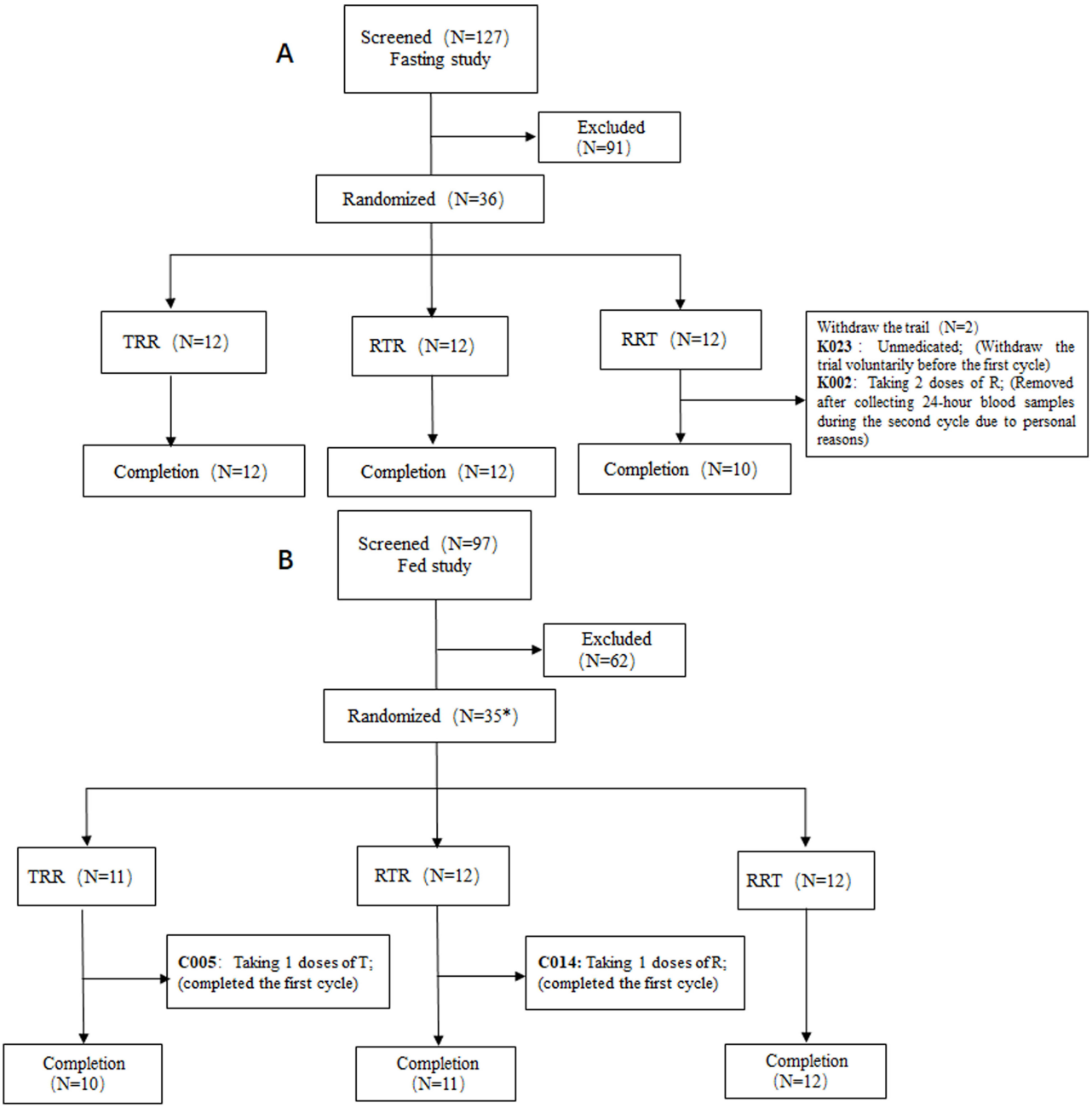

Figure 1 The cluster situation, completion, and dropout of subjects in this study (**A**) the fasting study; (**B**) the fed study.

reference formulations in healthy volunteers. Bioequivalence evaluations of two oral formulations of valsartan/amlodipine using the RSABE and ABE methods are listed in Table 2 and Table 3, respectively. In the trial under fasting conditions, the S_{wr} of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan (Table 2) were found to be ≥0.294, with $CV_{WR} \geq 30\%$; the RSABE method was therefore employed, and the point estimates of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were all within the approximate range of 0.80–1.25, while the critical bounds were all less than 0. The CV_{WR} of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for amlodipine (Table 3) under both fasting and fed conditions, and for valsartan (Table 3) in the study under fed conditions, were all found to be <30%. Thus, the ABE method was employed, and the GMRs of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were found to fall within the range 80%–125%. The data indicate that both the formulations are bioequivalent, regardless of whether they were administered under fasting or fed conditions. The results of ANOVA revealed the absence of significant effects of variations in the administration sequence, formulation factors, and administration period on the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan

Table 1 Pharmacokinetic Metrics of the Test and Reference Formulations of Valsartan/Amlodipine

Parameters (unit)	Fasting Study		Fed Study	
	N(T)=34	N(R)=70	N(T)=34	N(R)=67
Valsartan				
T_{max} (h)	3.00(1.50, 7.00)	3.00(1.50, 6.50)	4.00(1.50, 12.00)	4.00(1.50, 7.00)
C_{max} (ng/mL)	2720±1420	2510±1170	1940±669	1760±587
AUC_{0-t} (h*ng/mL)	16,280±7576	14,986±6805	12,634±4278	12,411±3996
$AUC_{0-\infty}$ (h*ng/mL)	16,873±7758	15,434±6919	13,471±4136	12,970±4184
$T_{1/2}$ (h)	6.88±10.12	4.99±1.16	5.34±2.01	5.56±2.45
$AUC\_\%_{Extrap}$ (%)	3.78±3.00	3.58±3.27	3.77±1.41	4.23±2.37
Amlodipine				
T_{max} (h)	5.00(4.50, 7.00)	5.50(4.50, 10.00)	5.00(2.50, 24.00)	5.00(2.00, 12.00)
C_{max} (ng/mL)	3.53±0.80	3.45±0.86	3.99±2.25	3.95±1.74
AUC_{0-t} (h*ng/mL)	107.2±24.2	105.0±27.6	136.5±108.8	136.0±94.3
$AUC_{0-\infty}$ (h*ng/mL)	147.3±35.1	145.2±40.7	223.0±234.1	219.2±210.2
$T_{1/2}$ (h)	38.24±5.94	38.20±8.98	46.20±11.15	47.06±11.02
$AUC\_\%_{Extrap}$ (%)	26.87±5.02	27.01±6.95	33.03±7.57	33.65±7.52

Notes: Data are presented as the arithmetic mean ± standard deviation, except for T_{max}, which is represented as median (minimum-maximum).

Abbreviations: AUC, area under the plasma concentration–time curve; AUC_{0-t}, AUC from time zero to last quantifiable concentration point; $AUC_{0-\infty}$, AUC from time zero to infinity; C_{max}, the peak concentration; T_{max}, time to C_{max}; $T_{½}$, the elimination half-life; λ_z, the elimination rate constant.

and amlodipine in the trial under fasting conditions. Similarly, significant effects of variations in the administration sequence and formulation factors on the C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan were not observed in the trial under fed conditions. For amlodipine, there was absence of any significant effect of variation in the administration sequence on these parameters (Supplemental Table S1).

Safety Analysis

The subject K023 was excluded from the safety set owing to withdrawal from the study under fasting conditions before the commencement of the first cycle (without taking any drugs), leaving 35 subjects who were subsequently enrolled. A total of 21 AEs were reported in 16 subjects, resulting in an AE incidence of 45.7% (16/35); of these, seven subjects (7/35 or 20.0%) experienced a decrease in BP. All AEs were assessed as grade 1 as per the CTCAE standard, except for one case of skin abrasion, which was a grade 2 AE. Additionally, all the AEs were resolved. A total of 23 AEs occurred in 14 of the 35 subjects in the trial under fed conditions, resulting in an AE incidence rate of 40.0% (14/35); of these, hypotension occurred in four subjects (4/35, 11.4%). All the AEs were assessed as grade 1 and were resolved. No serious AE was reported during either of the studies under fasting or fed conditions. A detailed breakdown of the AEs is provided in Table 4.

Discussion

A randomized, open-label, three-cycle, three-sequence, partial-repeat, and crossover study was performed to evaluate the bioequivalence of two fixed-dose combination tablets of valsartan/amlodipine. Two NMPA-specified methods ABE and RSABE were employed in this study for the evaluation of bioequivalence. The results showed that the 90% confidence intervals (CIs) of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ fell within the acceptable bioequivalence range for both the studies under fasting and fed conditions, indicating that the two formulations are bioequivalent.

The PK and bioequivalence of valsartan and amlodipine formulations such as valsartan capsules[12] and valsartan/amlodipine tablets[13–18] have been reported previously. Previous PK studies of the fixed-dose amlodipine/valsartan (10/160 mg) formulation in healthy Korean[14,17,18] and American[16] subjects involved two-cycles drug administration, and the three studies on Korean subjects were conducted only in the fasting group. By contrast, the current study was conducted

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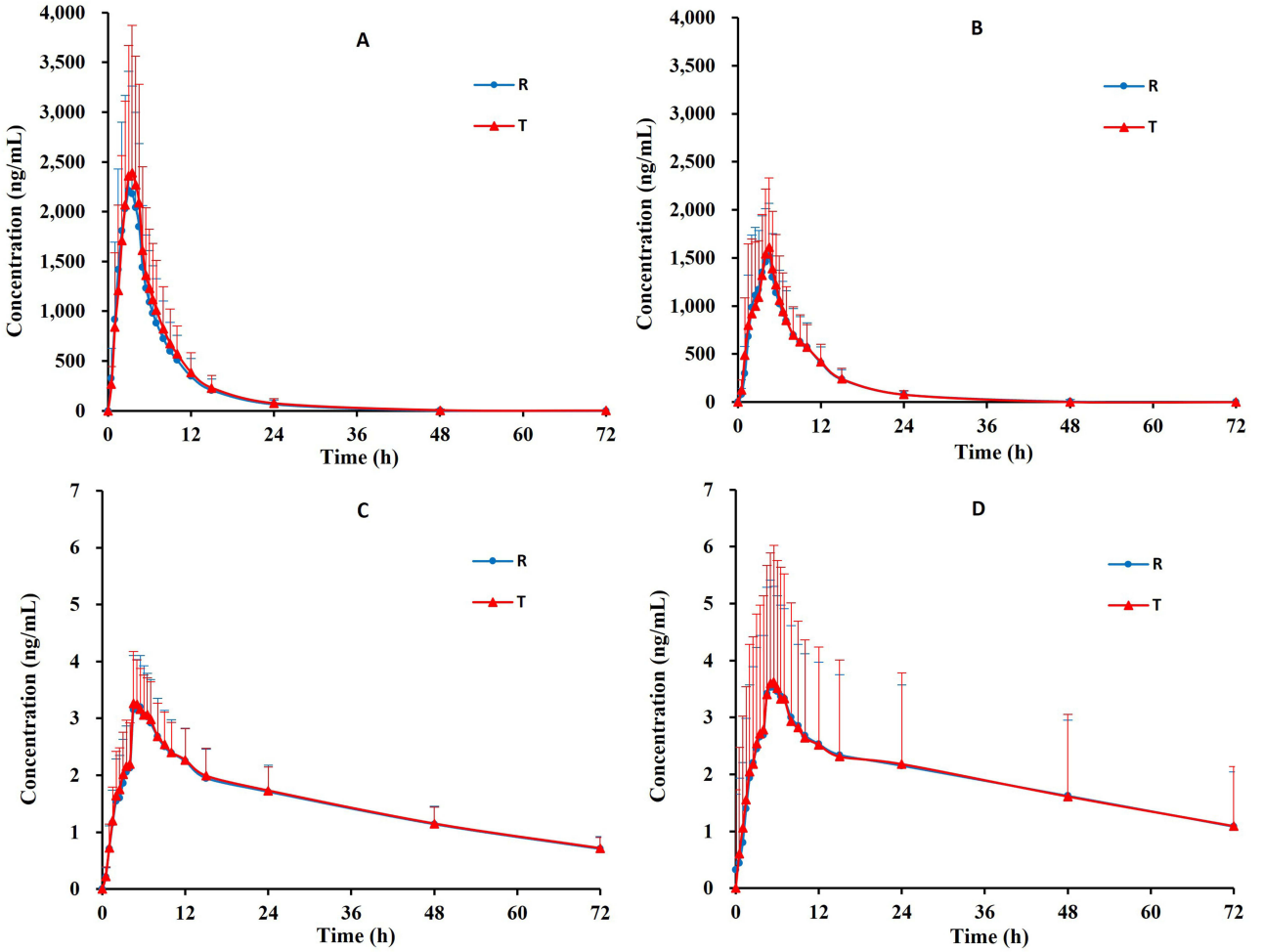

Figure 2 Average plasma concentration-time curve after a single dose of valsartan/amlodipine tablets in the fasting and fed studies. Fasting: valsartan(**A**) and amlodipine (**C**); Fed: valsartan (**B**) and amlodipine (**D**).

under both fasting and fed conditions. Valsartan has been confirmed to be a highly-variable drug, while amlodipine has low variability and longer half-life.[7,12,19] Taking these characteristics into account, a three-period partial replicate design was employed by administering the R formulation twice in each sequence to yield the TRR, RTR, and RRT sequences. According to the "Draft Guidance on Amlodipine Besylate; Valsartan" issued by the FDA[9] and the "Guiding Principles for the Investigation of Human Bioequivalence for Pharmaceuticals Based on Pharmacokinetic Parameters"[10] issued by the NMPA, a 72-h time point has been recommended for truncating the AUC. An AUC_{0-t} coverage of less than 80% of

Table 2 The RSABE Results of Valsartan in the Fasting Study

Study	Component	PK Parameters (unit)	RSABE						CV_{WR} (%)	S_{WR}
			T		R		Pointest	Critbound		
			N	GM	N	GM				
Fasting	Valsartan	C_{max} (ng/mL)	34	2365	68	2170	1.0805	−0.0878	49.04	0.464
		AUC_{0-t} (ng*h/mL)	34	14,455	68	13,047	1.0991	−0.0499	40.53	0.390
		$AUC_{0-\infty}$ (ng*h/mL)	34	15,024	68	13,539	1.1015	−0.0430	38.48	0.372

Abbreviations: RSABE, reference-scaled average bioequivalence; T, test formulation; R, reference formulation; CV_{WR}, within-subject coefficient of variation; S_{WR}, within-subject standard deviation; pointest, point estimate; critbound, critical bound.

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Table 3 The ABE Results of Amlodipine in the Fasting and Fed Study, and Valsartan in the Fed Study

Study	Component	PK Parameters (unit)	ABE						CV_{WR} (%)	S_{WR}
			T		R		GMR (%)	90% CI		
			N	GM	N	GM				
Fasting	Amlodipine	C_{max} (ng/mL)	34	3.45	70	3.33	103.76	98.38~109.43	19.40	0.192
		AUC_{0-t} (ng*h/mL)	34	103.7	70	101.2	102.51	97.52~107.77	16.39	0.163
		$AUC_{0-\infty}$ (ng*h/mL)	34	142.1	70	139.2	102.13	96.78~107.77	14.63	0.146
Fed	Valsartan	C_{max} (ng/mL)	34	1742	67	1602	108.74	99.25~119.14	23.79	0.235
		AUC_{0-t} (ng*h/mL)	34	11,613	67	11,368	102.16	96.68~107.95	14.90	0.148
		$AUC_{0-\infty}$ (ng*h/mL)	34	12,673	67	12,335	102.74	97.39~108.38	14.13	0.141
Fed	Amlodipine	C_{max} (ng/mL)	32	3.40	63	3.47	97.90	94.28~101.67	12.66	0.126
		AUC_{0-t} (ng*h/mL)	32	107.1	63	111.9	95.68	93.08~98.35	8.19	0.082
		$AUC_{0-\infty}$ (ng*h/mL)	32	157.6	63	166.4	94.71	90.91~98.67	10.16	0.101

Abbreviations: ABE, average bioequivalence; T, test formulation; R, reference formulation; GMR, geometric mean ratio; CI, confidence interval; CV_{WR}, within-subject coefficient of variation; S_{WR}, within-subject standard deviation.

Table 4 Adverse Events of Valsartan/Amlodipine Tablets Under Fasted or Fed Studies in Healthy Chinese Subjects

System Category	Adverse Event	Fasting (N=35)		Fed (N=35)	
		Case	n(%)	Case	n(%)
Various inspections	Blood pressure decreased	8	7(20.0)	6	4(11.4)
	Leukocyturia	2	2(5.7)	0	0(0.0)
	Urine erythrocyte increased	2	2(5.7)	0	0(0.0)
	Urine protein increased	1	1(2.9)	0	0(0.0)
	TG elevated	2	2(5.7)	6	6(17.1)
	Serum potassium decreased	0	0(0.0)	1	1(2.9)
	Hyperuricemia	1	1(2.9)	3	3(8.6)
	γ-GGT elevated	0	0(0.0)	1	1(2.9)
	ALT elevated	0	0(0.0)	1	1(2.9)
	First-degree atrioventricular block	1	1(2.9)	0	0(0.0)
	Ventricular premature repolarization	0	0(0.0)	1	1(2.9)
Infectious and invasive diseases	Urinary bacteria positive	2	2(5.7)	0	0(0.0)
Various injuries	Skin abrasion	1	1(2.9)	0	0(0.0)
	Foot skin trauma	1	1(2.9)	0	0(0.0)
Ear and vestibular diseases	Earache	0	0(0.0)	1	1(2.9)
Various neurological disorders	Headache	0	0(0.0)	1	1(2.9)
Respiratory system diseases	Oral and pharyngeal pain	0	0(0.0)	1	1(2.9)
Systemic diseases	Fever	0	0(0.0)	1	1(2.9)
Total		21	16 (45.7)	23	14 (40.0)

Abbreviations: TG, triglyceride; γ-GGT, γ-glutamyl transferase; ALT, alanine aminotransferase.

$AUC_{0-\infty}$ is allowed for drugs with long elimination half-life using $AUC_{0-72\ h}$ instead of AUC_{0-t}. In our research, $AUC_{\_\%Extrap}$ of amlodipine in both studies (under fasting and fed conditions) was above 20%, which may be due to the truncation of AUC at 72 h.

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In our study, the median T_{max} for valsartan was 3 h in the trial under fasting conditions and 4 h under fed conditions, with a median $T_{1/2}$ of approximately 5–7 h under both conditions; for amlodipine, the median T_{max} was approximately 5 h irrespective of the diet condition, while the median $T_{1/2}$ was approximately 38 and 47 h in the studies under fasting and fed conditions, respectively. These data are in good agreement with previously-published PK data in healthy Chinese and Korean subjects.[14,17,18] The median T_{max} values for valsartan are consistent with those reported previously for healthy subjects in America[16] (approximately 2.5 h under fasting and 4 h under fed conditions); however, the median $T_{1/2}$ values were longer for the American subjects (approximately 10 h). The median T_{max} values (approximately 8 h) for amlodipine in the American subjects were longer while the median $T_{1/2}$ values (approximately 46 h) were almost identical compared to the corresponding values obtained in the current study. This observation suggests a deferred absorption of amlodipine and slower elimination of valsartan in healthy American subjects compared to the Chinese subjects. We surmise that this is attributable to inter-racial differences, given that China and Korea are Asian countries while the United States is in North America; however, further data need to be acquired to confirm this supposition. Furthermore, the PK parameters C_{max} and AUC in the current study were found to be comparable with those of previously-published PK data from healthy Chinese adults.[13,15] However, the C_{max} and AUC values could not be directly compared with those reported in studies on Korean and American subjects due to variations in the dosage, given that 160/10 mg dosage was used in those studies.[14,16–18]

Amlodipine exhibited low variability and longer half-life in the current study, which is in alignment with the results of previous studies.[13,15] The CV_{WR} of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan were >30% (49.04%, 40.53%, and 38.43%, respectively) and the S_{wr} values were >0.294 in the study under fasting conditions; however, in the study under fed conditions, the CV_{WR} of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for valsartan was <30% (19.40%, 16.39%, and 14.63%, respectively). The intraindividual variability of valsartan was reduced under the influence of food. Further, the intraindividual variability of valsartan was compared with those of previous reports[12,15] and found to be consistent in that the intraindividual variability under the fed condition was lower than that under the fasting condition.

In our study, the PK parameters C_{max} and AUC_{0-t} for amlodipine were nearly identical under the fasting and fed conditions, which is largely consistent with the results of a bioequivalence study conducted in healthy Chinese subjects.[15] Furthermore, a preliminary evaluation of the PK data for valsartan under the fasting and fed conditions revealed that the main PK parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were decreased under the fed condition compared to the corresponding values under the fasting condition. Following the intake of a high-calorie and high-fat meal, the median C_{max} was decreased by approximately 30%, while the total exposure (AUC) was slightly decreased (by approximately 20%). Additionally, the median T_{max} for valsartan was delayed by approximately 1 h in the study under fed conditions compared to the fasting condition. These results are consistent with trends observed in previous bioequivalence studies, indicating that the intake of meals decreased the rate and extent of absorption of valsartan but failed to exert any impact on the systemic exposure to amlodipine.[15,20] This is attributable to the fact that valsartan is highly lipid-soluble but practically insoluble in water; a high-fat meal delayed and affected the absorption of valsartan as its intake could cause physiological changes,[21] including changes in bile production, stomach acidity, and gastrointestinal motility. Moreover, food increases the pH of gastric juice, thus increasing the degree of dissociation of the weakly-acidic drug valsartan, which is not conducive to its absorption in the stomach. Additionally, the intake of food slows down gastric emptying, thereby increasing the retention time of valsartan in the stomach and reducing its absorption in the small intestine.

Previous studies in healthy American subjects[16] showed that the bioavailability of valsartan was similar under fed and fasting conditions and that the effect of food was minimal or none when fixed-dose combination tablets of valsartan/amlodipine (160/10 mg) were administered with food. Various factors may contribute to this difference, including ethnicity, genetic variations in metabolic enzymes, and the crystalline forms of valsartan employed. Valsartan has been found to be a polycrystalline drug, with amorphous, I–IX, and A-F crystalline forms; the various crystalline forms differ in their solubility, which affects the degree of drug absorption and bioavailability.[22] A comparison of the rates of dissolution of different formulations of valsartan/amlodipine tablets in a variety of dissolution media would be an interesting avenue of exploration in the future.

The study design excluded subjects with SBP < 100 mmHg or DBP < 60 mmHg during the screening period or with a history of postural hypotension. Additionally, a series of precautions were taken to mitigate risk, including the

provision of a snack (toasted bread) at 9 pm the day before drug administration in the study under fasting conditions and the uniform administration of 200 mL of lukewarm boiled water 2 h after drug intake for replenishing the blood volume. Compared to the perious studies, relatively fewer subjects (20% and 11.4% in the studies under fasting and fed conditions, respectively) experienced the AEs of decreased BP during our study, and none of these subjects exhibited obvious clinical symptoms related to hypotension. A previous bioequivalence study with a fixed-dose combination tablet of valsartan/amlodipine (160/10 mg) in healthy Korean subjects excluded those with SBP ≤ 100 mmHg or DBP ≤ 65 mmHg during the screening period,[18] and the current study was conducted with the same purpose. Further, the AEs such as leukocyturia, increased protein in urine, and first-degree atrioventricular block on ECG were observed for the first time in the current study and have not been mentioned in the drug instructions or any previous studies.[13–18] All the AEs were mild, and recovery was noticed during the follow-up. Study drug-related severe AEs were not reported.

The limitation of the current study stems from the fact that it was conducted in young and healthy subjects whose selection was based on narrow inclusion and exclusion criteria; the PK parameters obtained herein may therefore not translate accurately to the entire patient population. In addition, previous research indicates that significant PK interactions between valsartan and amlodipine are improbable due to their distinct metabolic pathways. Valsartan is predominantly metabolized by the CYP2C9 enzyme in the liver, and amlodipine, by CYP3A4.[23] In terms of pharmacodynamics, valsartan and amlodipine lower BP by inhibiting the action of angiotensin II and dilating blood vessels, respectively, thus complementing each other. The combination of these drugs can synergistically lower BP in a more effective manner.[13,24] Another limitation of the current study is that we primarily investigated the PK properties of fixed-dose combination tablets of valsartan/amlodipine, but did not conduct separate studies on the oral administration of the component drugs valsartan and amlodipine. Consequently, data regarding the potential for drug interactions could not be obtained.

Conclusion

The results obtained in the current study suggest that the test formulation of fixed-dose combination tablets of valsartan/amlodipine (80/5 mg) was bioequivalent to the reference formulation under both fasting and fed conditions. The pharmacokinetics of the generic formulation is similar to the test formulation in healthy Chinese subjects. Both the formulations were generally well tolerated. The results of this study provide support for the marketing of the new generic valsartan/amlodipine tablet in China.

Data Sharing Statement

The data set used during the current study is available from the corresponding author upon reasonable request.

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Disclosure

The authors declare no conflicts of interest in this work.

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