Original Article

Assessment of Bioequivalence and Safety of a Generic Sofosbuvir Product in Healthy Chinese Volunteers under Fasting and Fed Conditions

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Abstract

Background and objective: To evaluate the bioequivalence and safety of a generic (or test) sofosbuvir 400-mg tablet *versus* a brand-named (or reference) sofosbuvir (Sovaldi®) 400-mg tablet in healthy Chinese volunteers under the fasting and fed conditions.

Methods: In this single-dose, randomized, open-label, two-sequence, four-period, crossover study, 52 healthy adult Chinese volunteers were enrolled for the fasting (n = 26) and fed (n = 26) conditions. Under each condition, subjects were randomized to receive initial treatment according to either the test-reference-test-reference or the reference-test-reference-test sequence, and then the treatment was switched to the other sequence after a 7-day washout period. Plasma concentrations of sofosbuvir were measured by high-performance liquid chromatography-tandem mass spectrometry. Non-compartmental pharmacokinetic (PK) analysis was performed using Phoenix WinNonlin software to derive PK parameters for sofosbuvir. Adverse events (AEs) were monitored during the study.

Results: All 52 subjects completed the study. The observed PK parameters, including $t_{1/2}$, T_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, were similar between the generic and brand-named sofosbuvir products under fasting and fed conditions. The 90% confidence intervals of test/reference ratios for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were within the bioequivalence acceptance range. One subject experienced an AE while taking the reference product under the fasting condition, whereas six experienced nine AEs (six and three, respectively, while taking the generic and reference products). All AEs were mild.

Conclusions: The generic sofosbuvir is bioequivalent to the brand-named sofosbuvir under both fasting and fed conditions, and the generic sofosbuvir is as safe and well tolerated as the brand-named product in healthy Chinese volunteers.

Keywords: Sofosbuvir; Pharmacokinetics; Bioequivalence; Safety.

Abbreviations: HCV, hepatitis C virus; CHC, chronic hepatitis C; WHO, World Health Organization; FDA, the US Food and Drug Administration; PK, pharmacokinetic; GCE, generic consistency evaluation; CFDA, the China Food and Drug Administration; BMI, body mass index; AEs, adverse events; GLS, geometric least square; CI, confidence interval; ABE, the average bioequivalence method; RSABE, the reference-scaling average bioequivalence method; HVD, highly variable drug.

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Introduction

Hepatitis C virus (HCV) infection is one of the main causes of chronic liver disease, with the number of chronically infected persons worldwide estimated to be about 185 million.[1] HCV carries a significant health burden, contributing to 27% of liver cirrhosis and 25% of hepatocellular carcinoma globally.[2] The World Health Organization (WHO) has set the ambitious goal of eliminating HCV as a major global public health threat by 2030.[3] Timely and effective antiviral therapy for patients with HCV, including those

with chronic hepatitis C (CHC), can reduce liver damage and relieve liver fibrosis, thus controlling development of the disease.[4]

Sofosbuvir, a representative of the direct-acting antivirals, is a uridine nucleotide analogue inhibitor of HCV NS5B polymerase that potently inhibits RNA replicons of genotypes 1–6 and demonstrates a high genetic barrier to resistance. It is phosphorylated within the host hepatocyte to the active triphosphate form, and by competing with the natural nucleotides, causes premature RNA chain termination in the viral genome.[5] The brand-named sofosbuvir (Sovaldi®) was approved by the U.S. Food and Drug Administration (FDA) for the treatment of HCV infection in 2013 and then was marketed in China in 2017. It has been incorporated as a first-line agent in the latest guidelines for HCV treatment.[6] Because of its excellent pharmacokinetic (PK) profile, sofosbuvir can be administered orally in a single daily dose. *In vitro*, it exerts potent antiviral effects against HCV.[5,7] Previous clinical studies have shown that compared with the traditional pegylated interferon with ribavirin program, sofosbuvir, either in combination with pegylated interferon/ribavirin or in interferon-free combinations, such as sofosbuvir plus vipatavir, shortens the treatment time and improves the sustained virologic response and safety profile of patients.[5,8–11]

In China, where 10 million individuals are infected with HCV, sofosbuvir is one of the most commonly used drugs for HCV.[12] However, the cost of the brand-named sofosbuvir (Sovaldi®) is high (CNY 19,660 or approximately USD 2,800, for one course), and cannot be reimbursed by the medical insurance system in China,[5] which restricts the application of this highly efficacious drug in the country. Generic consistency evaluation (GCE) is a key program in China substituting expensive brand-named original drugs with cheap generic drugs. With GCE approval by the China Food and Drug Administration (CFDA), generic drugs can replace brand-named original drugs in clinical practice. Thus, the GCE program is an effective approach for assessing the quality of generic drugs, thus ensuring the safety and efficacy of drugs and saving medical costs.[13] Therefore, the development of a cheap generic sofosbuvir that has an equivalent PK profile, with similar clinical efficacy and safety, would reduce the economic burden, increase the application of the drug for patients with HCV infection, and consequently help achieve the goal set by the WHO. Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd. developed a generic sofosbuvir product, which was approved by the CFDA in 2016 for phase II clinical trials in treating CHC. Moreover, studies on the PKs and bioequivalence of the product in healthy subjects are also required by the CFDA.

Therefore, the aim of this study was to evaluate the bioequivalence and safety of this generic sofosbuvir, with reference to the brand-named sofosbuvir (Sovaldi®), in healthy Chinese volunteers.

Subjects and methods

Subjects

Healthy male and female volunteers aged 18 to 45 years and with a body mass index (BMI) ranging from 19 to 26 (minimal body weight of 45 kg for females and 50 kg for males), were eligible to participate in the study. Subjects were excluded if they were found to have significant cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, or hematologic disorder or any other relevant clinically significant medical condition, as evaluated by a physical examination and clinical laboratory tests. In addition, subjects with current or previous tobacco or alcohol addictive consumption, drug abuse, or who were taking any prescription, over-the-counter, or investigational medications within 14 days of screening were excluded. Female subjects who were pregnant or lactating were also excluded. Heterosexually active subjects who participated in the study agreed to use protocol-specified contraceptive methods 2 weeks before, during, and 6 months after the study.

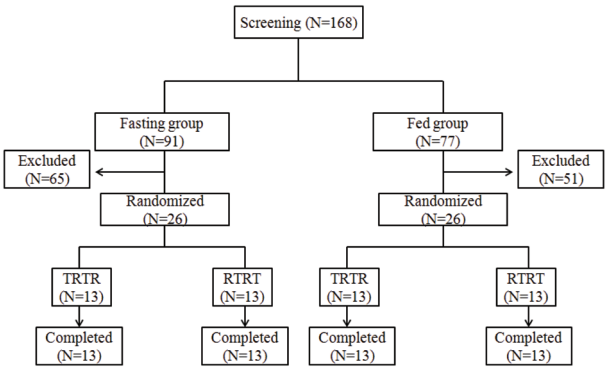

Fig. 1. Recruitment and randomization of the subjects in the study of a test (T) and a reference (R) formulations of sofosbuvir under fasting and fed conditions.

The clinical protocol was approved by the Institutional Review Board on Ethics of the Third Hospital of Changsha, following the Clinical Trial Authorization of the CFDA (Approval No. 2016L03881). It was also registered at ChinaDrugTrials.org.cn (identifier: CTR20170117). Written informed consent was provided by all subjects, and the clinical study was conducted in accordance with the ethical principles for human studies of the Declaration of Helsinki, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the CFDA Guidelines and regulations for Good Clinical Principles.

Study design

This study was performed with a single-dose, randomized, open-label, two-sequence, four-period, crossover trial design, to evaluate the bioequivalence and safety of the generic sofosbuvir under both fasting and fed conditions. Eligible subjects were screened and enrolled for the fasting and fed conditions. Under each condition, subjects were randomized to receive initial treatment according to either the test-reference-test-reference (TRTR) or reference-test-reference-test (RTRT) sequence, and then the treatment was switched to the other sequence after a 7-day washout period (Fig. 1). Under the fasting condition, a single dose of either the generic or test sofosbuvir (400 mg tablet, Lot No. 180601; manufactured and supplied by Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd., Nanjing, China) or the brand-named or reference sofosbuvir (Sovaldi®, 400 mg tablet, Lot No. 17SB001D1; manufactured by Gilead Sciences Cork, Ireland and supplied by Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd.) was administered to each subject with 240 mL water after at least 10-h overnight fasting. Under the fed condition, subjects consumed an FDA-standardized high-fat, high-calorie meal containing 800–1,000 kcal (approximately 150 kcal protein, 250 kcal carbohydrates, and 500–600 kcal fat) within 30 min after at least 10-h overnight fasting. This was followed by a single dose of either test or reference product administered to each subject with 240 mL water (Fig. 1).

Table 1. Demographic characeristics and body mass index of subjects recruited to the study for the fasting and fed conditions

Demographics	Fasting (n = 26)	Fed (n = 26)
Male/Female (N)	18/8	18/8
Age (years)	27.50 ± 7.61 (18–44)	26.40 ± 7.35 (18–45)
Height (cm)	164.42 ± 6.71 (152–178)	163.96 ± 6.64 (153–176)
Weight (kg)	58.81 ± 6.87 (46.5–74.4)	59.93 ± 6.12 (49.5–72.5)
BMI (kg/m^2)	21.70 ± 1.65 (19.2–25.3)	22.29 ± 1.82 (19.7–25.8)

BMI, body mass index. Data on age, height, weight, and BMI are expressed as the mean ± standard deviation (range).

Blood collection and sample preparation

Venous blood samples for sofosbuvir plasma concentrations were collected by inserting a catheter into the forearm vein prior to administration. Under the fasting condition, blood samples were collected within 1 h before dosing, and then 0.167, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 6, 8, 12, 24, 48, and 72 h after dosing. Under the fed condition, blood samples were collected within 1 h before dosing and high-fat, high-calorie breakfast, and then 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 48, and 72 h after dosing. At each timepoint, a volume of 3 mL blood was collected into heparinized tubes and centrifuged at 1,500 g and 4 °C for 10 min. The collected plasma was maintained at the study site in an ultra-deep freezer (below −60 °C) for PK analysis.

Determination of plasma sofosbuvir concentrations and PK parameters

The plasma concentrations of sofosbuvir were determined by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Sample separation was performed on the ultimate XB-C18 column (2.1 mm × 100 mm, 3 μm; Welch Materials Inc., West Haven, CT, USA) and an analytical column connected with a C18 guard column (Guard Cartridge System, USA) at a temperature of 40 °C. The gradient system consisted of solvent A (0.2% formic acid containing 10.0 mM ammonium acetate) and solvent B (methanol) at a flow rate of 0.3 mL/min. For the analysis of sofosbuvir, sofosbuvir-13C-d3 was used as the internal standard. The gradient program was as follows: 28% solvent B (0–0.4 min), 70% solvent B (0.5–3.2 min), 100% solvent B (3.3–4.3 min), and 28% solvent B (4.4–6.0 min). Positive-mode electrospray ionization was selected for mass spectral analysis, and m/z 530.2→243.1 and m/z 534.2→247.1 for sofosbuvir and sofosbuvir-13C-d3, respectively, were chosen as the mass transitions to detect ions in the multiple reaction monitoring mode. The standard calibration curves for sofosbuvir in human plasma was established within the concentration range of 3.0–2,000.0 ng/mL. The intra-day and inter-day precision and accuracy values of the samples were acceptable, and the relative standard deviations were all <15.0% for the low quantity, middle quantity, and high quantity controls. The intra-day and inter-day precision, relative standard deviations, and accuracy values of the linearity and the lower limit of quantifications were all <20.0%. The recoveries were ranged from 93.2% to 100.6%. The utilized method as indicated by the validation was suitable for large amounts of biomedical samples and provided a reference for several clinical applications and PK studies of sofosbuvir. Noncompartmental PK analysis was performed using the validated Phoenix WinNonlin version 7.0 software to derive PK parameters from plasma sofosbuvir concentrations versus time; the primary endpoints were C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, and the secondary endpoints were T_{max}, $T_{1/2z}$, and λ_z.

Safety assessment

All subjects randomized to receive any of the study drugs in the study were included in the safety analysis. Safety was evaluated by continuously monitoring vital signs, electrocardiography, hematology, biochemistry, urinalysis, and clinical manifestations at baseline, during the dosing and sampling at the designated time points following drug administration, and the day after study completion. Adverse events (AEs) were defined as abnormalities that were considered clinically significant by the investigators after randomization and classified by their intensity into mild, moderate, and severe. Subjects with AEs were further followed up until recovery or improvement.

Statistical analysis and determination of bioequivalence

The PK parameters ($C_{max,}$ AUC_{0-t} and $AUC_{0-\infty}$) were derived using unadjusted plasma concentration-time curve, and logarithmically converted. Then, analysis of variance was conducted using a fixed effects model for a four-way crossover design to evaluate the ratio and 90% confidence interval (CI) of the test/reference. According to the bioequivalence standards of the FDA, if S_{WR} (within-subject variability of reference product, within-subject variability (CV%) $= 100 * \sqrt{e^{S^2_{WR}} - 1}$) was <0.294 for either AUC_{0-t}, $AUC_{0-\infty}$ or C_{max} of the reference product, then the average bioequivalence (ABE) method was used to determine the bioequivalence between the test and reference products, which was defined if the 90% CI of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ fell within 80–125%. If S_{WR} was ≥ 0.294 for either AUC_{0-t}, $AUC_{0-\infty}$ or C_{max} of the reference product, then the reference-scaling average bioequivalence (RSABE) method was used for that measure, and the bioequivalence was defined if the 95% upper confidence limit was ≤0 and the predicted geometric mean ratio for the test/reference ratio was within the range of 0.80–1.25.[14]

Results

Subjects

Overall, 168 subjects were screened, 91 for the fasting condition and 77 for the fed condition. Sixty-five and fifty-one subjects were excluded from the fasting and fed conditions, respectively.

Table 2. Pharmacokinetic parameters of generic (or test) and reference products of sofosbuvir under fasting and fed conditions

Parameter	Fasting		Fed	
	Test	Reference	Test	Reference
T_{max} (h)	0.42 (0.333,2.25)	0.42 (0.333,1.375)	1.63 (0.5,5)	1.56 (0.875,5)
C_{max} (ng/mL)	980.77 ± 547.32	1,026.97 ± 495.51	722.75 ± 308.15	807.85 ± 361.85
AUC_{0-t} (h·ng/mL)	847.55 ± 323.00	815.61 ± 304.85	1,070.67 ± 330.90	1,078.71 ± 303.30
$AUC_{0-\infty}$ (h·ng/mL)	858.35 ± 319.92	821.30 ± 305.39	1,085.47 ± 334.79	1,083.84 ± 309.95
λ_z (1/h)	1.42 ± 0.32	1.45 ± 0.25	1.50 ± 0.20	1.54 ± 0.24
$T_{1/2Z}$($\times 10^{-1}$h)	5.35 ± 2.05	5.26 ± 1.60	4.79 ± 0.68	4.65 ± 0.79

T_{max}, time to C_{max}; C_{max}, maximum sofosbuvir concentration; AUC_{0-t}, area under the concentration curve from 0 time to the last time point; $AUC_{0-\infty}$, area under the concentration curve from 0 time to infinity; $T_{1/2}$, terminal elimination half-life; λ_z, first-order elimination rate constant. All data are expressed as mean ± standard deviation, except for T_{max}, which is expressed as median (range).

Thus, a total of 52 eligible subjects were enrolled in the study, 26 and 26 for the fasting and fed conditions, respectively. Then these subjects for each condition were equally randomized to follow the TRTR (n = 13) or RTRT (n = 13) sequence. All subjects completed the study according to the study protocol (Fig. 1). There were no differences between the subjects for the two conditions in demographic characteristics, height, weight, and BMI (Table 1)

PK parameters

The PK parameters of the generic and brand-named sofosbuvir products are summarized in Table 2; there were no significant differences in $t_{1/2}$, T_{max}, C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ between the two groups. The mean plasma concentration-time curves and semi-logarithmic curves of the products after a single dose are shown in Figures 2 and 3, and there were no significant differences in the

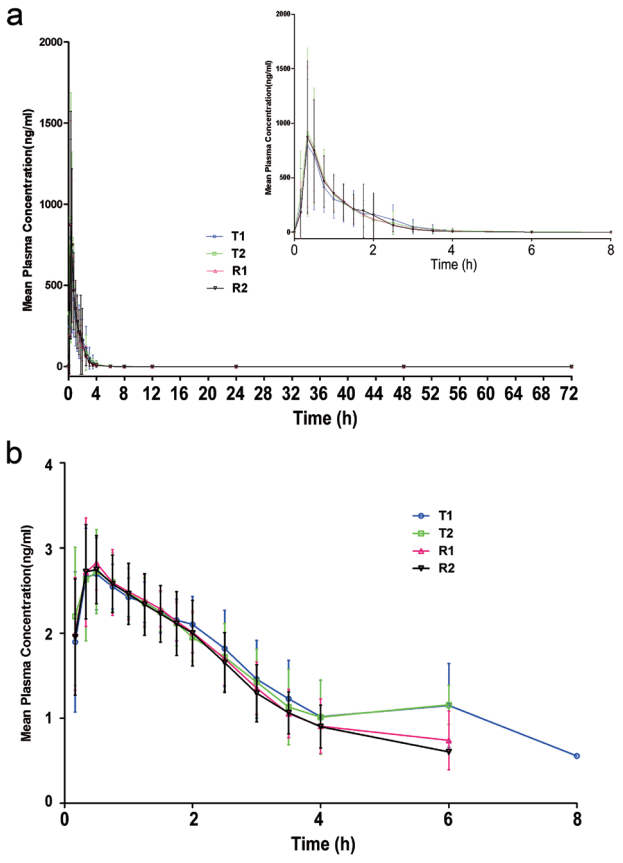

Fig. 2. Mean plasma concentration-time curves (a) and semi-logarithmic curves (b) of the generic or test (T) and the band-named or reference (R) products of sofosbuvir under the fasting condition.

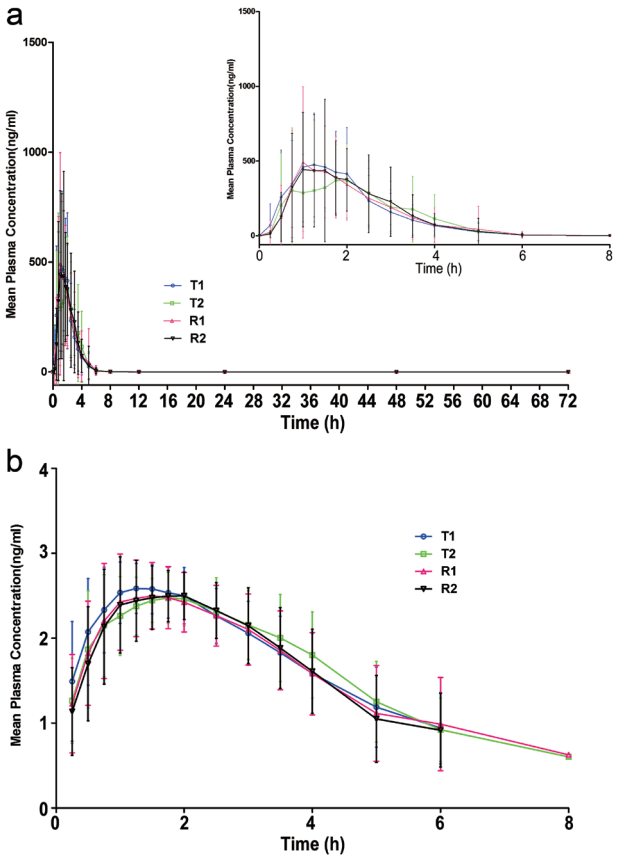

Fig. 3. Mean plasma concentration-time curves (a) and semi-logarithmic curves (b) of the generic or test (T) and the brand-named or reference (R) products of sofosbuvir under the fed condition.

Table 3. Bioequivalence analysis of sofosbuvir by logarithmic transformation after a single 400 mg dose under fasting and fed conditions, as determined by the RSABE method

Parameters	Fasting				Fed			
	N	S_{WR}	Point estimate (90% CI)	Criteria limit of 95% CI	N	S_{WR}	Point estimate (90% CI)	Criteria limit of 95% CI
C_{max}(ng/mL)	26	0.54	0.89 (0.76–1.05)	−0.119	26	0.44	0.91 (0.82–1.02)	−0.083
AUC_{0-t}(h*ng/mL)	26	0.33	1.04 (0.97–1.11)	−0.054	26	0.17	0.99 (0.94–1.04)	−0.014
$AUC_{0-\infty}$(h*ng/mL)	25[a]	0.26	1.05 (0.99–1.12)	−0.029	24[b]	0.17	1.00 (0.95–1.05)	−0.015

[a]The number of measured concentrations was less than three for one subject (SK017) in the elimination phase of period 3, and thus λz could not be calculated and consequently the $AUC_{0-\infty}$ of this subject could not be used for equivalence analysis. [b]The number of measured concentrations was less than three for two subjects (SC001 and SC004) in the elimination phase of period 3, and thus λz could not be calculated and consequently the $AUC_{0-\infty}$ of these two subjects could not be used for equivalence analysis.

Table 4. Bioequivalence analysis of sofosbuvir by logarithmic transformation after a single 400 mg dose under fasting and fed conditions, as determined by the ABE method

Parameters	Fasting				Fed			
	N	GMR	90% CI	Power%	N	GMR	90% CI	Power%
AUC_{0-t} (h*ng/mL)	–	–	–	–	26	99.11	94.33–104.13	>99.99
$AUC_{0-\infty}$ (h*ng/mL)	25[a]	105.29	97.31–113.93	97.41	24[b]	100.13	95.08–105.44	>99.99

GMR, geometric mean ratio; CI, confidential interval. [a]The number of measured concentrations was less than three for one subject (SK017) in the elimination phase of period 3, and thus λz could not be calculated and consequently the $AUC_{0-\infty}$ of this subject could not be used for equivalence analysis. [b]The number of measured concentrations was less than three for two subjects (SC001 and SC004) in the elimination phase of period 3, and thus λz could not be calculated and consequently the $AUC_{0-\infty}$ of these two subjects could not be used for equivalence analysis.

mean plasma concentration between the two groups at the various time points.

Bioequivalence of the generic product

Under the fasting condition, S_{WR} values for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.540, 0.326, and 0.255, respectively, with C_{max} and AUC_{0-t} exceeding the regulatory limit of 0.294. Therefore, the RSABE method was applied for C_{max} and AUC_{0-t}. It was shown that the 95% upper confidence limit was <0 for both the C_{max} and AUC_{0-t}, and the test/reference geometric least square (GLS) mean values for the point estimates of C_{max} and AUC_{0-t} were 0.89 and 1.04, respectively, which were within the range of 0.80–1.25. As the $AUC_{0-\infty}$ was below the regulatory limit of 0.294, the ABE method was applied for the analysis of $AUC_{0-\infty}$. It was shown that the ratio of test/reference GLS mean value was 105.29% (90% CI: 97.31–113.93%) for $AUC_{0-\infty}$, which was within the accepted bioequivalence limit (Tables 3 and 4). In the fed condition, S_{WR} values for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.435, 0.166, and 0.168, respectively; the C_{max} exceeded the regulatory limit of 0.294. So the RSABE method was applied for C_{max}, the 95% upper confidence limit and the test/reference GLS mean values for the point estimates of C_{max} were <0 and 0.91, which were within the range of 0.80–1.25. The AUC_{0-t} and $AUC_{0-\infty}$ were <0.294; the ABE method was conducted analyzing the AUC_{0-t} and $AUC_{0-\infty}$. The ratios of the test/reference GLS means were 99.11% (90% CI, 94.33–104.13) and 100.13% (90% CI, 95.08–105.44%) for AUC_{0-t} and $AUC_{0-\infty}$, respectively, which were within the accepted bioequivalence limits (Tables 3 and 4).

Table 5. Incidence of adverse events in the subjects while taking the test or reference formulation of sofosbuvir under fasting and fed conditions

Adverse event	Fasting (N = 26)		Fed (N = 26)		Total (N = 52)
	Test	Reference	Test	Reference	
Elevated triglyceride	0	1	0	1	2
Elevated bilirubin	0	0	1[a]	1[a]	2
Rash	0	0	1#	0	1
Decreased globulin	0	0	1#	0	1
Elevated total bile acid	0	0	1	0	1
Stomachache	0	0	1*	0	1
Diarrhea	0	0	0	1*[a]	1
Elevated serum cholesterol	0	0	1*	0	1
Total	0	1	6	3	10

[a]The adverse event (AE) was likely related to the study drug. *One subject experienced three AEs (*i.e.* stomachache, diarrhea and elevated serum cholesterol); #another experienced two AEs (*i.e.* rash and decreased globulin).

Safety

Throughout the study, a total of 10 AEs were observed (Table 5). Of the 26 subjects under the fasting condition, 1 subject had a mild elevated triglyceride while taking the reference sofosbuvir, which seemed unrelated to the study drug. Of the 26 subjects under the fed condition, 6 (23.1%) experienced nine AEs: three AEs (two mild elevated bilirubin and one diarrhea) were likely related to the study drug, and the other AEs were considered unrelated to the study drug. Throughout the course of this study, all reported AEs were mild in intensity, and no subject withdrew from the study.

Discussion

In this study, all PK parameters including C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were similar between the test and reference products in healthy Chinese subjects under both fasting and fed conditions. Despite differences in T_{max}, there were no significant differences in C_{max}, AUC, and $t_{1/2}$ between the fasting and fed conditions. Overall, the mean plasma concentration-time curves of the generic sofosbuvir and Sovaldi® were similar, regardless of whether the drug was administered under fasting or fed conditions. Throughout the study, AEs were observed in 13.5% of the subjects (3.8% and 23.1% under fasting and fed conditions, respectively). All reported AEs were mild in intensity, and no subject withdrew from the study.

A drug is regarded as a highly variable drug (HVD) if the CV% in the PK measures of C_{max} and/or AUC is greater than 30%.[15] Since 2006, the FDA has recommended the RSABE method to estimate the bioequivalent of HVDs, which requires that subjects receive twice the reference product to account for with-subject variability. Therefore, a partial replicated (three-way crossover: TRR, RTR or RRT) or a fully replicated (four-way crossover: TRTR or RTRT) study should be performed, and the number of subjects enrolled must be at least 24. The equivalence threshold criteria for HVDs set in The Guidance for Bioequivalence Studies of Highly Variable Drugs (draft),[16] published by the CFDA in 2018, are consistent with that by the FDA. As sofosbuvir is a highly variable drug, the present bioequivalence study was performed with a single-dose, randomized, open-label, two-sequence, four-period, crossover trial design, under fasting and fed conditions. According to the results of the present study, the main PK parameters, including T_{max}, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, were similar between the test and reference products under both conditions. Therefore, the two products of sofosbuvir meet the equivalence criteria under both fasting and fed conditions. It should be stated that although the elimination half-life of sofosbuvir is less than 1 h, and blood samples 8 h post-dosing would be sufficient for the bioequivalence study as shown in Figure 2, collection of the blood samples was extended for up to 72 h post-dosing for determination of PKs of the generic product and its metabolite.[17]

When administered in the fasting condition, the test and reference sofosbuvir products were rapidly absorbed, both with a T_{max} of 0.42 h. In addition, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were similar between the test and reference formulations. Both formulations were rapidly eliminated, with half-lives of 0.535 and 0.526 h, respectively. Previously, it was reported that this generic sofosbuvir had similar T_{max}, C_{max} and $AUC_{0-\infty}$ to that of the brand-named drug in Chinese subjects,[18] but these parameters were slightly larger than those of the brand-named drug in Japanese and Caucasian populations.[19,20] It is likely that the differences in population and time of blood collection accounted for the different results. When administered in the fed condition, the C_{max}, AUC, and T_{max} were also similar between the test and reference sofosbuvir products in this study, concordant with the PK parameters reported in the FDA reports for the brand-named sofosbuvir.[21] It was observed that, under the fed condition, the absorption of sofosbuvir was delayed with the T_{max} of 1.6 h, and the sofosbuvir exposure (AUC) was increased by 1.29-fold, compared to the fasting condition. These findings may be explained by that fact that high-fat foods retard gastric emptying and inhibit epithelial efflux transporters, leading to the blockade of sofosbuvir export and suggesting that the administration of sofosbuvir with food may increase treatment efficacy.[22]

In this study, sofosbuvir was well tolerated in healthy Chinese volunteers for both formulations. AEs were observed in 3.8% and 23.1% under fasting and fed conditions, respectively; the reasons for the higher rate observed in the fed condition may be related to the subjects' physiological status. According to the physician who determined if an AE was related to the study drug, only three AEs observed under the fed condition were considered to be related to the study drug: one (mild elevated bilirubin) occurred on the generic product, and two (mild elevated bilirubin and diarrhea) on the reference product. After appropriate management, all AEs were recovered. There were no significant differences in the severity and frequency of AEs between the two formulations. Subjects with AEs were further followed up until recovery or improvement. These data suggest that the test sofosbuvir is safe and can offer a new alternative to the brand-named sofosbuvir for millions of patients with HCVs and thus support its clinical development.

Future directions

The future studies are mainly about the re-evaluation in large clinical samples, including effectiveness, safety, and pharmacoeconomic evaluation.

Conclusions

The generic sofosbuvir 400-mg tablet is bioequivalent to the reference sofosbuvir (Sovaldi®) 400-mg tablet under both fasting and fed conditions. In addition, the generic sofosbuvir is as safe and well tolerated as the reference product in healthy Chinese volunteers. These findings suggest that these two products can be used interchangeably in clinical practice.

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Conflict of interest

The study drug, sofosbuvir tablets, was supplied by Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd. Yujie Liu is an employee of Nanjing Chia Tai Tianqing Pharmaceutical Co., Ltd. All other authors have no conflict of interests related to this publication.

Author contributions

Xin Li, the principal investigator of this paper, directed this study. All authors contributed to the data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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