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Bioequivalence and safety assessment of test vs. reference canagliflozin tablets in healthy Chinese volunteers: a randomized, open-label, single-dose, two-sequence, two-period crossover study under fasting and fed states

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Bioequivalence and safety assessment of test vs. reference canagliflozin tablets in healthy Chinese volunteers: a randomized, open-label, single-dose, two-sequence, two-period crossover study under fasting and fed states

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Abstract

Background: Diabetes Mellitus Type 2 is a disease that is becoming increasingly challenging in global public health. Due to their cardiorenal protective benefits, SGLT2 inhibitors, a class of antidiabetic medications, are currently a vital treatment for type 2 diabetes. In this study, healthy Chinese volunteers subjected to feeding or fasting were assessed on the safety and bioequivalency of 100 mg test formulation of canagliflozin tablet in relation to the reference innovator 100 mg tablet formulation.

Methods: An open label, randomized, two-period crossover study with a washout period of seven days was used to reduce any carry-over effect from the drugs administered. Fifty-six subjects who met all the inclusion and exclusion criteria were enrolled and delineated into two groups, i.e., the fed group and the fasting group. To determine the drug concentration after a single oral administration of 100 mg, plasma was obtained from individuals administered the reference and test drugs. To quantify canagliflozin in the plasma, a validated HPLC-MS/MS technique was utilized. Key pharmacokinetic characteristics were studied through plasma concentration versus time analysis. All participants in the two groups (28 per group) completed the study.

Results: The primary pharmacokinetic parameters of the test formulation were statistically analyzed and found to be equivalent to the reference formulation, meeting all regulatory bioequivalency requirements. In the case of Cmax, AUC0-t, and AUC0-∞ geometric mean ratios, all the 90% confidence intervals were within the expected bioequivalence limits of 80.00% to 125.00%. Moreover, it was noted that there was a similarity in the safety and tolerance aspects between the two formulations among the subjects in the study.

Conclusion: Overall, results from this trial provide proof of bioequivalence of the test canagliflozin product with the innovator product in healthy Chinese subjects under both fasting and fed conditions. The results support the clinical equivalence of both preparations, and the test formulation is a reliable alternative for clinical use.

Trial registration: This trial was registered on the China Drug Trials registry (http://www.chinadrugtrials.org.cn) on June 13, 2022 (registration number: CTR20221376), and retrospectively registered on the Chinese Clinical Trial Registry (ChiCTR; http://www.chictr.org.cn) on September 29, 2026 (registration number: ChiCTR2600133557).

Human Ethics and Consent to Participate declarations: The Independent Ethics Committee at Panyu Central Hospital in Guangzhou City, Guangdong Province, China, approved the study protocol (Approval No. PYZXYYEC [2022-06]-01). All healthy volunteers provided written informed consent to participate in the study prior to its registration.

Keywords: Randomized cross-over study, type 2 diabetes mellitus, pharmacokinetics, safety, drug safety and pharmacovigilance

Introduction

Diabetes mellitus type 2 (T2DM) continues to be among the commonest public health issues in the world. According to estimations based on the 11th Edition of the International Diabetes Federation Diabetes Atlas, there will be approximately 589 million people affected by diabetes by 2025 [1]. Over the last 20 years, there have been notable increases in the prevalence of T2DM amongst the Chinese population, increasing from 7.53% (95% CI: 7.00-10.69%) in 2005 to 13.7% (95% CI: 12.6-14.8%) in 2023 [2, 3]. In a similar manner, there have been notable increases in the prevalence of metabolic syndrome, which is a contributory factor to both T2DM and heart disease, within economically advanced areas of China [4].

The discovery of drug classes such as glucagons, which provide a number of clinical advantages, has greatly increased the therapeutic arsenal for type 2 diabetes in recent years. One of the cornerstone therapies in

modern T2DM management is the use of sodium-glucose cotransporter-2 (SGLT2) inhibitors [5, 6]. By specifically blocking SGLT2 transporters in the kidney's proximal convoluted tubules, these SGLT2 inhibitors—canagliflozin, empagliflozin, dapagliflozin, and ertugliflozin—mainly reduce hyperglycemia. This results in glucose excretion in the urine and decreases the reabsorption of filtered glucose [7, 8]. Their complex pleiotropic activities, which include glycemic control, intraglomerular pressure regulation, systemic metabolism augmentation, oxidative stress attenuation, and potential anti-senescence activity, have been linked to the well-established cardiorenal protective advantages [9–13].

The clinical use of Canagliflozin (cGIP), an SGLT2 inhibitor, as therapy for T2DM has been associated with various favorable cardiovascular and renal endpoints in addition to the hypoglycemic effect of the drug [14]. Particularly, canagliflozin is effective in slowing the development of Diabetic Nephropathy [15, 16], where according to the CREDENCE study, the nephroprotective effect of SGLT2 inhibitors works independently of their glucose lowering properties [17, 18]. Moreover, there is clear evidence demonstrating that SGLT2 inhibitors can greatly lower the chances of adverse cardiovascular events (MACE), particularly heart failure and sudden cardiac death [19]. Additional evidence of canagliflozin's cardiorenal preventative benefits is in its ability to lower levels of stress biomarkers [20–22] and improve validated risk assessment scores for kidney disease. Network meta-analyses show that all SGLT2 inhibitors appear to have cardiovascular benefits, despite differences in effect sizes on particular endpoints and underlying effects (off-target mechanisms) [23, 24].

The treatment of eligible patients with SGLT2 inhibitors is still not ideal despite this high-quality evidence of efficacy, with significant variances found between facilities [25], suggesting a gap between evidence and practice. Additionally, the bulk of Chinese drug clinical trials for diabetic kidney disease (2013–2023) were bioequivalence studies, and current generic drug development is essential to improving patients' access to and affordability of these medications [26, 27].

In this context, bioequivalence studies are the regulatory-accepted method to demonstrate that a generic drug has a similar rate and extent of absorption compared to the listed reference drug, and so should be therapeutically equivalent [28, 29]. One of the key requirements for clinical interchangeability of generic products is evaluation of pharmacokinetic properties, including the likely effect of food, during bioequivalence testing [30, 31].

The aim of this study was thus to assess the bioequivalence and safety of the 100 mg generic test canagliflozin tablet versus the innovator reference canagliflozin tablet in the presence of food in healthy Chinese subjects. The clinical pharmacology data collected during this trial will aid the regulatory approval and routine

clinical application of this generic medication, thereby contributing to an increased availability of this valuable cardiorenal protective agent to eligible patients.

Methods

Drugs

The test formulation used in this study was 100 mg strength canagliflozin tablets which were manufactured by Shandong Phoenix Pharmaceutical Co., Ltd., based in Shandong Province, China. The batch number of the test preparation was 5021791, and its valid shelf life extended from November 17, 2021, to October 31, 2023. The reference formulation was the commercially available original canagliflozin product, marketed under the trade name INVOKANA® with a 100 mg specification, produced by Janssen-Cilag S.p.A in Beerse, Belgium. The product bore the batch number LFL1800 and had a validity period from June 13, 2021, to May 31, 2023. Prior to the initiation of the trial, we verified the quality of both formulations, and the quantification results showed that the active pharmaceutical ingredient content of the test preparation was 101.5% of the labeled amount, while that of the reference preparation was 103.1%, with the difference in active ingredient content between the two preparations limited to less than 5%. R and T preparations were shielded from the light and stored at 20–25 ℃ in a dry environment.

Volunteers

This study utilized a randomized, two-period, self-crossover, single-dose design conducted under both fasting and fed states. For the statistical evaluation of bioequivalence, the type I error rate (α) was predefined as 0.05, and the statistical power (1-β) was set at 80%. Sample size calculation was done using PASS 11.0 (https://www.ncss.com/). Twenty-four subjects per cohort were deemed sufficient to establish bioequivalence between the two formulations. Considering the possibility of dropouts, 28 healthy subjects were recruited to each of the fasting and fed groups and the total number of 56 volunteers was deemed a suitable number of subjects for bioequivalence studies and were equally distributed in two sequence groups to receive either test or reference formulation.

Supplementary Data 1 provides comprehensive details on the main inclusion and exclusion criteria. Prior to the start of any experimental procedures, each participant gave written consent following a detailed explanation of the nature and purpose of the study, its methods and risks, its anticipated advantages, and the right of participants to terminate participation in the study at any point with no negative repercussions. Throughout each study period, vital signs and adverse events (AEs) were monitored at scheduled time points. On day 11, all

subjects underwent a thorough safety evaluation and were discharged from the clinical research center once all assessments were completed.

Research design

In this study, a randomized, open-label, two-formulation, one-dose, two-sequence, two-period cross-over design was employed. This design for the study is depicted in Figure 1 below.

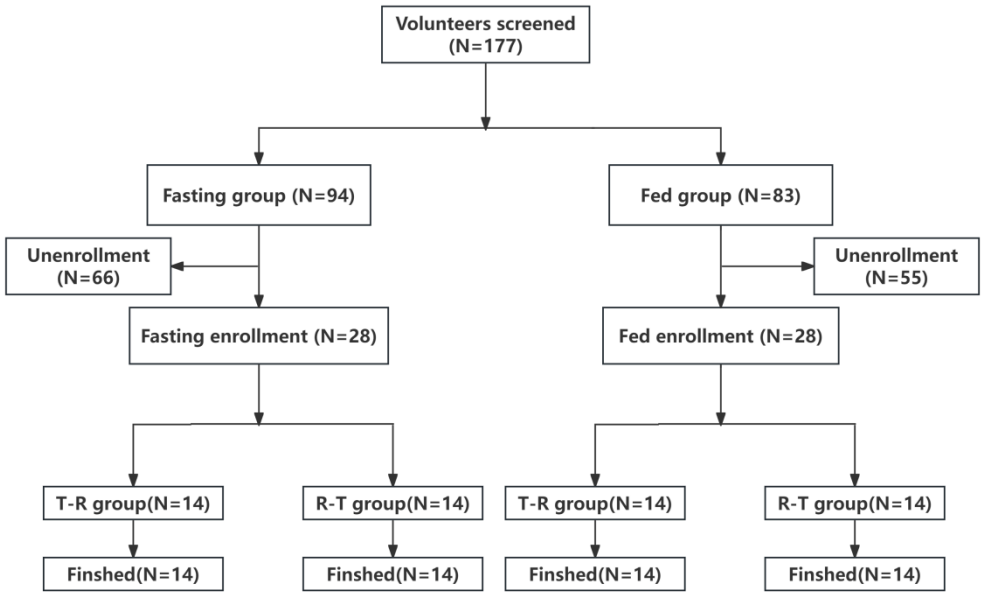


Fig. 1 Schematic representation of the study design for the bioequivalence test performed under fasted and fed states.

There were 56 healthy participants in all, split into 28 fasting and 28 fed individuals. Before receiving the medication, each participant underwent a thorough screening and was admitted to the clinical research facility 24 hours in advance. After this, through random allocation into 1:1 treatment ratios, they were randomly assigned to either the T-R or R-T sequences of treatments. This guaranteed that there would be balanced allocation to the treatment groups, hence avoiding any selection bias. Patients in the T-R treatment sequence group were first administered the test formulation, followed by the reference formulation, while patients in the R-T treatment sequence group were first administered the reference formulation, followed by the test formulation.

In order to achieve total clearance of the drug, a washout phase of seven days was included between both stages of treatment. Each of the test and reference drugs were taken following at least 10 hours of fasting by the subjects. For the fasting group, the T and R preparations (100 mg) were administered orally in 240 mL of warm water. The fed-state cohort kept the same meal plans for the duration of the trial and consumed an 800–1000

calorie, high-fat lunch half an hour before dosing. Standard meals were given four and ten hours following treatment, and the amount of fluid ingested was limited for an hour before and after the drug administration. Throughout the whole trial, participants were under continuous monitoring from qualified clinical staff and were not allowed to engage in any physically demanding activities. In accordance with the study protocol, each subject was given a normal breakfast, lunch, and dinner to guarantee consistent eating across the various treatment periods.

Sample collection

Venous blood samples (4 mL) were collected at predetermined time points, including pre-dose (0 h) and post-dose intervals, following administration. In the fasting cohort, samples were obtained at 1.0, 1.5, 2.0, 2.25, 2.5, 2.75, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, and 72.0 h post-administration, while in the fed cohort, samples were collected at 0.5, 1.0, 1.33, 1.67, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, and 72.0 h. Each blood sample was collected in a tube containing EDTA-K2 as anticoagulant. The tubes were then gently inverted to mix the blood and the anticoagulant together, after which, the tubes were placed at room temperature temporarily before undergoing centrifugation.

Processing and storage of plasma study samples

In all sample processing procedures, the time frame in which they were conducted was within the limits defined for the chemical stability of canagliflozin in the blood specimens. Each sample was centrifuged for 10 minutes at 1700 × g within 1.5 hours of the venous blood collection, with the temperature being carefully maintained at 2–8 °C throughout the centrifugation process. Following centrifugation, plasma was separated from whole blood at room temperature and divided into two identical aliquots: one for quantitative drug concentration analysis and the other for long-term archival storage. Storage procedures that had been validated included two methods of storing the plasma specimens: in one method, the plasma was stored at temperatures of -10°C to -30°C for 2 hours after collection, followed by transfer to an ultra-cold freezer maintained at temperatures of -60°C to -90°C within 24 hours; in another method, plasma was stored at -60°C to -90°C within 2 hours of centrifugation.

Bioanalytical assay to determine drug concentrations

The exact quantification of the canagliflozin compound in the plasma samples taken from subjects in this clinical research study required the development and validation of a highly reliable bioanalytical method. In developing the bioanalytical method for canagliflozin, all procedures were done according to the international bioanalytical method validation standards set forth by both the Chinese Pharmacopoeia Commission and the US

Food and Drug Administration (FDA) using samples obtained from healthy volunteers. Canagliflozin plasma concentrations in all EDTA-K2 treated plasma samples were analyzed by LC-MS/MS technique.

Linearity analysis was carried out through calibration curves that showed a high degree of linearity from 5.00 to 2500 ng/mL. Lower limits of quantitation (LLOQ) and upper limits of quantitation (ULOQ) were found to be 5.00 ng/mL and 2500 ng/mL, respectively. All whole blood samples were centrifuged within 1.5 hours of collection at 1700 × g for 10 minutes at 4°C. Two identical aliquots of the resultant plasma layer were separated at room temperature (ambient temperature) and designated for long-term backup archival storage and quantitative drug concentration analysis, respectively. The separated plasma aliquots were either immediately deposited in a -80°C freezer within two hours of centrifugation, or they were stored at -20°C within two hours and moved to a -80°C ultra-low freezer within twenty-four hours. Long-term stability assessment confirmed that canagliflozin in plasma remained stable for up to 36 days at approx. -10°C to -30°C and 65 days at approx. -60°C to -80°C. The maximum storage duration for the study samples was 26 days from sample collection to the completion of analytical testing, which fully met the stability specifications of the validated method.

Stable isotope-labeled canagliflozin-d4 (CAS 1997338-61-0) was used as the internal standard (IS) for sample pre-treatment. The sample was prepared using a protein precipitation procedure, using acetonitrile as the protein precipitant. In brief, the internal standard working solution was added to each plasma sample before the addition of acetonitrile for the precipitation of proteins. Aggressive vortexing of the mixture was followed by centrifugation at 1700 × g for 15 minutes at a controlled temperature of 4 °C. To quantify the amounts of canagliflozin in plasma samples using the HPLC-MS/MS method, the separated supernatant was maintained at a temperature range of 2–8 °C.

The compound was determined in plasma using a Shimadzu LC-20ADXR liquid chromatograph with an AB Sciex Triple Quad 4500 mass spectrometer for bioanalysis. Separation was carried out on a Welch Ultimate XB C18 analytical column (2.1 × 50.0 mm, 5.0 μm). The solvent system was Mobile Phase A (1 mM ammonium bicarbonate in water) and Mobile Phase B (acetonitrile). Chromatographic analysis was conducted at a flow rate of 1.00 mL/min with an initial organic content of 35.0%. Further details are provided in Table 1.

Table 1 Gradient elution conditions

Time (min)	Module	Function	Organic phase content (%)
0.01	Pumps	Pump B Conc.	35.0
1.30	Pumps	Pump B Conc.	55.0

1.40	Pumps	Pump B Conc.	95.0
2.00	Pumps	Pump B Conc.	95.0
2.10	Pumps	Pump B Conc.	35.0
2.70	System Controller	Stop	

For this quantitative test, the ionization source was electrospray ionization (ESI), and the data collecting mode was multiple reaction monitoring (MRM), with a total run duration of 2.7 minutes per sample. The optimal MRM ion transitions for quantification of canagliflozin and stable isotope-labeled internal standard (IS) were m/z 443.1→365.1 and m/z 447.1→369.1, respectively. The test showed excellent linearity over the concentration range of 5.00 to 2500 ng/mL. The mean extraction recovery of the internal standard was 103.9%, and intra- and inter-day precision of canagliflozin quantification were both found to be less than 6.0%.

Pharmacokinetic analysis

The pharmacokinetic parameters of canagliflozin were evaluated by means of the non-compartmental analytical methodology conducted on the Phoenix WinNonlin software (Version 8.3). The parameters evaluated include C_{max} (maximum plasma concentration), T_{max} (time to T_{max}), $t_{1/2}$ (terminal elimination half-life), AUC_{0-t} (area under the concentration-time curve from time zero to the last measured concentration), and $AUC_{0-\infty}$ (area under the concentration-time curve from time zero extrapolated to infinity). The calculations for the AUC used the linear trapezoidal rule. All further analyses were conducted on SAS software (Version 9.4).

Bioequivalence evaluation

Transformation using the natural log scale was conducted on all three parameters used in the study (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$). Subsequently, a two-way ANOVA test, suitable for two-period crossover bioequivalence design, was performed. In the ANOVA model, the random effect term was "subject" nested within "sequence", while the fixed effects factors were "sequence", "formulation", and "period". The bioequivalence of both formulations was proven if all the 90% confidence intervals (CI) for T/R GMRs for primary endpoints lay within an acceptable range of 80.00%-125.00% as defined by the regulation. All the analysis was done using the SAS package of programs (Version 9.4).

Safety assessments

This randomized, open-label, two-period crossover trial was designed and reported in accordance with the CONSORT (CONsolidated Standards Of Reporting Trials) 2010 Statement guidelines for reporting parallel-group randomized trials, adapted for crossover designs. A completed CONSORT checklist is provided as an additional file.

All adverse events (AEs) reported during the trial underwent a standardized and rigorous causality assessment performed by qualified clinical investigators. This study was performed according to the good clinical practice guidelines of the International Conference for Harmonisation (ICH GCP) as well as the Standard Operating Procedures (SOPs) of the clinical research center.

In the current evaluation, four main aspects associated with every individual adverse event were assessed. The first aspect to be evaluated was temporal relationship between the occurrence of an AE and exposure to the drug being investigated, i.e., canagliflozin. Second, consistency between the identified AE and the established safety profile of the medication being investigated was also determined. Third, potential factors that might influence the occurrence of an AE were also taken into consideration.

The causative link between AE and the drug under investigation was determined through causality categories: definitely, probably, possibly, possibly not, and definitely not, related to the adverse event. Every AE documented within the course of the trial was tracked until a full recovery occurred or until the patient's condition stabilized. In line with worldwide clinical trial standards, all AEs that were found to be either definitely, probably, or possibly related to the test drug were categorized as adverse drug reactions (ADRs).

Results

Study population

Of the 177 volunteers screened for participation in this bioequivalence trial, 121 were excluded during the screening process. The remaining 56 subjects were recruited for the study, with 28 allocated to the postprandial group and 28 to the fasting group. The total number of 56 subjects was retained throughout the study procedure, with no subject withdrawing from the trial. There were similarities in baseline demographics between the two treatment sequences. Complete baseline demographic data for all enrolled subjects are summarized in Table 2.

Table 2 Baseline demographic and clinical characteristics of all enrolled trial subjects

Characteristics	Fasting (N = 28)	Fed (N = 28)
Male	21 (75%)	25 (89.29%)
Female	7(25%)	3 (10.71%)
Age (years)	26.3 (±5.25)	27.9 (±6.81)
Height (cm)	166.96 (±6.468)	166.55 (±5.570)
Weight (kg)	61.41 (±6.904)	62.55 (±5.419)
BMI (kg/m2)	21.97 (±1.581)	22.54 (±1.532)

Pharmacokinetic properties

The mean plasma concentration-time curve for canagliflozin under fasting and non-fasting conditions after a single administration of the test and reference drugs is shown in Figures 2 and 3, respectively. Pharmacokinetic parameters of both formulations are presented in Table 3. Visual inspection of the concentration–time curves indicated substantial overlap in pharmacokinetic (PK) profiles between the test and reference formulations under both fasting and postprandial conditions. However, a statistically significant reduction in C_{max}, $AUC_{0–t}$, and $AUC_{0–\infty}$ was observed in the postprandial state compared with the fasting state, suggesting that food intake decreases the bioavailability of canagliflozin.

Table 3 Summary of pharmacokinetic parameters for test and reference canagliflozin formulations in healthy Chinese subjects under fasting and postprandial conditions

Parameters	Fasting (N = 28)		Fed (N = 28)	
	Test formulation	Reference formulation	Test formulation	Reference formulation
T_{max} (h)[a]	2.00 (1,4.5)	2.00 (1,4.5)	1.67 (1,5)	2.00 (1,4.5)
C_{max} (ng/mL)[b]	1052.6±197.06	1131.3±247.41	961.8±293.68	951.6±229.87
AUC_{0-t} (ng·h/mL)[b]	7095.418±1530.2042	7030.829±1544.8965	6416.055±1012.5678	6470.755±1060.5872
$AUC_{0-\infty}$ (ng·h/mL)[b]	7295.189±1596.7970	7217.498±1636.2009	6586.901±1043.3134	6678.489±1084.8847
$t_{1/2}$ (h)[b]	11.843±4.4644	12.170±5.7169	12.809±6.1862	12.966±6.7666

[a] Presented as median (minimum–maximum); [b] Presented as mean ± standard deviation. All subjects received a single 100 mg oral dose of canagliflozin.

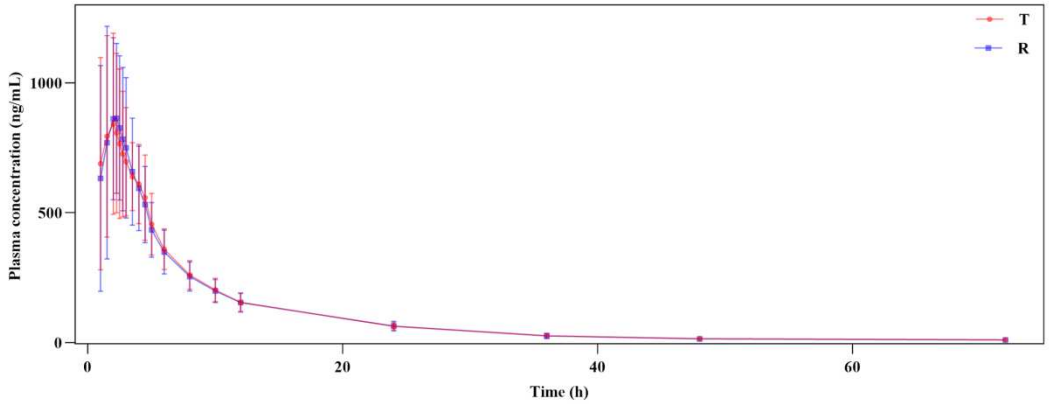


Fig. 2 Mean plasma concentration-time profiles (mean ± SE) under fasting conditions.

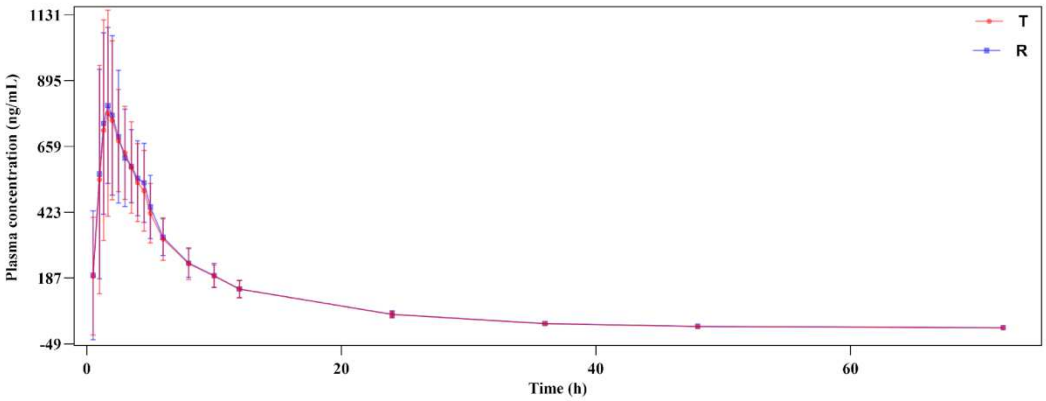


Fig. 3 Mean plasma concentration-time profiles (mean ± SE) under fed conditions.

Bioequivalence observed for test and reference formulations

Table 4 summarizes the bioequivalency assessment results under both postprandial and fasting settings. The key pharmacokinetic parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for the fasting group were geometric mean ratios (GMRs, test/reference) of 93.83%, 101.07%, and 101.28%, respectively. The corresponding GMRs for these parameters in the fed state were 98.76%, 99.33%, and 99.86%. The regulatory bioequivalency acceptance standards were satisfied by all PK parameters. The 90% confidence intervals (CIs) of all major parameters fell entirely within the regulatory criteria acceptable range of 80.00% - 125.00%. The results show that the two formulations are bioequivalent to each other in both the fed and fasting states.

Table 4 Summary of bioequivalence statistical results for canagliflozin test and reference formulations in healthy subjects

	Fasting (N = 28)			**Fed (N = 28)**		
PK Parameters	GMR (%)	CV (%)	90% CI for GMR (%)	GMR (%)	CV (%)	90%CI for GMR (%)
C_{max} (ng/mL)	93.83	13.88	88.10-99.93	99.86	23.72	89.75-111.09
AUC_{0-t} (ng·h/mL)	101.07	5.90	98.39-103.82	99.33	5.09	97.05-101.66
$AUC_{0-\infty}$ (ng·h/mL)	101.28	5.81	98.64-104.00	98.76	5.58	96.28-101.30

Abbreviations: GMR-geometric mean ratio (test/reference); CV-coefficient of variation; 90% CI, 90% confidence interval. All parameters met the 80.00%–125.00% bioequivalence acceptance range.

Safety assessment and tolerability profile

A total of 24 adverse events occurred in 12 of 28 subjects in the fasting cohort during the safety evaluation. Adverse events were never regarded as serious, and no subjects were withdrawn from the trial because of adverse events. Likewise, with the fed group, 8 of 28 subjects had adverse events, none of which were deemed serious adverse events or resulted in subjects withdrawing. No adverse events of Grade II severity or greater were reported. The most commonly seen side effect of both the fasting and the fed groups was a decrease in diastolic blood pressure. The overall findings of the study suggested good safety and tolerability profiles for all the participants.

Discussion

According to the IDF Diabetes Atlas 2024 (https://idf.org/our-network/regions-and-members/western-pacific/members/china/), over 589 million individuals worldwide suffer from diabetes mellitus (DM), a chronic metabolic condition marked by persistent hyperglycemia. Over 90% of China's 148 million diabetics (11.9% of the population) have type 2 diabetes mellitus (T2DM) [6]. The illness and its aftereffects significantly impair patients' physical and emotional well-being and quality of life, which has resulted in a significant problem in medical practice. Sodium-glucose cotransporter 2 (SGLT2), one of the main transporters in charge of reabsorbing glucose from the kidney's proximal tubular cells, is essential for maintaining glucose homeostasis throughout the body [7]. Pharmacological blockade of SGLT2 decreases glucose in the urine, results in better fasting and after-meal blood sugar control without altering insulin production and thus, has beneficial effects in reducing risk of hypoglycemia [8]. Canagliflozin is the first SGLT2 inhibitor approved by the FDA that is effective in the improvement of several metabolic parameters in patients with T2DM [30].

Pharmacokinetic studies showed that the oral bioavailability of canagliflozin tablets is, on average, 65% and the plasma protein binding is high (99%), predominantly to albumin. The drug is primarily metabolized by UDP-glucuronosyltransferase enzymes (UGT1A9 and UGT2B4) and only about 7% is metabolized via cytochrome P450 (CYP) 3A4. The renal (33% elimination) and fecal (60%) routes are the pathways for elimination of canagliflozin. Although the pharmacokinetic properties of canagliflozin have been demonstrated in the literature, to date, data for healthy Chinese subjects are limited.

The aims of the current trial were to assess the pharmacokinetics (PK) of the generic canagliflozin tablets (test product, Shandong Phoenix Pharmaceutical Co., Ltd) in comparison to the reference formulation (Janssen-Cilag S.p.A), to demonstrate the bioequivalence of the two drug products, and to estimate their safety

profile. Recruitment for the clinical trial involved healthy subjects from China. Both formulations were taken orally in a single dose either after fasting or after eating. Examination of the curves depicting plasma concentration over time (Figure 2) revealed very similar results for both formulations in both study settings.

In a fasted state, comparison of PK parameters revealed very similar pharmacokinetic behavior in both formulations, with only slight variations seen in the lower AUC_{0-t} and $AUC_{0-\infty}$ values of the reference formulation (Table 3). When co-administered with high-fat food, the test formulation showed a marked decrease in C_{max}, AUC_{0-t}, $AUC_{0-\infty}$ and T_{max}, indicating decreased bioavailability and slower absorption rate after a high-fat meal. A similar pattern was observed with the reference formulation, as the maximum concentration of drug after administration (C_{max}), plasma concentration-time area within 24 hours following drug administration (AUC_{0-24}), and plasma concentration-time area following drug administration ($AUC_{0-\infty}$) were all reduced significantly when food was consumed, but the elimination half-life (t½) was prolonged. This indicates that food may delay the absorption of canagliflozin. The overall conclusions reached in our statistical analyses establish a strong effect of food on the bioavailability of canagliflozin that precludes bioequivalence (BE) of the product under investigation. Notably, this finding is contradictory to previously published reports showing no significant correlation between food intake and PK profile of canagliflozin [31, 32]. The hypothesis is that a high calorie and high-fat diet may affect the gastrointestinal physiological function, impacting the observed in vivo bioavailability of canagliflozin.

Bioequivalency of the test and reference formulations was demonstrated by the 90% confidence intervals of the GMRs for the primary pharmacokinetic parameters (AUC_{0-t}, C_{max}, and $AUC_{0-\infty}$) being fully contained within the bioequivalence acceptability interval of 80.00% to 125.00%. According to safety data, all formulations were well tolerated, with reports of 35 AEs, all classified as Grade 1. During the study, no significant AEs or fatalities were reported. In both fed and fasting settings, the test and reference canagliflozin pills were bioequivalent, and their safety data did not differ.

Conclusion

This study successfully demonstrated bioequivalence of the test formulation of canagliflozin to its reference product in healthy Chinese volunteers under both fasting and feeding states, with no differences in safety and tolerance between the two formulations. Food had a significant effect on both formulations in terms of their absorption kinetics. The pharmacokinetic results showed that the canagliflozin tablets produced by Shandong Fenghuang Pharmaceutical Co., Ltd are as safe and effective as the reference product and can be used in a

clinical setting.

Abbreviations

Abbreviation	Full Form
ADRs	Adverse Drug Reactions
AEs	Adverse Events
ANOVA	Analysis of Variance
AUC	Area Under the Concentration-Time Curve
AUC_{0-t}	Area Under the Concentration-Time Curve from Time Zero to the Last Measured Concentration
$AUC_{0-\infty}$	Area Under the Concentration-Time Curve from Time Zero Extrapolated to Infinity
BE	Bioequivalence
BMI	Body Mass Index
CAS	Chemical Abstracts Service
CGIP	Canagliflozin
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CREDENCE	Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation
CV	Coefficient of Variation
CYP	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
DM	Diabetes Mellitus
EDTA-K_2	Ethylenediaminetetraacetic Acid Dipotassium Salt
ESI	Electrospray Ionization
FDA	Food and Drug Administration
GMR	Geometric Mean Ratio
HPLC-MS/MS	High Performance Liquid Chromatography-Tandem Mass Spectrometry
ICH	International Conference for Harmonisation
ICH GCP	International Conference for Harmonisation Good Clinical Practice
IS	Internal Standard
LLOQ	Lower Limit of Quantitation
MACE	Major Adverse Cardiovascular Events
MRM	Multiple Reaction Monitoring
N	Number
PK	Pharmacokinetics
SE	Standard Error
SGLT2	Sodium-Glucose Cotransporter-2
SOPs	Standard Operating Procedures

T2DM	Type 2 Diabetes Mellitus
$t_{1/2}$	Terminal Elimination Half-Life
T_{max}	Time to Maximum Plasma Concentration
UGT	UDP-Glucuronosyltransferase
UGT1A9	UDP-Glucuronosyltransferase 1A9
UGT2B4	UDP-Glucuronosyltransferase 2B4
ULOQ	Upper Limit of Quantitation

Declarations

Ethics approval and consent to participate

The ethical guidelines of the Declaration of Helsinki, the Good Clinical Practice (GCP) standards, the ICH recommendations, and the pertinent national regulations in China were adhered to when conducting the clinical research. The Independent Ethics Committee at Panyu Central Hospital in Guangzhou City, Guangdong Province, China, approved the study protocol (Approval No. PYZXYYEC [2022-06]-01). The independent location of the trial was the Affiliated Panyu Central Hospital of Guangzhou Medical University's Phase I Clinical Trial Research Center. This research was registered in the China Drug Trials registry (http://www.chinadrugtrials.org.cn; CTR20221376 (July 13, 2022) and the Chinese Clinical Trial Registry (http://www.chictr.org.cn; ChiCTR2600133557 (September 29, 2026). All healthy volunteers provided written informed consent to participate in the study prior to its registration.

Consent for publication: Not Applicable. This manuscript does not contain any identifying images, personal details, or clinical details of participants that could compromise anonymity.

A formal informed consent form was signed by each participant prior to their participation in this study.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

D.M.T. and W.X.L. conceived and designed the study. D.M.T. collected the study data and created the main content. J.F.K. and M.Q.C. performed the data analysis. G.C.S. prepared all figures. X.T.Z. and H.Y.Z. prepared all tables. D.M.T. and W.X.L. wrote the initial draft of the manuscript. G.C.S. edited and critically revised the manuscript. All authors reviewed and provided feedback on earlier drafts, and approved the final version of the manuscript. The authors declare that no artificial intelligence tools were used in the research process or manuscript writing, and all data were generated internally.

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