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CLINICAL TRIAL REPORT

Bioequivalence Study of Palbociclib Tablets in Healthy Volunteers

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Objective: Bioequivalence of palbociclib tablets was evaluated in healthy volunteers under fasting and fed conditions in this study.

Methods: This bioequivalence trial, which randomized subjects to receive palbociclib under fed or fasted conditions, generated these results. High-performance liquid chromatography-mass spectrometry (HPLC-MS) was employed to determine palbociclib concentrations in plasma from collected blood samples. Pharmacokinetic (PK) parameters were calculated using the non-compartmental analysis (NCA) module within Phoenix WinNonlin version 8.2. Statistical analysis of key pharmacokinetic parameters-maximum plasma concentration (C_{max}), area under the concentration-time curve from zero to last quantifiable time ($AUC_{0\text{-}t}$), and area under the curve from zero to infinity ($AUC_{0\text{-}\infty}$)-was conducted using the bioequivalence (BE) module within WinNonLin. A total of 68 healthy subjects were enrolled and randomized to either a fasted or a fed group. All subjects were randomized into T-R and R-T sequences (T: test formulation; R: reference formulation).

Results: The geometric mean ratios (T/R) of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of palbociclib in plasma were 97.96%, 96.16%, and 96.02% under fasting conditions; The geometric mean ratios (T/R) of C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ of palbociclib in plasma were 95.47%, 96.49%, and 96.36% under fed conditions. All 90% confidence intervals for the geometric mean ratios were contained entirely within the range of 80.00% to 125.00%. Under the fasted and fed conditions, the test preparation and the reference preparation of palbociclib tablets were bioequivalent. Adverse events (AEs) occurred at similar rates in the fasted and fed groups.

Conclusion: The result indicated that the test preparation and the reference preparation of palbociclib tablets were bioequivalent under the fasted and fed conditions. The safety of the two preparations was good.

Clinical Trial Registration: This trial was registered on the Chinese Clinical Trial website (http://www.chinadrugtrials.org.cn/index.html # CTR20220977).

Keywords: bioequivalence, breast cancer, palbociclib, safety, pharmacokinetics

Introduction

Among women globally, breast cancer is the most frequently occurring cancer and the top contributor to cancer-related fatalities.[1] The incidence of breast cancer has been increasing in recent years, and studies have shown that the number of breast cancer-related deaths worldwide is expected to reach 760,000 by 2025, posing a great threat to women's health.[2] Palbociclib is a new orally available small molecule inhibitor of cell cycle protein-dependent kinases (CDK) 4 and 6.[3,4] Palbociclib inhibits cell proliferation by inhibiting the binding of CDK4/6 to cyclin D, resulting in G1-S phase cell cycle arrest and reduced expression of E2F transcription factors and inhibition of downstream signaling.[5] Palbociclib was developed by Pfizer Inc. in the US in 2015, the FDA granted accelerated review approval for palbociclib to be marketed. In 2018, the palbociclib prodrug was approved for marketing in China. This drug is authorized for postmenopausal patients diagnosed with locally advanced or metastatic HR-positive, HER2-negative breast cancer. It is recommended to be administered alongside an aromatase inhibitor as the first-line endocrine treatment. (Instructions for palbociclib tablets (trade name: Ibrance®)). Bioequivalence studies of

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palbociclib capsules have been conducted domestically and internationally, but only a limited number of studies have been reported, for instance, Chu NanNan et al[6] reported that 60 healthy volunteers received 125 mg of palbociclib capsules under fasting and postprandial states, and found that the test formulation was bioequivalent to the reference formulation. However, studies on the bioequivalence of palbociclib in tablet dosage forms have not been found to date.

In this study, palbociclib tablets developed by Hebei Pharmaceutical Co. Ltd. were used as the test formulation, and palbociclib tablets (trade name: Ibrance) produced by Pfizer Germany were used as the reference formulation.[7] LC-MS /MS was employed to determine palbociclib concentrations in human plasma. This study conducted a bioequivalence evaluation in accordance with the requirements of the current technical guidelines,[8,9] which provides a theoretical basis for the drug's registration and its use in clinical practice.

This study aimed to assess and compare the pharmacokinetic properties and bioequivalence of two different palbociclib tablet preparations in healthy subjects during fasted and fed states. This investigation aimed to elucidate their in vivo performance characteristics and generate evidence supporting the approval of the test formulation for the Chinese market.

Materials, Objects and Methods

Study Drugs

The pharmacokinetic (PK) and bioequivalence (BE) studies utilized two palbociclib tablet formulations: the test (T) formulation from Hebei Pharmaceutical Co. Ltd. (125 mg per tablet, batch R46220203) and the reference (R) formulation, Ibrance® (125 mg per tablet, batch FK8574), produced by Pfizer Germany. Palbociclib reference substance (purity: 99.7%, batch number: 1827–099A1), which was provided by TLC PharmaChem Limited, Canada; Palbociclib-d8 (Chemical purity: 99.1%, isotopic purity: 98.8%, batch number: 2023–064A3), which was provided by TLC PharmaChem Limited, Canada.

The analytical work of bioequivalence study was undertaken with the help of liquid Chromatography Mass Spectrometer (Shimadzu LCMS-8060, Japan).

Methodological validation was carried out in accordance with the guidelines issued by the National Medical Products Administration's Pharmacopoeia Commission.[10]

Subject Selection

The participant cohort for this research was derived from a bioequivalence study undertaken at the Clinical Trial Institution of Hebei General Hospital. The Ethics Committee of Hebei General Hospital approved the study protocol and its amendments (approval No. 2022–05). The bioequivalence study registration is documented on the Chinese Clinical Trial website (http://www.chinadrugtrials.org.cn/index.html #CTR20220977. date: May 09, 2022). The time for the first subject to sign informed consent was May. 23, 2022.

The Chinese Clinical Trial website, despite its common use, lacks recognition by the WHO. Therefore, the bioequivalence trial underwent retrospective registration with the Chinese Clinical Trial Registry, a WHO-accredited platform. [https://www.chictr.org.cn/] (number: ChiCTR2500095813, date: January 13, 2025). This research was conducted in compliance with the ethical standards of the Declaration of Helsinki and adhered to Good Clinical Practice (GCP) guidelines established by both China's NMPA and the International Conference on Harmonization (ICH).[11] All participants retained the right to withdraw from the study at their discretion at any point.

Informed consent was signed by all subjects. Thirty-six healthy participants, averaging 29.7 ± 8.18 years of age, underwent the fasting test. Mean height was 168.35 ± 8.06 cm, mean body mass was 63.99 ± 8.42 kg, and mean body mass index was 22.51 ± 1.83 kg/m^2. Thirty-two healthy participants, averaging 30.00 ± 8.12 years of age, underwent the fed test. Mean height was 167.33 ± 8.41 cm, mean body mass was 63.87 ± 7.69 kg and mean body mass index was 22.77 ± 1.64 kg/m^2. The baseline characteristics for each participant are summarized in Table 1.

Entry Criteria

Healthy male and female subjects aged 18 years or older were included in the study. Males had a minimum body mass requirement of 50.0 kg, compared to 45.0 kg for females. All participants had a body mass index (BMI) within the range

Table 1 Demographic Baseline

Variable	Fasted Group	Fed Group
Age(years)		
Mean ± SD	29.75 ± 8.18	30.00 (8.12)
Median (Q1; Q3)	28.00 (22.00, 38.75)	29.50 (22.25, 36.00)
Min; Max	20.00, 45.00	19.00, 46.00
Sex n (%)		
Male	27.00 (75.00)	21.00 (65.60)
Female	9.00 (25.00)	11.00 (34.40)
Height (cm)		
Mean ± SD	168.35 (8.06)	167.33 (8.41)
Median(Q1; Q3)	169.75 (161.25, 174.38)	168.75 (160.13, 173.00)
Min; Max	153.50, 189.50	148.50, 183.00
Weight (kg)		
Mean (Std)	63.99 (8.42)	63.87 (7.69)
Median (Q1; Q3)	63.00 (58.10, 69.05)	64.30 (57.45, 69.45)
Min; Max	50.60, 87.80	49.00, 79.60
BMI (kg/m^2)		
Mean (Std)	22.51 (1.83)	22.77 (1.64)
Median (Q1; Q3)	22.40 (20.83, 24.35)	22.50 (21.73, 24.08)
Min; Max	19.10, 25.80	19.40, 25.80

Note: Data are the mean±SD, except sex (male/female), which is in %.
Abbreviations: BMI, body mass index; SD, standard deviation.

of 19.0 to 26.0 kg/m^2, including the threshold values. Subjects had no history of cardiovascular, endocrine, gastrointestinal, urinary, respiratory, dermatologic, neurologic, or psychiatric disorders.

Exclusion Criteria

Individuals were excluded based on the presence of clinically significant abnormalities: in vital signs, physical examination, laboratory tests, 12-lead electrocardiogram (ECG), chest X-ray, alcohol breath test, or drug screening. Individuals with a history of food or drug allergies were also excluded. Additional exclusion criteria included the use of any medications or supplements within 14 days prior to screening; blood donation or significant blood loss (≥400 mL) within 3 months prior to screening; receipt of blood transfusions or use of blood products; drug use within 3 months prior to screening or a history of substance abuse within the past 3 years. Participants who consumed fruits known to affect the metabolism of the study drug, such as dragon fruit, mango, or grapefruit, within 3 days prior to drug administration were excluded. Likewise, those who had consumed chocolate or any caffeinated or xanthine-containing food or beverages within 48 hours before dosing were not eligible for participation.

Grouping, Treatment and Blood Sample Collection

Employing a two-period, two-sequence replicated crossover design, this single-center, randomized, open-label bioequivalence study incorporated a 10-day washout interval between each treatment cycle. A total of 36 subjects participated in the fasting and 32 subjects in the fed tests. Randomization was performed separately for the fasting and postprandial trials. Within each trial, participants were assigned 1:1 to either sequence A (TR) or B (RT) for the fasting trial, and sequence C (TR) or D (RT) for the postprandial trial. Subjects abstained from food for a minimum of 10 hours overnight. On the first day of each cycle, the subjects orally took 125 mg of the test preparation or the reference preparation respectively. The fed group had a high-fat (provides about 50% of the calories in food) and high-calorie (800–1000 kCal) breakfast, the subjects finished their breakfast within 30 minutes and began to take the medicine at about 8 am and took it with 240 mL of water. Pre-dose (0 h) and post-dose blood samples for PK analysis were obtained at the following times: 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0, 11.0, 12.0, 24.0, 48.0, 72.0, 96.0, and 120.0 hours. The amount of blood to be collected each time was 4 mL. The blood specimens were collected in K_2EDTA-coated tubes and then subjected to centrifugation at 1700 g for 10 minutes. Following centrifugation, the plasma layer was carefully aliquoted and preserved in ultra-low temperature freezers maintained between −60 °C to - 90 °C.

Measurement Methods and Blood Sample Handling

Chromatographic Condition

Separation was achieved on a GL Sciences InertSustain C18 column (50.0 mm × 2.1 mm, 3 μm particle size). The mobile phase consisted of two components: (A) an aqueous solution containing formic acid, 1.0 M ammonium acetate, and water in a volume ratio of 1:1:500, and (B) pure methanol. The separation was carried out using a flow rate of 0.4 mL per minute, with the column maintained at 40 °C. Sample injections of 5 microliters were employed for the chromatographic analysis. A gradient elution was employed, increasing mobile phase B from 45% to 100% over 4.2 minutes.

Mass Spectrometry Conditions

A mass spectrometer equipped with an electrospray ionization source operating in the positive ion mode and multiple reaction monitoring was employed for detection, where ion transitions for palbociclib and the internal standard were 448.2→380.2 m/z and 456.3→388.2 m/z, respectively, with specific source parameters and compound-dependent settings including dwell time (200 ms), Declustering Potential (DP) (100 V, 155 V), Entrance Potential (EP) (6 V, 13 V), Collision Energy (CE) (40 V), and collision cell exit potential (13 V, 23 V).

Blood Sample Handling

The sample was melted and vortexed. 50.0 μL of samples (standard curve samples, quality control(QC) Samples, samples to be measured) were pipetted into a 96-well plate. 50.0 μL of blank human plasma was added to double-blank and zero samples. 30.0 μL of the internal standard working solution was added to other samples. 200 μL of acetonitrile was added to all samples. Samples were vortexed for 10 min and centrifuged at 2200 rpm for 10 min at room temperature. 450 μL of diluent was added to a clean 96-well plate; 50.0 μL of supernatant was pipetted into the 96-well plate, the 96-well plate was placed into the autosampler.

Methodological Examination and Evaluation

The methodological validation of the liquid-liquid coupling method was done by Nanjing Kelitai Pharmaceutical Technology Co.

Specificity

The retention time of palbociclib and the internal standard were 1.42 and 1.39 min, respectively. Six different matrices (blank, hemolyzed, and high-fat) were used to detect the analyte and the internal standard. Results demonstrated that there were no interference between the analyte and the matrices, and there were no interference between the analyte and the internal standard either, indicating good method specificity. The LC-MS chromatograms for palbociclib and the palbociclib-D8 are given in Figure 1.

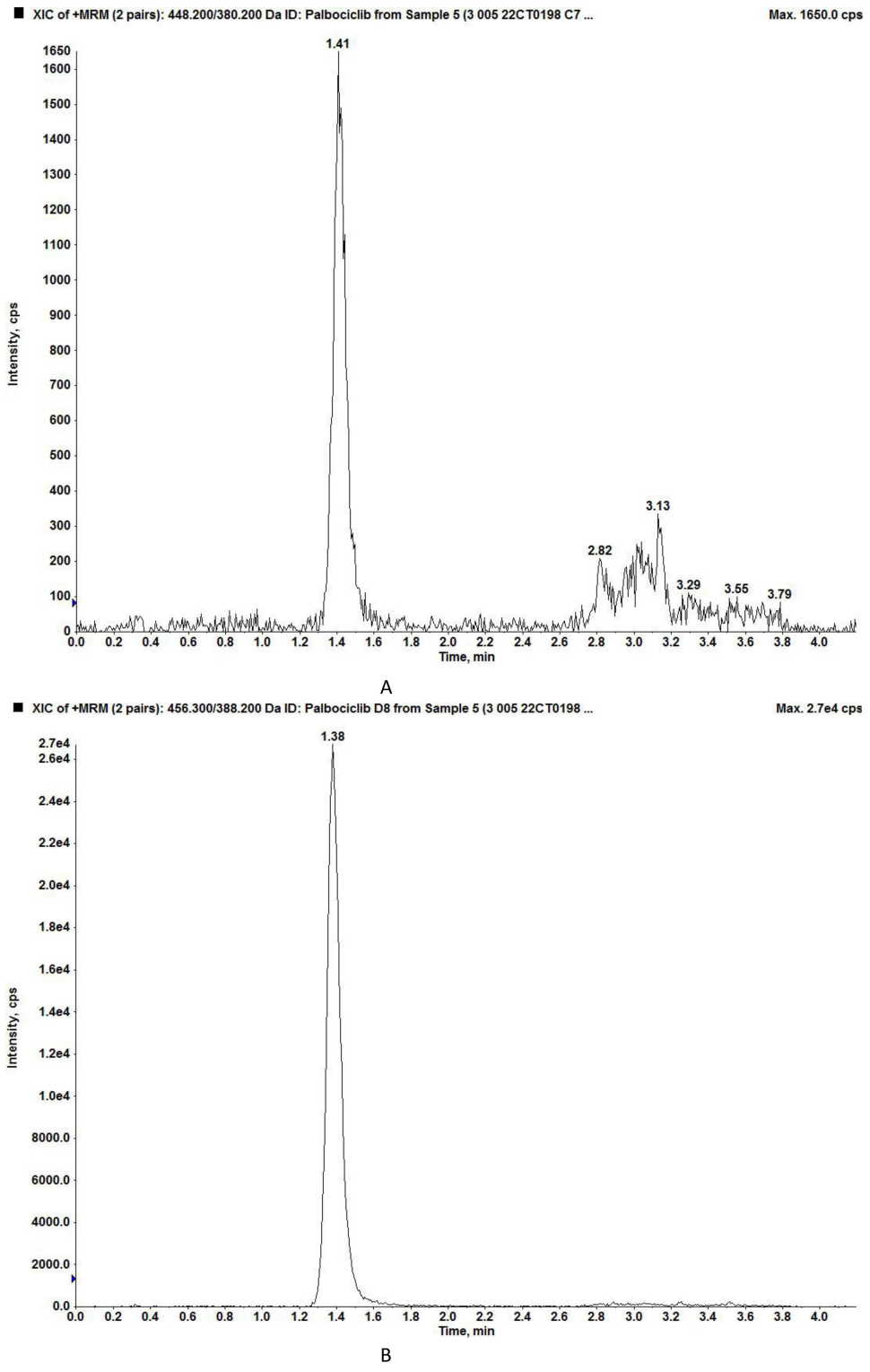

Figure 1 Typical chromatogram of palbociclib. (**A**) palbociclib (**B**) palbociclib-D8.

Method's Quantification Range and Lower Quantification Threshold

The standard curve samples were prepared at seven mass concentrations of palbociclib: 0.50 (lower limit of quantification, LLOQ), 1.00, 4.00, 20.00, 80.00, 120.00, and 150.00 (upper limit of quantification, ULOQ) ng/mL. The plasma samples were processed as described, and the chromatograms were recorded. The concentration of the substance to be

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measured is plotted as the horizontal coordinate, while the vertical coordinate represents the ratio of the peak area of the substance to the internal standard. The standard curve equation was calculated using linear regression. The linear range for palbociclib blood concentrations was 0.50 to 150.00 ng/mL, with a standard curve equation of $y = 1.04 \times 10^{-1} x + 7.17 \times 10^{-3}$ ($r = 0.9996$). The lower limit of quantification was 0.50 ng/mL.

Precision and Recovery

Preparation of palbociclib quality control samples at five mass concentrations: 0.50 ng/mL (LLOQ), 1.20 ng/mL (lower limit of quantification, LQC), 10.00 ng/mL (geometric middle quality control, GMQC), 50.00 ng/mL (middle quality control, MQC), and 115.00 ng/mL (high quality control, HQC). Six samples were collected for each mass concentration, and measurements were conducted over a period of three days. Assessment of intra- and inter-batch accuracy and precision. The preparation of quality control (QC) samples for the determination of palbociclib at low, medium, and high mass concentrations (1.20, 50.00, and 115.00 ng/mL) included 6 replicates per concentration alongside 18 double-blank samples. The recovery rate was evaluated by comparing the response value of the test substance in a single QC sample to that of a double-blank sample spiked with the test substance and internal standard after pretreatment. The results were shown in Table 2.

Stromal Effect

Human plasma has no effect on the results of palbociclib and the internal standard measurements. The hemolyzed matrix has no effect on the results of palbociclib and the internal standard measurements. The high-fat matrix has no effect on the results of palbociclib and the internal standard measurements.

Stability

Human plasma samples demonstrated good stability when left at room temperature for 18.5 hours. The stability of plasma samples was maintained at both −20 °C and −70 °C through 5 freeze-thaw cycles. Long-term freezing stability was observed at −20 °C for 31 days and 88 days, with similar results at −70 °C over the same durations. Processed samples remained stable in the autosampler at 8 °C for 4 days and 13 hours.

Statistical Processing

The calculation of major pharmacokinetic parameters and bioequivalence evaluation were performed using Phoenix WinNonLin 8.2 software. The main pharmacokinetic parameters of palbociclib, including C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$, were log-transformed. Analysis of variance (ANOVA) and 90% confidence interval (CI) analyses were conducted. The bioequivalence criteria were set at 80.00% to 125.00%.

Table 2 Accuracy, Precision, and Recovery of Palbociclib in Human Plasma Were Determined by Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

Drug	Concentration (ng/mL)	Intra -day (n = 6)			Inter -day (n =18)			Relative Recovery (%)
		Measured (ng/mL, $\bar{x} \pm s$)	RSD (%)	RE (%)	Measured (ng/mL, $\bar{x} \pm s$)	RSD (%)	RE (%)	
Palbociclib	0.50	0.50 ± 0.01	2.47	0.60	0.51 ± 0.02	3.24	2.00	-
	1.20	1.23 ± 0.04	3.04	2.50	1.24 ± 0.03	2.73	3.33	95.86
	10.00	10.33 ± 0.12	1.17	3.30	10.20 ± 0.24	2.37	2.00	-
	50.00	51.60 ± 1.07	2.07	3.20	50.44 ± 1.24	2.46	0.88	96.01
	115.00	117.50 ± 1.87	1.59	2.17	114.44 ± 2.99	2.62	−0.49	96.29

Abbreviations: RSD, relative standard deviation; RE, relative error.

Results

Subject

The fasting test screened 124 subjects. Thirty-six subjects were enrolled, with 35 completing the trial and 1 subject withdrawing early. All 36 enrolled subjects were included in the following analysis sets: Full Analysis Set (FAS), Safety Analysis Set (SS), Pharmacokinetic Concentration Set (PKCS), Pharmacokinetic Parameter Set (PKPS), and Bioequivalence Analysis Set (BES). Among these subjects, K036 voluntarily withdrew from the trial before the start of the second cycle; therefore, only the first-cycle data were included in PKCS, PKPS, and BES. The Fed test screened 96 subjects; 32 were enrolled, 29 completed the trial, and 3 withdrew early. Subject C001 was withdrawn during the second treatment cycle due to elevated blood HCG levels. Subject C031 was discontinued from the second cycle due to an adverse event (abdominal pain and diarrhea). Subject C030 was withdrawn from the study due to a family member's hospitalization, this occurred following blood collection conducted 12.0 hours after completion of dosing in the second cycle. FAS, SS, PKCS, PKPS, and BES all had thirty-two subjects. For subjects C001 and C031, only first-cycle data were included in PKCS, PKPS, and BES. Subject C030, who had two cycles of data, was included in PKCS, PKPS, and BES; however, only C_{max} from the second cycle was incorporated into PKPS and BES. As shown in Figure 2.

Plasma Concentration-Time Profile

Mean blood concentration-time curves of oral palbociclib were compared between fasting and postprandial conditions in healthy subjects. The results for the test and reference formulations are presented in Figure 3.

Pharmacokinetic Metrics

Following oral dosing in healthy volunteers (fasting and fed states), the key pharmacokinetic parameters of the test and reference palbociclib tablet formulations are detailed in Table 3.

Bioequivalence Analysis

In the fasting group, the geometric mean ratios of palbociclib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$were 97.96%, 96.16%, and 96.02%, respectively. The 90% confidence intervals (CI) for palbociclib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 93.89%-102.21%, 93.11%-99.31%, and 92.97%-99.17%, respectively. The intra-individual variabilities of palbociclib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$were 10.54%, 7.98%, and 8.00%, respectively. In the fed group, the geometric mean ratios of palbociclib C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$were 95.47%, 96.49% and 96.36%, respectively. The 90% confidence intervals

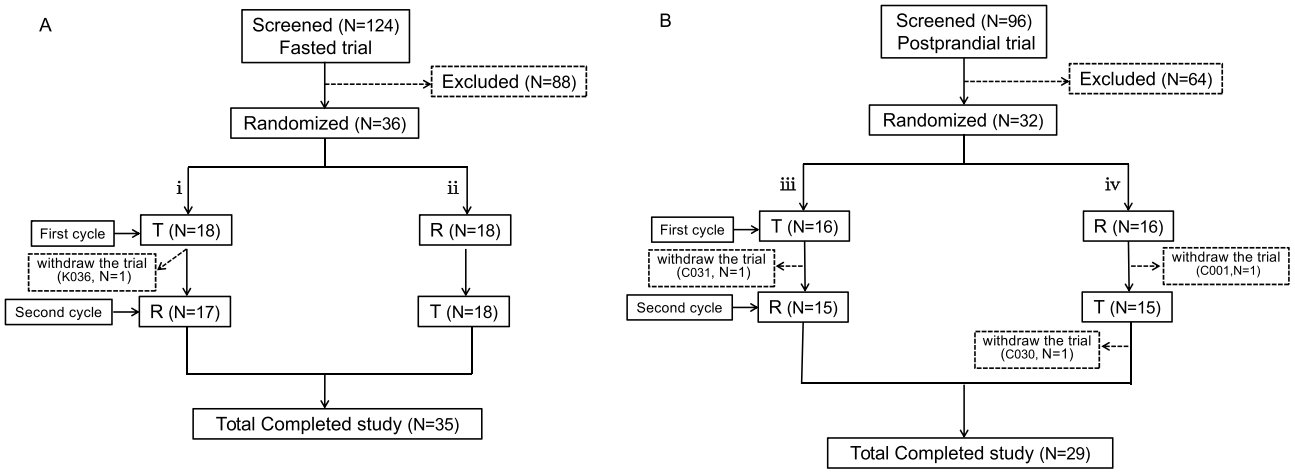

Figure 2 Subjects flow chart. Flow chart of the subjects in the fasted state (**A**). Drug T is given in cycle 1, Drug R is given in cycle 2 (I). Drug R is given in cycle 1, Drug T is given in cycle 2 (II). Flow chart of the subjects in the fed state (**B**). Drug T is given in cycle 1, Drug R is given in cycle 2 (III). Drug R is given in cycle 1, Drug T is given in cycle 2 (IV).
Abbreviation: N, the number of subjects.

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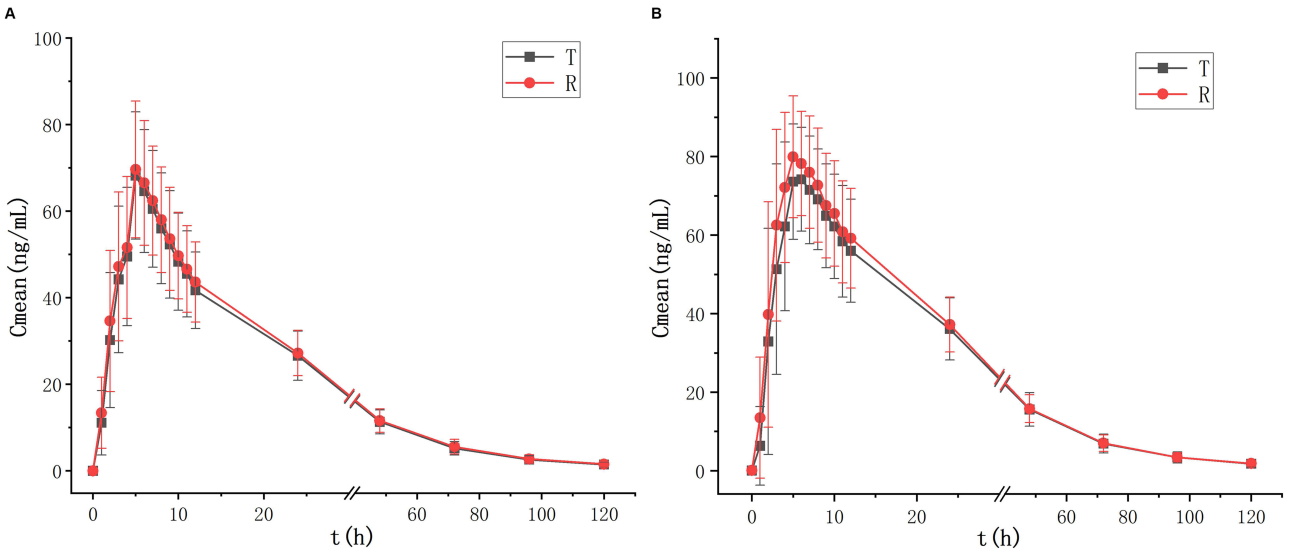

Figure 3 Mean plasma concentration-time curves after taking the test (T) and reference (R) preparations in healthy subjects. (**A**) Fasting (**B**) Fed.

(CI) for palbociclib C_{max}, AUC_{0-t} and $AUC_{0-\infty}$were 92.72%-98.29%, 94.01%-99.03% and 93.82%-98.97%, respectively. The intra-individual variabilities of palbociclib C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were 6.66%, 5.83% and 5.99%, respectively.

The 90% confidence intervals for the ratios of the geometric means of C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (test vs reference formulations of palbociclib) were within the range of 80.00% to 125.00%, confirming the bioequivalence of the two preparations.

Safety Assessment

All adverse reactions in this trial were Grade 1 (CTCAE 5.0). No serious adverse events or reactions occurred. A total of 7 adverse drug reactions occurred in 2 subjects during the fasting trial, with an overall incidence rate of 5.6%. Among these, 1 case (5 occurrences) were reported in the test preparation group, and 1 case (2 occurrences) were observed in the reference preparation group. A total of 14 adverse drug reactions occurred in 5 subjects during the postprandial trial. The overall incidence of adverse drug reactions was 15.6%. Among these, 3 cases (7 instances) were reported in the test preparation group, and 2 cases (7 instances) were observed in the reference preparation group. AE incidence rates for participants under fasting and fed conditions are shown in Table 4.

Table 3 The Main Pharmacokinetic Parameters of Palbociclib After Taking the Test and Reference

Parameter	Fasting		Fed	
	Test (n = 36)	Reference (n = 35)	Test (n= 31)	Reference (n = 31)
C_{max} (ng/mL)	69.68 ± 14.76	71.35 ± 15.29	79.72 ± 15.27	84.66 ± 14.44
AUC_{0-t} (ng×h/mL)	1754.12 ± 371.04	1822.22 ± 358.63	2288.61 ± 438.65	2394.02 ± 398.79
$AUC_{0-\infty}$ (ng×h/mL)	1805.67 ± 383.73	1878.59 ± 372.53	2350.03 ± 456.64	2459.72 ± 411.77
T_{max} (h) *	4.99 (4.99, 8.99)	4.99 (2.99, 7.99)	4.99 (1.99, 10.99)	4.99 (1.99, 11.99)
$t_{1/2}$ (h)	23.72 ± 2.91	23.87 ± 3.91	22.74 ± 3.48	23.58 ± 3.57

Notes: preparations in healthy subjects ($\bar{x} \pm s$). *Medium(min, max); C_{max}: maximum concentration; AUC_{0-t}: area under the concentration-time curve from zero to the final measurable concentration; $AUC_{0-\infty}$: area under the concentration-time curve from time zero to infinity; T_{max}: Time to reach maximum concentration; $t_{1/2}$: elimination half-life.

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Table 4 Summary of AEs

Parameter	Fasted Group						Fed Group					
	T (N = 36)			R (N = 35)			T (N = 31)			R (N = 31)		
	n	%	E	n	%	E	n	%	E	n	%	E
Sum	9	25.0	20	5	14.3	9	5	16.1	12	3	9.7	10
AE severity												
Grade 1	9	25.0	20	5	14.3	9	5	16.1	12	3	9.7	10
≥Grade 1	0	0	0	0	0	0	0	0	0	0	0	0
Drug correlation												
Highly Possible related	0	0	0	0	0	0	0	0	0	0	0	0
Possible related	1	2.8	5	1	2.9	2	3	9.7	7	2	6.5	7
Possible unrelated	9	25.0	15	5	14.3	7	5	16.1	5	2	6.5	2
Name of AE												
Lymphocyte count decreased	1	2.8	2	2	5.7	2	0	0.0	0	0	0.0	0
TG elevated	2	5.6	2	1	2.9	1	1	3.2	1	0	0.0	0
Urine leukocyte positive	1	2.8	2	1	2.9	2	0	0.0	0	0	0.0	0
White blood cell count decreased	1	2.85	1	1	2.9	1	1	3.2	1	0	0.0	0
Direct bilirubin elevated	2	5.6	2	0	0.0	0	0	0.0	0	0	0.0	0
Blood bilirubin elevated	2	5.6	2	0	0.0	0	0	0.0	0	0	0.0	0
HGB decreased	1	2.8	1	1	2.9	1	1	3.2	1	2	6.5	2
CK-MB elevated	2	5.6	2	0	0.0	0	0	0	0.0	0	0	0.0
Red blood cell count decreased	1	2.8	1	0	0.0	0	1	3.2	1	2	6.5	2
Hematocrit decreased	1	2.8	1	0	0.0	0	1	3.2	1	1	3.2	1
Urine erythrocyte positive	0	0.0	0	1	2.9	1	0	0.0	0	0	0.0	0
Cells were detected in the urine	0	0.0	0	1	2.9	1	0	0.0	0	0	0.0	0
CK elevated	1	2.8	1	0	0.0	0	0	0.0	0	0	0.0	0
Blood magnesium decreased	1	2.8	1	0	0.0	0	0	0.0	0	0	0.0	0
Blood sodium decreased	1	2.8	1	0	0.0	0	0	0.0	0	0	0.0	0
Neutrophil count decreased	1	2.8	1	0	0.0	0	1	3.2	1	0	0.0	0
γ-glutamyltransferase elevated	0	0.0	0	0	0.0	0	1	3.2	1	0	0.0	0
Alanine aminotransferase elevated	0	0.0	0	0	0.0	0	1	3.2	1	0	0.0	0
Human chorionic gonadotropin elevated	0	0.0	0	0	0.0	0	0	0.0	0	1	3.2	1
Hyperuricemia	0	0.0	0	0	0.0	0	0	0.0	0	1	3.2	1
Blood fibrinogen decreased	0	0.0	0	0	0.0	0	1	3.2	1	0	0.0	0
Upper respiratory tract infection (URTI)	0	0.0	0	0	0.0	0	1	3.2	1	0	0.0	0
Tenosynovitis	0	0.0	0	0	0.0	0	0	0.0	0	1	3.2	1
Celialgia	0	0.0	0	0	0.0	0	1	3.2	1	0	0.0	0
Diarrhea	0	0.0	0	0	0.0	0	1	3.2	1	0	0.0	0

Abbreviations: T, test formulation; R, reference formulation; E, cases of adverse events; AE, adverse event; TG, triglyceride; HGB, hemoglobin; CK-MB, creatine kinase isoenzyme; CK, creatine kinase; URTI, upper respiratory tract infection.

Discussion

Studies have demonstrated that palbociclib, whether used alone or in combination with endocrine therapy, immunotherapy, chemotherapy, or other treatments, can significantly prolong survival in patients with hormone receptor-positive breast cancer, improve objective response rates, and demonstrate good clinical efficacy.

Bioequivalence studies of palbociclib capsule dosage forms are less frequently reported in China. Domestic scholars Yanchao Wang et al reported that palbociclib capsule (125 mg administered orally) in a 2-cycle experimental design demonstrated bioequivalence under both fasting and postprandial conditions.[12] Qian Wang et al[13] confirmed the bioequivalence of a palbociclib test formulation (T) to its reference (R) in healthy Chinese subjects under fasting and

fed conditions. Single-dose results showed that for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, the 90% confidence intervals for T/R ratios were all within the acceptable bioequivalence range of 80.00% to 125.00%. Ana Ruiz-Garcia et al[14] observed bioequivalence in healthy volunteers following oral administration of palbociclib capsules under high-fat, low-fat, moderate-fat diets, and fasting conditions; food intake does not affect palbociclib exposure. There are no domestic research reports on the bioequivalence of palbociclib tablet dosage forms, this study provides the first evidence demonstrating the bioequivalence of palbociclib tablets in both fasting and postprandial states.

Common adverse effects of palbociclib include neutropenia, infection, leukopenia, fatigue, nausea, anemia, hair loss, and diarrhea. These adverse effects may be alleviated by dose reduction or temporary discontinuation of the drug. Few patients need to stop the drug permanently. Palbociclib was generally well tolerated with no specific cumulative or delayed toxicity.[15] All adverse reactions observed in this study were grade 1 and resolved following drug discontinuation. These results indicate that a single dose of palbociclib exhibits a favorable safety profile in healthy subjects.

In this trial, the T_{max} of the reference formulation palbociclib in the fasting group was 4.99 h, with an elimination half-life of 23.87 ± 3.91 h, while in the postprandial group, the T_{max} was also 4.99 h and the elimination half-life was 23.58 ± 3.57 h. These results suggest that eating does not affect the rate and extent of absorption of palbociclib, which is consistent with the findings of the Ana Ruiz-Garcia study.

Our study yielded encouraging outcomes; however, several limitations were identified. While our study confirmed the pharmacokinetic (PK) equivalence of the generic palbociclib to the reference product, comprehensive investigations remain necessary to establish therapeutic bioequivalence for biosimilars relative to their reference drugs. The trial's sample size also presented a limitation. To minimize drug exposure in participants, a two-period crossover design was employed involving 68 subjects. The limited sample size and single-dose administration design constrained a thorough safety evaluation of the two drugs. The participant cohort consisted of individuals who were relatively young and in good health, research on the application of this medicine in the elderly had not yet been explored.

Conclusion

Under both fasting and fed conditions, the palbociclib test tablet (T) formulation demonstrated comparable bioavailability to the reference (R) formulation, meeting bioequivalence (BE) requirements. Food did not affect the absorption of palbociclib. Both formulations demonstrated safety and tolerability. The results justify progression to the next phase of clinical trials for palbociclib tablets and aid in their clinical implementation within China.

Data Sharing Statement

The dataset utilized in this study is accessible through the corresponding author (Wanjun Bai) upon submission of a reasonable request.

Informed Consent

All participants provided written informed consent.

Disclosure

The authors report no competing interests.

References

1. Rybinska I, Mangano N, Tagliabue E, et al. Cancer-associated adipocytes in breast cancer: causes and consequences. *Int J Mol Sci*. 2021;22(7):3775. doi:10.3390/ijms22073775
2. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209–249. doi:10.3322/caac.21660
3. Kish JK, Ward MA, Garofalo D, et al. Real-world evidence analysis of palbociclib prescribing patterns for patients with advanced/metastatic breast cancer treated in community oncology practice in the USA one year post approval. *Breast Cancer Res*. 2018;20(1):37. doi:10.1186/s13058-018-0958-2
4. Dhillon S. Palbociclib: first global approval. *Drugs*. 2015;75(5):543–551. doi:10.1007/s40265-015-0379-9
5. Clark AS, McAndrew NP, Troxel A, et al. Combination paclitaxel and palbociclib: Results of a Phase I trial in advanced breast cancer. *Clin Cancer Res*. 2019;25(7):2072–2079. doi:10.1158/1078-0432.CCR-18-0790

6. Chu N, Zhang L, Wang J, et al. Bioequivalence study of palbociclib capsules in healthy Chinese subjects under fasting and fed conditions. *Clin Drug Invest*. 2021;42(1):1–11. doi:10.1007/s40261-021-01098-3
7. State Drug Administration. Announcement of the state drug administration on the release of the catalog of reference preparations for generic drugs (the twenty-second batch): no. 56 of 2019. 2019. Available from: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20190827163001195.html. Accessed October 30, 2022.
8. State Food and Drug Administration. Technical guidelines for human bioequivalence studies of generic chemical drugs using pharmacokinetic parameters as endpoint evaluation indicators. 2016. Available from: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20160318210001725.html. Accessed October 30, 2022.
9. State Food and Drug Administration. Circular of the general administration on the release of three technical guidelines on the selection and determination of reference preparations for general oral solid dosage forms: no. 61 of 2016. 2016. Available from: http://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20160318210001725.html. Accessed October 30, 2022.
10. Guiding principles for the validation of quantitative analysis methods for biological samples. National Pharmacopoeia Commission, 2020.
11. M13A the bioequivalence of oral solid immediate-release preparations. The International Conference on Harmonization, 2024.
12. Chao Wang Y, Wang Q, Dong J, et al. Study on the bioequivalence of palbociclib capsules in human. *China Pharm*. 2023;34(12):1498–1502.
13. Wang Q, Pan J, Fan X, et al. Bioequivalence study of palbociclib capsules in human under fasting and postprandial conditions. *Chin J Pharmacoepidemiol*. 2023;32(10):1104–1112.
14. Ruiz-Garcia A, Plotka A, O'Gorman M, Wang DD. Effect of food on the bioavailability of palbociclib. *Cancer Chemother Pharmacol*. 2017;79(3):527–533. doi:10.1007/s00280-017-3246-4
15. Dieras V, Rugo HS, Schnell P, et al. Long-term pooled safety analysis of palbociclib in combination with endocrine therapy for HR +/HER2- advanced breast cancer. *J Natl Cancer Inst*. 2019;111(4):419–430. doi:10.1093/jnci/djy109