



# Bioequivalence Study of Tebipenem Pivoxil in Healthy Chinese Adults

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## Abstract

**Background and Objective** Tebipenem pivoxil (TP) is a carbapenem and is applied against pneumonia, otitis media, and sinusitis. This study compared the pharmacokinetics (PK) and safety of a test (T) preparation and reference (R) preparation of TP in healthy Chinese adults.

**Methods** This study was a single-center, randomized, open, single-dose (fasting/postprandial) oral administration, two-agent, two-sequence, two-cycle, crossover bioequivalence trial. A total of 60 participants were enrolled (24 fasting and 36 postprandial). All participants were randomly assigned to the TR sequence and RT sequence. Subsequently, they switched T sequences or R sequences 7 days later. PK blood samples were collected according to the protocol, plasma TP concentration was determined by liquid chromatography-mass spectrometry, main PK parameters were calculated based on a non-compartment model, and adverse events were recorded during the test.

**Results** In the feeding arm, the geometric mean ratio of maximum concentration ( $C_{max}$ ) was 89.84% (90% confidence interval 84.33–95.70), the geometric mean ratio of area under the plasma concentration–time curve from time 0 to last time of quantifiable concentration ( $AUC_{0-t}$ ) was 86.80% (83.62–90.10), and the geometric mean ratio of area under the plasma concentration–time curve from time 0 to infinity time of quantifiable concentration ( $AUC_{0-\infty}$ ) was 86.90% (83.73–90.20), which were within the acceptable range of bioequivalence (80–125%). In the fasting arm, the geometric mean ratio of  $C_{max}$  was 96.07% (89.62–102.99), the geometric mean ratio of  $AUC_{0-t}$  was 93.09% (90.47–95.78), and the geometric mean ratio of  $AUC_{0-\infty}$  was 93.09% (90.48–95.77), which was within the acceptable range of bioequivalence (80–125%). Hence, the T preparation and R preparation of TP had bioequivalence in the fasting arm and feeding arm of the clinical trial. In addition, all adverse events were mild, and no severe adverse events were noted.

**Conclusion** Preparations T and R of TP were bioequivalent in the fasting and postprandial groups in clinical trials, and TP was safe.

## Key Points

Both the test preparation and the reference preparation of tebipenem granules showed bioequivalence and good safety in healthy Chinese participants under postprandial/fasting conditions. This study provided data support for the marketing of domestic tebipenem.

The granulated administration method used in this study can ensure drug exposure in vivo to a greater extent. A reference for drug administration in the granular dosage form in clinical trials was provided.

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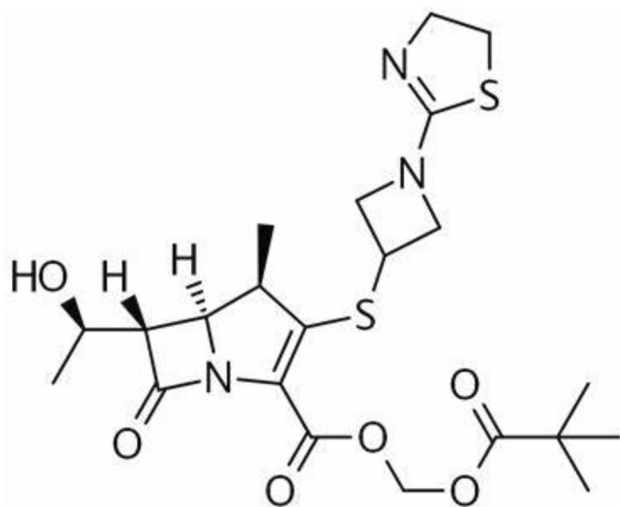
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## 1 Introduction

Tebipenem pivoxil (TP) is a carbapenem and is applied commonly against pneumonia, otitis media [1], and sinusitis [2]. TP restrains penicillin-binding proteins and destroys the cell walls of pathogens [3]; therefore, it is less toxic for mammals [4].

The chemical structure of TP is shown in Fig. 1. A structural peculiarity of TP is that thiazole at the C3 side chain forms a prodrug by interacting with C2 carboxylic acids [5], which results in assimilation of oral drugs. The oral absorption of TP is better than that of most  $\beta$ -lactam antibiotics. TP has a broad antibacterial spectrum. It has a stronger antibacterial activity than penicillin or cephalosporins. *Escherichia coli*, *Klebsiella* species, *Haemophilus* species, and *Legionella* species are more sensitive to TP than imipenem, cefdinir, amoxicillin, and levofloxacin in pediatric patients [6]. Recent in vitro and animal studies have shown TP to be active against *Shigella* species [7], and one clinical trial found that it could be effective against bacterial pneumonia in children [8].

The binding rate of TP to serum proteins in vitro is 67% [9]. TP can be distributed in the sputum, middle-ear mucosa, maxillary-sinus mucosa, tonsilla palatina (adults) [10], and middle-ear secretions (children) [11]. TP is absorbed from the gastrointestinal tract and has antibacterial activity [12]. The main excretion pathway of TP is urine [13]. Studies have shown that, in people with normal renal function and those with renal impairment (creatinine clearance rate [CCR] < 80 ml/min), after taking TP (250 mg, oral [p.o.] administration), renal clearance and urinary excretion are reduced, the area



**Fig. 1** Chemical structure of tebipenem pivoxil.  $C_{22}H_{31}N_3O_6S_2$  [(2,2-dimethylpropanoyl)oxy]methyl (4R,5S,6S)-3-[[1-(4,5-dihydro-1,3-thiazol-2-yl)azetidino-3-yl]sulfanyl]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylate

under the plasma concentration–time curve from time 0 to infinity time of quantifiable concentration ( $AUC_{0-\infty}$ ) and the maximum concentration ( $C_{max}$ ) is increased, and the elimination half-life ( $t_{1/2}$ ) is prolonged, together with deteriorated renal function (CCR < 80 ml/min) [14].

Pfizer (New York, NY, USA) were the first to develop TP. Then TP granules were developed by Meiji Seika Kaisha Ltd (Tokyo, Japan) in Aug 2009. But there are no TP granules in China's marketplace. The study of bioequivalence in clinical trials is extremely important for our clinical demand, and Lunan Pharmaceutical Group Corporation carried out such a trial in Zhejiang Provincial People's Hospital. The bioequivalence of TP acquired from Lunan Pharmaceutical Group (test [T] preparation) and TP (Orapenem<sup>®</sup>) obtained from Meiji Seika Kaisha Ltd (reference [R] preparation) was assessed in healthy people in the fasting state or fed state. At the same time, the pharmacokinetics (PK) and safety of the T preparation and R preparation were examined.

## 2 Materials and Methods

### 2.1 Ethics Authorization

The protocol for this clinical trial was ratified (certificate number 2019YW016) by the Ethics Committee of Zhejiang Provincial People's Hospital (Hangzhou, China) on 31 July 2019. The feeding arm and fasting arm of this clinical trial were started on 19 September 2019 and 22 October 2019, respectively, at the Phase I Clinical Research Center of Zhejiang Provincial People's Hospital. All the participants provided written informed consent and were screened. Finally, 60 people (24 in the fasting arm, 36 in the feeding arm) entered the clinical trial, and 59 people completed it (one participant of the feeding arm dropped out because of adverse events [AEs]).

### 2.2 Study Design

This was a single-center, randomized, open-label, single-dose, oral medication, two-drug crossover trial. TP produced by Lunan Pharmaceutical Group (T preparation) and Orapenem<sup>®</sup> (R preparation) were compared in terms of bioequivalence. A fasting group and a feeding group were created.

Thirty-six healthy people were required for the feeding group, and 35 of them completed this trial. Twenty-four healthy individuals formed the fasting group and finished this trial. All the participants were assigned randomly to TR sequences and RT sequences equally. Subsequently, they exchanged T sequences or R sequences after 7 days. In the feeding arm, the participants had to eat a high-fat diet (the total calories of the food were about 800~1000 kcal,

of which protein provided about 150 kcal, carbohydrates provided about 250 kcal, and fat provided about 500–600 kcal) before taking TP granules.

### 2.3 Inclusion Criteria

The inclusion criteria were as follows: (1) Chinese people aged  $\geq 18$  years and  $\leq 65$  years; (2) body weight  $\geq 50$  kg (men) and  $\geq 45$  kg (women); (3) body mass index (BMI) 19.0–26.0 kg/m<sup>2</sup>; (4) participant fully understood the content, process, and possible AEs of the clinical trial; and (5) participant could complete the clinical trial according to its requirements.

### 2.4 Exclusion Criteria

The exclusion criteria were as follows: (1) a serious disease that the investigator deemed inappropriate for this clinical trial; (2) a history of serious digestive problems, epilepsy, or vitamin K deficiency; (3) clinically significant abnormal laboratory examinations or specialist tests (e.g., electrocardiography); (4) positivity for hepatitis B virus surface antigen, hepatitis C virus antibodies, *Treponema pallidum* antibodies, or human immunodeficiency virus (HIV) antibodies; (5) an allergy; (6) use of drugs that could interact with TP or change levels of liver enzymes; (7) special diets (including fruit from the Rutaceae family [e.g., pitaya, mango] or food containing xanthine derivatives [e.g., tea, coffee]) or strenuous exercise (football, basketball, or running  $> 30$  min); (8) tobacco smoking or regular consumption of alcohol; (9) a history of drug abuse/addiction; (10) donation of blood or a bleed  $> 400$  ml within 3 months before screening; (11) breastfeeding upon screening or would be breastfeeding after screening; (12) planning to have a child within the time from screening to 3 months after the end of the clinical trial, or unwilling to take contraception; (13) enrolment in another clinical trial and had taken a test drug within 3 months before screening, or participating in another clinical trial; (14) cannot tolerate venipuncture or had difficulty providing venous blood; (15) cannot follow a consistent diet (e.g., people who were lactose intolerant); (16) CCR  $< 80$  ml/min; and (17) poor compliance or other factors deemed unsuitable for this clinical trial according to the lead investigator.

### 2.5 Estimation of Sample Size

#### 2.5.1 Feeding Arm

Men and women were enrolled according to the Guidelines for Bioequivalence Studies issued by the National Medical Products Administration of China. High variation of TP

is not mentioned in the Guiding Principles for Bioequivalence Research of Tebipenem issued by the US Food and Drug Administration (FDA). In the bioequivalence study of TP, the intraindividual coefficient of variation (CV) of  $C_{\max}$  was 32.8%, the intraindividual CV of area under the plasma concentration–time curve from time 0 to last time of quantifiable concentration ( $AUC_{0-t}$ ) was 20.0%, and the intraindividual CV of  $AUC_{0-\infty}$  was 20.0%. If the significance level of the T preparation was set as 0.05/0.0491, the power would be 92.44/97.88 and the T/R would be 80–125%, and the cutoff would be set as 0.8–1.25. As a result, the minimum sample size would be 28. With the expulsion rate taken into account as 20%, the final enrolment number planned was 36.

#### 2.5.2 Fasting Arm

High variation of TP is not mentioned in the Guiding Principles for Bioequivalence Research of Tebipenem issued by the US FDA. In the bioequivalence study of TP, the intraindividual CV of  $C_{\max}$  was 34.1%, the intraindividual CV of  $AUC_{0-t}$  was 18.9%, and the intraindividual CV of  $AUC_{0-\infty}$  was 18.9%. If the significance level of the T preparation was set as 0.05, the power would be 0.80 and T/R would be 80–125%, and the cutoff would be set as 0.8–1.25. As a result, the minimum sample size would be 24.

### 2.6 Detection Method

The analytical method was liquid chromatography–mass spectrometry (LC-MS). The internal standard was tebipenem. The chromatographic column was Chr. C-100 CAPCELLPAKCR 1:4 2.0 mmI. D $\times$ 50 mm 5  $\mu$ ml OT:CR-10S/N:U16IE01088 Shiseido. The mobile phase was A (formic acid:saline:ultrapure water at 1:10:2000, v/v/v) and B (methyl alcohol:acetonitrile at 4:1, v/v). The flow rate was 0.4000 ml/min, and the sample size was 5  $\mu$ l. The detector was API4000 (SCIEX, Framingham, MA, USA). The LC-MS system consisted mainly of the Shimadzu LC-20AD system. The sample pretreatment method was protein precipitation. The linear range of tebipenem concentration was 5–5000 ng/ml, and the lower limit of quantitation was 5 ng/ml.

### 2.7 PK Assessments

Plasma samples were collected from all participants to measure TP levels at 0, 5, 10, 15, 30, and 45 min, as well as at

1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, and 10 h after TP administration. Samples of whole blood were placed in an ice bath before centrifugation ( $1700 \times g$  for 10 min at  $2-8^\circ\text{C}$ ) to collect plasma and stored at  $-70 \pm 10^\circ\text{C}$  for analyses.

## 2.8 PK Parameters

The drug level in blood was based on the non-compartmental model and calculated by SAS 9.3 ([www.sas.com/](http://www.sas.com/), America).  $C_{\max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-\infty}$ , time to reach maximum concentration ( $T_{\max}$ ),  $t_{1/2}$ , elimination rate constant ( $\lambda_z$ ), and  $AUC_{-\% \text{Extra}}$  (formula:  $[(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty}] \times 100\%$ ) were measured.

## 2.9 Safety Assessments

Safety assessments were based on clinical symptoms, laboratory measurements, AEs, physical examination, 12-lead electrocardiography, and vital signs. The AEs (clinical manifestations, severity, duration, treatment measures, outcome) were recorded to ascertain the relationship between AEs and TP.

## 2.10 TP Administration

### 2.10.1 Feeding Arm

All participants ate a high-fat meal 30 min before taking TP. They finished eating their meal within 30 min. The T preparation or R preparation was taken punctually.

### 2.10.2 Granules of TP Administration Route

TP granules (0.5 g, including 50 mg [potency] TP) were dissolved in a glass containing 240 ml of water. The participants took TP granules three times. First, the TP granules were dissolved in about 80 ml of water. Then a muddler was used to stir the granules in suspension. Participants took the TP immediately. Second, the residual TP was rinsed using a muddler and about 80 ml of water. Participants took the TP immediately. Third, residual TP on the muddler and glass was rinsed using remanent water, and the muddler was used for stirring. The participants took the TP immediately. The entire drug-taking process had to be completed in 1 min and the participants were not allowed to chew. The participants were not allowed to drink water 1 h before or after taking TP.

### 2.10.3 Fasting Arm

At about 8 a.m., the participants took TP as a T preparation or R preparation. The administration was as described in the feeding arm.

## 3 Results

### 3.1 Characteristics of Participants at Baseline

#### 3.1.1 Feeding Arm

Thirty-six people (30 men and six women) participated, and 35 individuals completed this part of the clinical trial. The mean age of the study cohort was  $26 \pm 5$  years. The bodyweight range was 51.4–78.4 kg. The BMI range was 19.4–25.5  $\text{kg}/\text{m}^2$ . The height range was 152.0–181.5 cm.

#### 3.1.2 Fasting Arm

Twenty-four individuals (21 men and three women) completed this part of the clinical trial. The mean age of the study cohort was  $26 \pm 5$  years. The bodyweight range was 54.3–84.7 kg. The BMI range was 19.6–25.4  $\text{kg}/\text{m}^2$ . The height range was 157.0–182.5 cm.

### 3.2 PK and Statistical Analyses

The individuals were separated into different sequences on the basis of random results (TR or RT). Blood samples were collected at 5, 10, 15, 30, and 45 min, as well as at 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, and 10 h after taking TP.

### 3.3 PK Characteristics

#### 3.3.1 $C_{\max}$

In the fasting arm, the  $C_{\max}$  of the T preparation and R preparation of TP was  $3050 \pm 499$  ng/ml and  $3189 \pm 600$  ng/ml, respectively. The ratio of the logarithmic geometric mean of  $C_{\max}$  was 96.07%. The 90% confidence interval (CI) was 89.62–102.99, and power was 99.68%.

In the feeding arm, the  $C_{\max}$  of the T preparation and R preparation of TP was  $1016 \pm 347$  ng/ml and  $1134 \pm 372$  ng/ml, respectively. The ratio of the logarithmic geometric mean of  $C_{\max}$  was 89.84%. The 90% CI was 84.33–95.70, and power was 92.44%.

#### 3.3.2 $T_{\max}$

In the fasting arm, the  $T_{\max}$  of the T preparation and R preparation of TP was  $0.40 \pm 0.16$  h (median 0.50 h; geometric mean 0.40 h) and  $0.35 \pm 0.13$  h (median 0.38 h; geometric mean 0.35 h), respectively. In the feeding arm, the  $T_{\max}$  of the T preparation and R preparation of TP was  $1.02 \pm 0.75$

h (median 1.33 h; geometric mean 1.02 h) and  $1.19 \pm 0.88$  h (median 1.50 h; geometric mean 1.19 h), respectively.

There was no significant difference in the  $T_{max}$  of TP between the T preparation and R preparation according to the non-parametric test.

### 3.3.3 $AUC_{0-t}$

In the fasting arm, the  $AUC_{0-t}$  of the T preparation and R preparation of TP was  $2831 \pm 560$  h\*ng/ml and  $3039 \pm 575$  h\*ng/ml, respectively. The ratio of the logarithmic geometric mean of  $AUC_{0-t}$  was 93.09%. The 90% CI was 90.47–95.78, and power was 100%.

In the feeding arm, the  $AUC_{0-t}$  of the T preparation and R preparation of TP was  $2289 \pm 518$  h\*ng/ml and  $2633 \pm 527$ h\*ng/ml, respectively. The ratio of the logarithmic geometric mean of  $AUC_{0-t}$  was 86.80%. The 90% CI was 83.62–90.10, and power was 97.88%.

### 3.3.4 $AUC_{0-\infty}$

In the fasting arm, the  $AUC_{0-\infty}$  of the T preparation and R preparation of TP was  $2843 \pm 563$  h\*ng/ml and 3052

$\pm 576$  h\*ng/ml, respectively. The ratio of the logarithmic geometric mean of  $AUC_{0-\infty}$  was 93.09%. The 90% CI was 90.48–95.77, and power was 100%.

In the feeding arm, the  $AUC_{0-\infty}$  of the T preparation and R preparation of TP was  $2302 \pm 518$  h\*ng/ml and  $2645 \pm 529$  h\*ng/ml, respectively. The ratio of the logarithmic geometric mean of  $AUC_{0-\infty}$  was 86.90%. The 90% CI was 83.73–90.20, and power was 98.18%.

### 3.3.5 Summary of Primary PK Parameters

The primary PK parameters ( $AUC_{0-t}$ ,  $AUC_{0-\infty}$ ,  $t_{1/2}$ ,  $C_{max}$ ) of our study are shown in Tables 1 and 2. Mean plasma concentration–time curves for TP are shown in Fig. 2.

## 3.4 Statistical Analyses

### 3.4.1 Fasting arm

A total of 1824 plasma samples (912 test samples and 912 backup samples) were collected for the fasting arm. The ratio of the logarithmic geometric mean of the  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  of the T preparation and R preparation of TP was 96.07%, 93.09%, and 93.09%, respectively. The

**Table 1** Pharmacokinetics of the fasting arm

	T preparation			R preparation		
	N	Mean (SD)	%CV	N	Mean (SD)	%CV
$T_{max}^*$ (h)	24	0.50 (0.25–0.75)	36.5	24	0.38 (0.25–0.50)	34.1
$C_{max}$ (ng/ml)	24	3050 (499)	16.4	24	3189 (600)	18.8
$AUC_{0-t}$ (h*ng/ml)	24	2831 (560)	19.8	24	3039 (575)	18.9
$AUC_{0-\infty}$ (h*ng/ml)	24	2843 (563)	19.8	24	3052 (576)	18.9
$t_{1/2}$ (h)	24	0.95 (0.28)	29.4	24	0.94 (0.19)	20.3

\* $T_{max}$  is expressed by the median (minimum - maximum value)

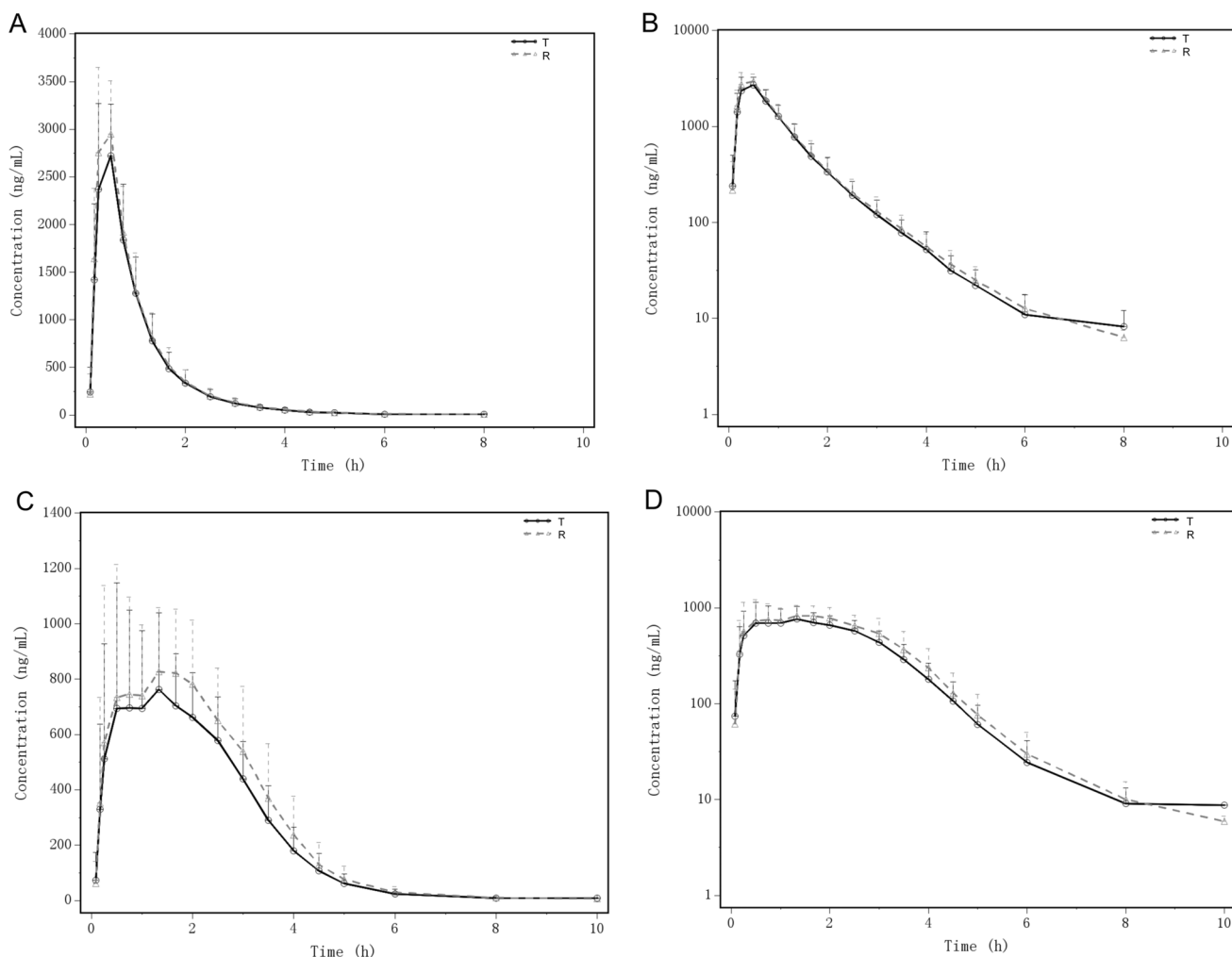
$AUC_{0-\infty}$  area under the plasma concentration–time curve from time 0 to infinity time of quantifiable concentration,  $AUC_{0-t}$  area under the plasma concentration–time curve from time 0 to last time of quantifiable concentration,  $C_{max}$  maximum concentration, CV coefficient of variation, R reference, T test,  $t_{1/2}$  elimination half-life,  $T_{max}$  time to maximum concentration

**Table 2** Pharmacokinetics of the feeding arm

	T preparation			R preparation		
	N	Mean (SD)	%CV	N	Mean (SD)	%CV
$T_{max}^*$ (h)	35	1.33 (0.25–3.00)	58.9	36	1.50 (0.25–3.00)	58.8
$C_{max}$ (ng/ml)	35	1016 (347)	34.1	36	1134 (372)	32.8
$AUC_{0-t}$ (h*ng/ml)	35	2289 (518)	22.6	36	2633 (527)	20.0
$AUC_{0-\infty}$ (h*ng/ml)	35	2302 (518)	22.5	36	2645 (529)	20.0
$t_{1/2}$ (h)	35	0.78 (0.15)	19.7	36	0.81 (0.17)	21.2

\* $T_{max}$  is expressed by the median (minimum - maximum value)

$AUC_{0-\infty}$  area under the plasma concentration–time curve from time 0 to infinity time of quantifiable concentration,  $AUC_{0-t}$  area under the plasma concentration–time curve from time 0 to last time of quantifiable concentration,  $C_{max}$  maximum concentration, CV coefficient of variation, R reference, T test,  $t_{1/2}$  elimination half-life,  $T_{max}$  time to maximum concentration



**Fig. 2** Mean plasma concentration–time curves for TP. **A** Mean plasma concentration–time curve for TP after a single oral dose in the fasting state. **B** Mean plasma concentration–time curve for TP after a single oral dose in the fasting state (semi-logarithmic graph). **C** Mean plasma concentration–time curve for TP after a single oral dose after

meals. **D** Mean plasma concentration–time curve for TP after a single oral dose after meals (semi-logarithmic graph). Note: Error bars represent the standard deviation. R reference, T test, TP tebipenem pivoxil

90% CI for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  was 89.62–102.99, 90.47–95.78, and 90.48–95.77, respectively. The CV of  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  was 14.09%, 5.75%, and 5.75%, and power was 99.68%, 100%, and 100%, respectively.

$C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  was 15.75%, 9.25%, and 9.23%, and power was 92.44%, 97.88%, and 98.18%, respectively.

### 3.4.2 Feeding arm

A total of 2698 plasma samples (1349 test samples and 1349 backup samples) were collected for the feeding arm. The ratio of the logarithmic geometric mean of the  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  of the T preparation and R preparation of TP was 89.84%, 86.80%, and 86.90%, respectively. The 90% CI for  $C_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-\infty}$  was 84.33–95.70, 83.62–90.10, and 83.73–90.20, respectively. The CV of

### 3.5 Safety Analyses

In the feeding arm, ten AEs occurred in four participants. In patient C001 (who had a T preparation of TP), alterations in levels of alanine transaminase, aspartate transaminase, and glutamyl transpeptidase were noted on 1 October 2019 (last day of the feeding arm of our clinical trial). These alterations had a relationship with the T preparation of TP according to the lead investigator. In patient C027 (T preparation of TP), an increase in the level of low-density lipoprotein-cholesterol was noted on 1 October 2019, and it had a relationship with the T preparation of TP. Patient C031 (R preparation of TP) experienced urticaria on 25 September 2019 (day 1 of

cycle 1), followed by increases in levels of bilirubin, direct bilirubin, and indirect bilirubin on 29 September 2019, and these AEs had a relationship with the R preparation of TP. Patient C017 (R preparation of TP) experienced an increased urinary level of glucose, but a relationship with TP was not suspected. A total of 32 out of 36 trial participants did not suffer AEs, and serious adverse events (SAEs) were not documented in any participant.

In the fasting arm, ten AEs occurred in five participants. In patient K003 (R preparation of TP), an increase in urinary leukocytes and a decrease in hemoglobin level were noted, but a relationship with the R preparation of TP was not suspected. Patient K007 (R preparation of TP) experienced an increase in levels of direct bilirubin, indirect bilirubin, and bilirubin, and these AEs had a relationship with the R preparation of TP. Patient K011 (R preparation of TP) experienced a left-ventricular high voltage and sinus arrhythmia, but a relationship with the R preparation of TP was not suspected. Patient K018 (R preparation of TP) had increased levels of direct bilirubin and bilirubin, and a relationship with the R preparation of TP was suspected. Patient K019 (T preparation of TP) experienced proteinuria, and this AE had a relationship with the T preparation of TP. Nineteen of 24 participants did not suffer an AE, and no participants suffered an SAE.

These results showed that the T preparation and R preparation of TP were safe.

## 4 Discussion

TP granules have been used to treat pneumonia, otitis media [1], and sinusitis [2]. Some scholars have suggested that TP should be used only if other antibiotics have proved non-efficacious [2, 2]. It was approved for sale in Japan in Aug 2009. In China, there is an urgent need for the development of domestic TP granules to address domestic clinical needs. The bioequivalence of the T preparation (produced by Lunan Pharmaceutical Group) and R preparation (Orapenem<sup>®</sup>) holds, and the preparations were well tolerated and safe. There were non-conspicuous differences in laboratory parameters, vital signs, and electrocardiography, and no SAEs, deaths, or withdrawal-related AEs were documented.

The study design referred to technical guidelines for the study of human bioequivalence of chemical generic drugs, with PK parameters as the end point evaluation index. Although TP granules are children's drugs [16], the study needed healthy and non-uniform sex adult volunteers. A CCR of < 80 could not be adopted in our bioequivalence trial; the literature of Nakashima et al. showed that CCR is important for TP granules absorption and metabolism [14]. In addition, it was found in a previous clinical trial that, compared with a single oral dose of tebipenem granules (200 potency), tebipenem combined with famotidine and antacids

(dried aluminum hydroxide gel, magnesium hydroxide), which increase gastric pH value, reduced plasma  $C_{max}$  by about 40–60% and  $AUC_{0-\infty}$  by 20–30%. The excretion rate in urine is reduced by about 20%, and the  $T_{max}$  is extended by 10–30 min [17]. Compared with tebipenem alone, the  $C_{max}$  and  $AUC_{0-\infty}$  of plasma tebipenem were increased,  $t_{1/2}$  was prolonged, renal clearance was decreased, and urinary excretion rate of tebipenem was decreased when tebipenem was combined with probenecid [18]. In view of the above data, these drugs are listed as contraindicated drugs in this trial.

Nakashima and colleagues [13] investigated the PK characteristics of TP (250 mg, p.o.) using a fasting arm and feeding arm in healthy adult men. In that study, the  $C_{max}$  of the feeding arm was lowered to about 60% that of the fasting arm, but  $AUC_{0-\infty}$  was approximately identical. Their data are, in general, consistent with our clinical trial (Tables 1 and 2). Food intake prolonged the  $T_{max}$  of TP in plasma, which is consistent with the trend reported in the literature of Nakashima and colleagues [13]. The clinical trials by Nakashima and colleagues compared the influence of food on the cumulative urinary excretion rate of TP; they found that food had almost no effect upon it. However, data on TP cumulative urinary excretion were not collected in our clinical trial. Therefore, the study may have a limitation in that the feeding arm compared differences in PK parameters in blood between the T preparation and R preparation after consumption of a high-fat diet, but the differences in the cumulative urinary excretion rate of TP were not compared. In the subsequent trials, the test of cumulative urine excretion rate of tebipenem could be taken into consideration.

The safety of TP has been demonstrated in a clinical trial in Japan [19]. In that clinical trial, 101 of 440 hospitalized children (23%) developed AEs. The main AE was diarrhea (19.5%). In another safety review, 23 of 432 patients (5.3%) had abnormal fluctuations in clinical laboratory parameters, with increased platelet counts as the primary AE. In this clinical trial, there were no adverse reactions (such as diarrhea, increased platelet count) that were common in previous clinical trials. The most common adverse reactions were abnormal liver function (four cases, 6.7%), such as elevated levels of alanine aminotransferase, aspartate aminotransferase, glutamyl transpeptidase, direct bilirubin, indirect bilirubin, and bilirubin. The differences in the types and rates of AEs may be related to the small size of the included population and sample size.

The unique administration method of granules should also be considered in this study. Granules cannot be swallowed like tablets, nor can they form a homogeneous liquid. An incorrect administration method may have led to inaccurate individual doses, resulting in the bioequivalence of T preparation and R preparation being invalid. The method of administration in this study can be used as a reference for granules administration.

## 5 Conclusions

In the fasting arm and feeding arm of this clinical trial, the T preparation and R preparation of TP were bioequivalent. No SAEs occurred in participants. TP appears to be a safe product.

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## Declarations

**Ethics Approval and Consent to Participate** This study passed the Medical Ethics Committee of Zhejiang Provincial People's Hospital review on 31 July 2019, and approval was obtained (no. 2019YW016). Written informed consents were obtained from all participants.

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**Competing Interests** Rui Hao, Yiming Shao, Sisi Lin, Yi Wu, Li Bian, and Yiwen Zhang declare no conflicts of interest.

**Consent for Publication** Not applicable.

**Code Availability** This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, the license permits any non-commercial use, sharing, adaptation, distribution, and reproduction in any format or medium.

**Authors' Contributions** This study was designed by YZ. RH contributed most to this work, and all authors read and approved the manuscript.

**Availability of Data and Materials** The data supporting the conclusions of this article are included within the article.

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