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ARTICLE

Bioequivalence of two oral formulations of tebipenem pivoxil hydrobromide in healthy subjects

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Abstract

Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is a novel oral carbapenem prodrug of tebipenem (TBP), the active moiety, currently in development for treating serious bacterial infections. This study assessed the bioequivalence (BE) of the clinical trial and registration tablet formulations of TBP-PI-HBr and evaluated the effect of food on the pharmacokinetics (PKs) of tebipenem. This was a single center, open-label, randomized, single-dose, three-sequence, four-period crossover, BE, and food-effect study. Subjects received single 600 mg oral doses of TBP-PI-HBr as the reference clinical trial tablet (treatment A) and test registration tablet (treatment B) formulations in alternating sequence while fasting, and then the test formulation under fed conditions. Whole blood samples were collected predose and at specified intervals up to 24 h postdose to evaluate TBP PK parameters. Safety and tolerability were monitored. Thirty-six healthy, adult subjects were enrolled and completed the study. The criteria for BE were met for the TBP-PI-HBr test (registration tablet) and reference (clinical trial tablet) formulations as the 90% confidence intervals for the geometric mean ratios for TBP area under the curve $(AUC)_{0\text{-}t}$, $AUC_{0\text{-inf}}$, and maximum plasma concentration (C_{max}) fell within the established 80% to 125% BE limits. Dosing with food had no meaningful effect on TBP PK parameters. Five (14%) subjects reported adverse events (AEs) of mild severity. No deaths, serious AEs, or discontinuations due to AEs were reported, and no clinically relevant electrocardiograms, vital signs, or safety laboratory findings were observed. The study results demonstrate the BE of oral TBP-PI-HBr registration and clinical trial tablet formulations and indicate that TBP-PI-HBr can be administered without regard to meals.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Tebipenem pivoxil hydrobromide (TBP-PI-HBr) prodrug was developed as the first oral carbapenem for treatment of serious bacterial infections due to gram-positive and gram-negative bacteria, including drug-resistant pathogens. The

TBP-PI-HBr formulation was developed for use in phase I and phase III clinical studies during clinical development. However, the oral tablet formulation was modified for registration purposes. Because the registration formulation had differences than the formulation used in early clinical development, a bioequivalence (BE) study was conducted and, within the same study, a food effect evaluation arm also was included.

WHAT QUESTION DID THIS STUDY ADDRESS?

This study evaluated the BE of a 300 mg TBP-PI-HBr registration tablet (test) formulation developed for commercial use (i.e., the intended marketed formulation) and the 300 mg clinical trial tablet formulation (reference) in healthy adults under fasting conditions and the effect of food on tebipenem (TBP) pharmacokinetics (PKs) for the registration tablet formulation.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

Clinical study and registration tablet formulations of oral TBP-PI-HBr were bioequivalent and administration of the registration tablet with food had no clinically relevant effect on the PK profile of TBP.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

The registration tablet formulation of oral TBP-PI-HBr is comparable to the clinical study formulation and can be administered without regard to meals for the treatment of serious bacterial infections.

INTRODUCTION

Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is a novel oral prodrug of active moiety tebipenem (TBP), a carbapenem antimicrobial that exhibits broad-spectrum in vitro and in vivo activity against both gram-positive and gram-negative bacteria, including extended-spectrum-β-lactamase-producing and fluoroquinolone-resistant Enterobacterales.[1] An unmet need exists for novel oral antimicrobials to treat severe bacterial infections, in particular when caused by drug-resistant pathogens. TBP-PI-HBr is in clinical development for the treatment of serious bacterial infections (e.g., complicated urinary tract infections), including those caused by multidrug-resistant pathogens.

The safety and pharmacokinetic (PK) profiles of TBP-PI-HBr were previously evaluated in a single and multiple-ascending dose study.[2] Following single oral doses of TBP-PI-HBr (100 to 900 mg), plasma exposure of TBP, the active moiety, increased in a dose proportional manner, with a mean TBP terminal half-life ($t_{½}$) of 1 h, and was consistent in the fasted and fed state. TBP plasma PK parameters were unchanged following dosing of 300 mg or 600 mg TPB-PI-HBr every 8 h over 14 days, and no accumulation was observed. The safety and PK properties of oral TBP-PI-HBr at the proposed clinical dose of 600 mg have been further characterized in subsequent phase I and phase III studies utilizing a TBP-PI-HBr 300 mg clinical trial tablet formulation.[2–5] The objective of this study was to evaluate the bioequivalence (BE) of a 300 mg TBP-PI-HBr registration tablet formulation (test) developed for the intended market formulation and the 300 mg clinical trial tablet formulation (reference) in healthy adults under fasting conditions at therapeutic dose (600 mg). Additionally, the effect of food on TBP PK for the registration tablet formulation and safety and tolerability of TBP-PI-HBr in healthy adult subjects was also evaluated.

METHODS

The study was conducted in accordance with the US Code of Federal Regulations and ethical principles of the Declaration of Helsinki, Good Clinical Practices, and the International Council for Harmonization guidelines. The study protocol and all amendments were reviewed by an institutional review board for the study center (Advarra). Informed consent was obtained from each subject in writing before randomization.

Study design

This study was designed based on the US Food and Drug Administration (FDA) guidelines for assessment of BE.[6,7] This was an open-label, randomized, single-dose, semi-replicate, three-sequence, four-period crossover, BE (under fasted conditions), and food-effect study (clinicaltrials.gov: NCT04421885). Subjects were randomized to one of three sequences (B-A1-A2-C, A1-B-A2-C, or A1-A2-B-C) and received a single oral dose of TBP-PI-HBr 600 mg (2 × 300 mg tablets) in each of four periods in a crossover design. In periods 1–3, subjects received either the reference clinical study tablet (treatment A) or the test registration tablet (treatment B) formulation under fasted conditions. In period 4, all subjects received the test registration tablet formulation under fed conditions (treatment C). Each subject received treatment A on two separate occasions, and treatments B and C on only one occasion each. A washout period of at least 7 days occurred between doses. Subjects were confined to the clinical research unit for the duration of the study.

On day 1 of treatment A and B sequences, doses were administered with 240 ml of water following an overnight fast of at least 10 h and fasting continued for at least 4 h postdose. Water (except water provided with each dosing) was restricted 1 h prior to and 1 h after each dose, but was allowed as needed at all other times. Other fluids could be given as part of meals and snacks but were restricted at all other times throughout the confinement period. On day 1 of treatment C, subjects were required to fast overnight for at least 10 h until 30 min prior to their scheduled dose, when they were given a high fat/high calorie breakfast, which was consumed within 30 min.[6] Subjects fasted for at least 4 h postdose.

Subject selection

Adult men or women 18 to 55 years of age inclusive were eligible if they had a body mass index ≥18.0 and ≤32.0 kg/m^2 and were medically healthy without clinically significant findings on medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG) or clinical laboratory testing. Women were non-pregnant and non-lactating, and if not postmenopausal, were required to use an acceptable form of contraception throughout the study.

Subjects were excluded for a history of any clinically significant medical or psychiatric condition that could interfere with the conduct of the study. In addition, subjects were excluded for a history or presence of alcoholism or drug abuse within the past 2 years; hypersensitivity reactions to study drug or related compounds; or any condition that could affect drug absorption. Use of any prescription or non-prescription medications within 14 days; use of any drugs known to be significant inducers of cytochrome P450 (CYP) 2C19 or CYP3A4 enzymes and/or P-glycoprotein; or use of any gastric acid-reducing medications; valproic acid or divalproex sodium; probenecid; and herbal products prior to the dosing and throughout the study was prohibited.

Study assessments

Study assessments included complete physical examinations, vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and oral temperature), 12-lead ECG, clinical laboratory tests (e.g., hematology, biochemistry, coagulation, and urinalysis), and monitoring of adverse events (AEs).

Whole blood samples were collected at the following timepoints: predose (0) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h postdose. Whole blood samples were assayed for TBP using a validated liquid chromatography tandem mass spectrometry method (Charles River Laboratories). Sample preparation involved addition of isopropyl alcohol (IPA) as a stabilizer during whole blood collection to prevent conversion of tebipenem pivoxil (TBP-PI) to TBP following sample collection. A 25 µl aliquot of mixed matrix (whole blood: IPA, [1:1], v/v) samples were extracted with 100% acetonitrile protein precipitation followed by dilution (1:4, v/v), with milli-Q water. A gradient program was used to elute the analytes using 0.1% formic acid in water and 0.1% formic acid in acetonitrile as mobile phase solvents, at a flow-rate of 0.65 ml/min. The total run time was 2.75 min and the retention times for the internal standard (tebipenem-D^5) and TBP was ~0.55–0.65 min.[8] The lower limit of quantitation for TBP was less than 0.0072 µg/ml. TBP-PI (prodrug) was not measured as based on previous results, TBP-PI was not detected in human plasma.[2] TBP blood concentrations were converted to plasma concentrations before the PK analysis using the following formula: plasma concentration = reported blood concentration × 3.6, where 3.6 represents the product of 1/plasmatocrit value of 1.8 (using an average plasmatocrit value of 0.55) and IPA dilution factor of 2.

Pharmacokinetic analysis

The following PK parameters were calculated using non-compartmental methods based on plasma TBP concentrations: area under the concentration-time curve from time 0 to the last observed non-zero concentration calculated by the linear trapezoidal method ($AUC_{0\text{-}t}$); area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-inf}}$); percent of $AUC_{0\text{-inf}}$ extrapolated, represented as $(1-AUC_{0\text{-}t}/AUC_{0\text{-inf}})\times 100$ ($AUC_{\%extrap}$); last observed (quantifiable) plasma concentration (C_{last}); maximum observed concentration (C_{max}); time to reach C_{max} (T_{max}); apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve (K_{el}); apparent first-order elimination $t_{½}$ calculated as 0.693/K_{el}; and time to reach C_{last}. All PK evaluations were performed using Phoenix WinNonlin version 8.1 or higher (Certara Inc.).

Statistical analysis

This sample size estimate was based upon a within-subject SD of 0.3 for TBP AUC assuming the residual variability would be 0.75 times the within-subject variability due to the use of a three-period crossover design for the BE portion of this study. Using this estimate of variability, a study including 36 subjects had a greater than 90% power to show BE to traditional.

BE limits of 0.80 to 1.25 assuming no true difference in the test (registration) and reference (clinical) formulation. Given that the TBP C_{max} appeared to be highly variable with SD (log scale) greater than 0.4, a replicate design was utilized where the reference product was repeated in two treatment periods.[7] This allowed a reference-scaled BE limit to be used for AUC or C_{max} when the within-subject SD was greater than 0.294. The sample size was considered sufficient to evaluate the magnitude of the potential food-effect on TBP PK.

Either a two one-sided test procedure or a reference-scaled average BE approach was used to assess the BE for AUC_{0-t}, AUC_{0-inf}, and C_{max} of TBP. The two one-sided test procedure was used if the within-subject variability was less than 0.294 (intrasubject coefficient of variation <30%). Within-subject variability for a specific PK parameter of the reference product was first determined through a model-based approach using a linear mixed model. Comparison of the test and reference PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max}) was conducted using an analysis of variance (ANOVA) model on log transformed PK parameters. To assess the effect of dosing with food on TBP PK, an ANOVA was performed on ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}. The ANOVA model included treatment as a fixed effect (for treatments B and C only) and subject as a random effect with calculation of least squares means (LSMs) and the difference between treatment LSMs. Point estimates and 90% confidence intervals (CIs) were constructed for the relevant contrasts from the ANOVA models. The point estimates and 90% CIs were back-transformed to provide estimates of the ratios of the geometric LSM and corresponding 90% CI. In the BE analysis, estimated geometric means were presented for each treatment, and ratios were expressed as a percentage relative to the reference treatment (treatment A). In the food effect analysis, estimated geometric means were presented for the fed and fasted state expressed as a percentage relative to the fasted state (treatment B). All statistical analyses were conducted using SAS version 9.4.

RESULTS

Thirty-six subjects were enrolled and completed the study, and all were included in PK and safety analyses. Baseline

TABLE 1 Baseline characteristics

	Treatment sequence		
	A1-A2-B-C (n = 12)	**A1-B-A2-C (n = 12)**	**B-A1-A2-C (n = 12)**
Age, years[a]	39.0 ± 8.4	41.3 ± 8.1	43.6 ± 6.8
Age range, years	21–54	20–54	31–55
Female, n (%)	5 (42)	3 (25)	3 (25)
Body mass index, kg/m^2[a]	27.7 ± 3.4	26.4 ± 2.8	28.1 ± 2.2
Race, n (%)			
White	12 (100)	10 (83)	11 (92)
Black or African American	0	2 (17)	1 (8)
Hispanic or Latino, n (%)	8 (67)	9 (75)	9 (75)

Note: Treatment A1: First administration of 600 mg (2 × 300 mg tablets) TBP-PI-HBr clinical study tablet administered at hour 0 on day 1, under fasted conditions.

Treatment A2: Second administration of 600 mg (2 × 300 mg tablets) TBP-PI-HBr clinical study tablet administered at hour 0 on day 1, under fasted conditions.

Treatment B: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fasted conditions.

Treatment C: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fed conditions.

Abbreviation: TBP-PI-HBr, tebipenem pivoxil hydrobromide.

[a]Mean ± SD.

characteristics are presented in Table 1. Most subjects were men (69%), White (92%), and with a mean age of 41 years.

Pharmacokinetics

Mean plasma TBP C_{max} was similar following administration of single doses of the clinical and the registration tablet formulation under fasted conditions (Figure 1). TBP geometric mean $AUC_{0\text{-}t}$, $AUC_{0\text{-inf}}$, and C_{max} values were comparable for the clinical (treatment A) and the registration tablet formulation (treatment B). TBP median T_{max} was ~1 h (range: 0.5–2.0 h) for the clinical and 1.3 h (range: 0.5–2.0 h) for the registration tablet formulation (Table 2). Similarly, mean $t_{½}$ values were comparable (range: 1.1 to 1.2 h) between the clinical and the registration tablet formulation under fasted conditions.

Mean plasma TBP concentrations over time were similar under fed and fasted conditions (Figure 2). When comparing TBP PK under fasted and fed conditions, geometric mean $AUC_{0\text{-}t}$ and $AUC_{0\text{-inf}}$ values were comparable for the registration tablet formulation under fasted (treatment B) and fed (treatment C) conditions (Table 2). The geometric mean C_{max} was lower under fed relative to fasted conditions (8.8 vs. 10.1 µg/ml). Median T_{max} was slightly delayed to 1.5 h (range: 0.7–4.0 h) for the registration tablet formulation under fed conditions, relative to fasted conditions (1.5 vs. 1.3 h). TBP mean $t_{½}$ was generally similar for the registration tablet formulation under fasted and fed conditions (1.2 vs. 1.0 h).

Based on the statistical comparisons of ln-transformed plasma TBP $AUC_{0\text{-}t}$, $AUC_{0\text{-inf}}$, and C_{max}, the reference (registration tablet formulation) formulation was bioequivalent to the test (clinical tablet formulation), as the 90%

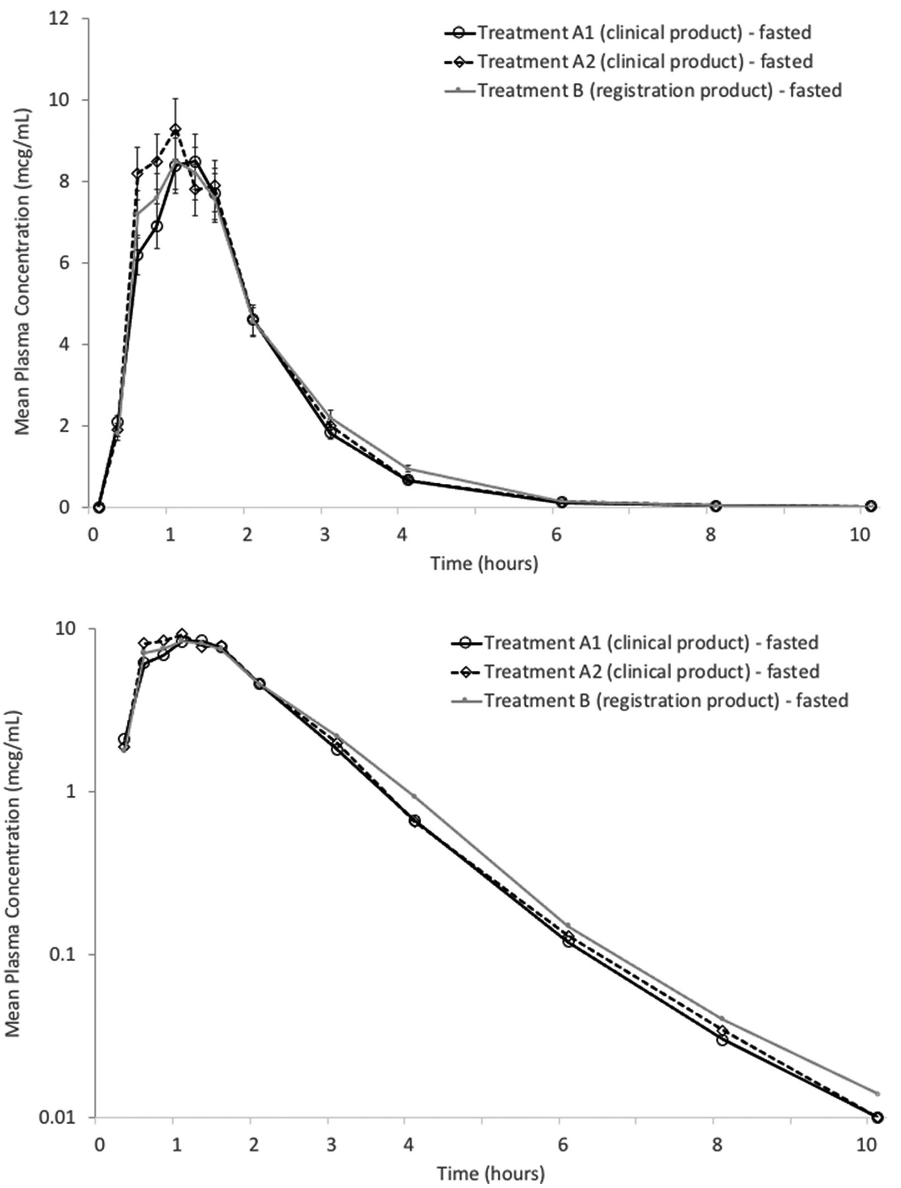

FIGURE 1 Arithmetic mean (SE) plasma tebipenem (TBP) concentration-time profile following a 600 mg dose of clinical study tablet (treatments A1 and A2) and registration tablet formulation (treatment B) of tebipenem pivoxil hydrobromide (TBP-PI-HBr; top: linear scale, bottom: semi-log)

TABLE 2 TBP Pharmacokinetic parameters for each treatment group

	Treatment group			
	A1 (n = 36)	**A2 (n = 36)**	**B (n = 36)**	**C (n = 35)**
C_{max} (μg/ml)	10.5 (28.3)	10.6 (40.7)	10.1 (40.5)	8.8 (58.3)
T_{max} (h)	1.0 (0.5, 2.0)	1.0 (0.5, 2.0)	1.3 (0.5, 2.0)	1.5 (0.7, 4.0)
$t_{1/2}$ (h)	1.1 ± 0.22	1.2 ± 0.22	1.2 ± 0.22	1.0 ± 0.13
$AUC_{0\text{-}t}$ (μg*h/ml)	16.2 (28.3)	16.9 (38.0)	16.9 (34.3)	18.8 (39.6)
$AUC_{0\text{-inf}}$ (μg*h/ml)	16.2 (28.3)	16.9 (38.1)	16.9 (34.3)	18.8 (39.5)

Note: Treatment A1: First administration of 600 mg (2 × 300 mg tablets) TBP-PI-HBr clinical study tablet administered at hour 0 on day 1, under fasted conditions.

Treatment A2: Second administration of 600 mg (2 × 300 mg tablets) TBP-PI-HBr clinical study tablet administered at hour 0 on day 1, under fasted conditions.

Treatment B: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fasted conditions.

Treatment C: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fed conditions.

Data for one subject for treatment C were excluded because the subject vomited within two times the median T_{max}.

AUC and C_{max} values are geometric mean (geometric CV%); T_{max} values are median (minimum, maximum); $t_{1/2}$ values are arithmetic mean ± SD.Abbreviations: $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last observed non-zero concentration calculated by the linear trapezoidal method; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 extrapolated to infinity; C_{max}, maximum plasma concentration; TBP, tebipenem pivoxil; $t_{1/2}$, terminal half-life; TBP-PI-HBr, tebipenem pivoxil hydrobromide; T_{max}, time to maximum plasma concentration.

CIs of the geometric mean ratios for each parameter fell within the established 80% to 125% BE limits (within-subject percent coefficient of variation <30% in the reference formulation for each parameter comparison). The geometric mean ratios were close to unity at ~102% for AUC and 96% for C_{max} (Table 3).

Administration with food had no effect on overall TBP exposure, as the 90% CIs of the geometric mean ratios for $AUC_{0\text{-}t}$ and $AUC_{0\text{-inf}}$ fell within the standard equivalence limits of 80% to 125% based on the statistical comparisons of ln-transformed plasma TBP PK parameters following registration tablet formulation administered under fed versus fasted conditions (Table 4). The geometric mean ratios for AUC were ~110%. Administration with food decreased TBP C_{max} by ~13%, which was statistically significant, as the lower bound of the 90% CI of the geometric mean ratio for C_{max} (74.8%) fell below the 80% to 125% limits. The median and range (minimum to maximum) of individual T_{max} values were slightly delayed suggesting a slower and extended absorption phase for the registration tablet formulation under fed relative to fasted conditions.

Safety

Across both formulations, TBP-PI-HBr was well-tolerated. Overall, five (14%) subjects reported 12 treatment-emergent AEs (TEAEs; Table 5) most commonly gastrointestinal in nature. All TEAEs were mild in severity and resolved during the study period. No deaths, serious AEs or discontinuations due to AEs were reported. No clinically significant ECG, vital signs, or clinical laboratory abnormalities were observed.

DISCUSSION

The TBP-PI-HBr prodrug was developed as the first oral carbapenem for treatment of serious bacterial infections due to gram-positive and gram-negative bacteria, including drug-resistant pathogens. A TBP-PI-HBr formulation was developed for use in phase I and phase III clinical studies during clinical development. A registration/commercial 300 mg film-coated tablet was developed with changes to film-coating and color, tablet image, and modification to the final formulation to produce a smaller tablet for ease of administration. No new excipients were added, but the amounts of excipients utilized were reduced so that a smaller tablet would deliver the same dose. Because the registration formulation had differences from the formulation used in early clinical development, a BE study was conducted and a food effect evaluation arm also was included within the same study.

In this study, subjects were randomized to treatment sequences to minimize assignment bias. A crossover design was used to reduce the residual variability for the BE

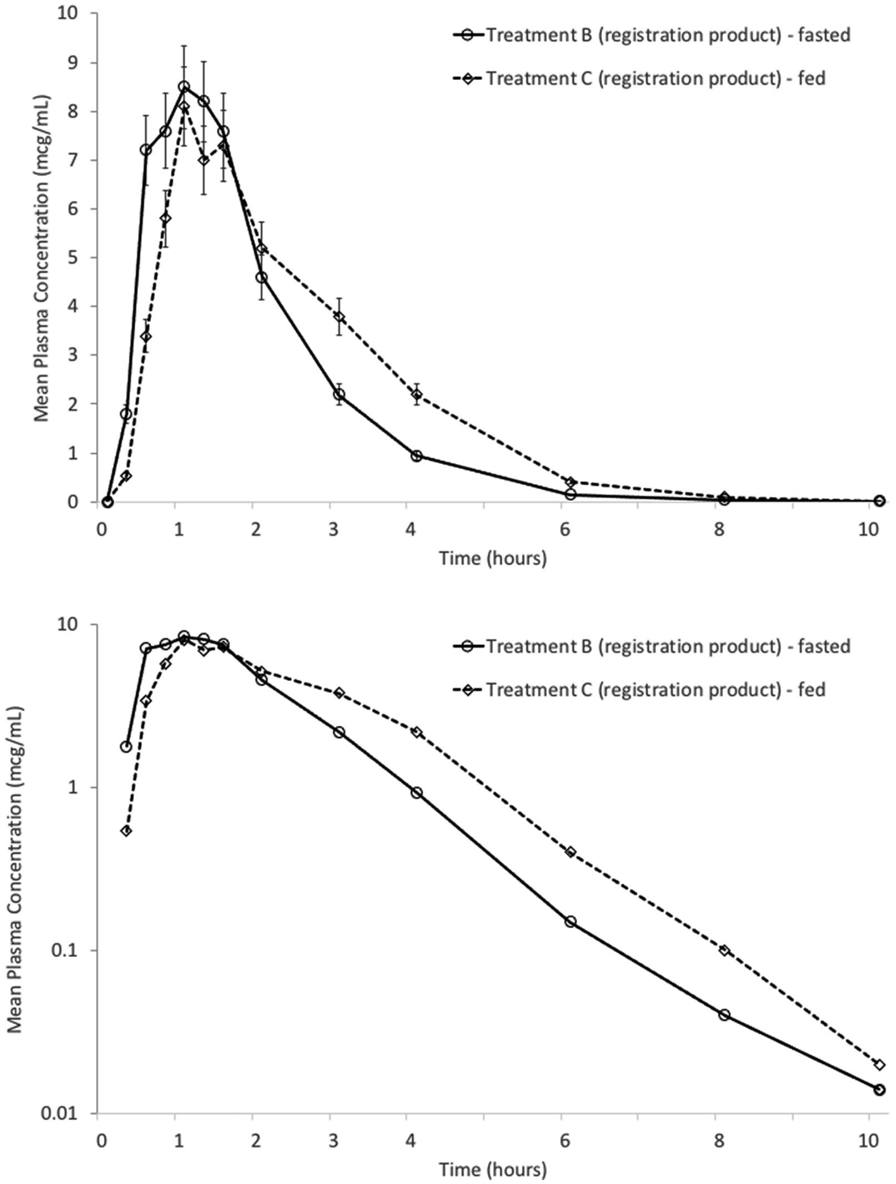

FIGURE 2 Arithmetic mean (SE) plasma tebipenem (TBP) concentration-time profile following an oral (600 mg) administration of registration tablet formulation of tebipenem pivoxil hydrobromide (TBP-PI-HBr) under fasted (treatment B) and fed conditions (treatment C) in healthy subjects (top: linear scale, bottom: semi-log)

portion so that each subject acted as their own control. A crossover design also reduces variability caused by subject-specific factors, increasing the ability to identify differences because of formulation. A semi-replicate design (in periods 1 through 3) was used to assess within-subject variability of the clinical study formulation (reference, treatment A). The CI criteria for acceptance of BE used the statistical scaling approach analysis if the within-subject variability (SD) of the reference formulation was greater than or equal to 29.4%.[9,10] Otherwise, the standard 80%–125% BE limits were applied. The washout period of 7 days between dosing periods was considered sufficient to prevent carryover effects of the preceding treatment, based on the TBP $t_{1/2}$ of ~1 h.

The results from this study showed that the registration tablet formulation and clinical tablet formulation of TBP-PI-HBr were bioequivalent (TBP C_{max} and $AUC_{0\text{-inf}}$ within the 80% to 125% limits) when administered orally under fasted conditions. Additionally, an FDA standard high-fat/high-calorie meal had no effect on the plasma exposure ($AUC_{0\text{-inf}}$) of TBP after administration of the TBP-PI-HBr registration tablet formulation.[6] TBP plasma exposure ($AUC_{0\text{-}t}$ and $AUC_{0\text{-inf}}$) was comparable under fed and fasted conditions. TBP C_{max} indicated a nominal decrease of ~13% after administration of the registration tablet formulation under fed conditions. Because the primary pharmacokinetic/pharmacodynamic driver of efficacy for TBP is plasma AUC,[11] which is not impacted by food, the slight decrease of 13% in C_{max} during the fed state is not considered clinically meaningful. In this study, the observed PK profile of TBP was consistent with that

TABLE 3 Statistical comparisons of plasma TBP PK parameters following administration of registration versus clinical tablet formulation during fasting conditions

Registration (treatment B) versus clinical tablet formulation (treatment A)							
	Treatment B		Treatment A				Intra-subject CV%
Parameter	Geometric LSMs	*n*	Geometric LSMs	*N*	GMR (%)	90% CI	Treatment A
$AUC_{0\text{-}t}$ (μg*h/ml)	16.9	36	16.5	72	102.1	96.9–107.6	20.8
$AUC_{0\text{-inf}}$ (μg*h/ml)	16.9	36	16.6	72	102.1	96.9–107.6	20.8
C_{max} (μg/ml)	10.1	36	10.6	72	95.6	87.1–104.9	29.4

Note: Treatment A: 600 mg (2 × 300 mg tablets) TBP-PI-HBr clinical study tablet administered at hour 0 on day 1, under fasted conditions (reference).Treatment B: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fasted conditions (test).

Parameters were ln-transformed prior to analysis.

Geometric LSMs were calculated by exponentiating the LSMs derived from the ANOVA.GMR = 100 × (test/reference).Intrasubject CV% = 100 × (square root (exp[residual] − 1)), where residual = Residual variance for the treatment from ANOVA.

The BE assessment approach was two one-sided tests procedure, and the BE acceptance bound was 80% to 125% when the reference formulation intra-subject CV% was <30%.

Abbreviations: ANOVA, analysis of variance; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last observed non-zero concentration calculated by the linear trapezoidal method; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 extrapolated to infinity; BE, bioequivalence; CI, confidence interval; C_{max}, maximum plasma concentration; CV%, coefficient of variation percentage; GMRs, geometric mean ratios; LSMs, least square means; PK, pharmacokinetic; TBP, tebipenem pivoxil; TBP-PI-HBr, tebipenem pivoxil hydrobromide.

TABLE 4 Statistical comparisons of plasma TBP PK parameters following administration of registration versus clinical tablet formulation under fed versus fasted conditions

Fed (treatment C) versus fasted (treatment B)						
	Treatment C		Treatment B			
Parameter	Geometric LSMs	*n*	Geometric LSMs	*n*	GMR (%)	90% CI
$AUC_{0\text{-}t}$ (μg*h/ml)	18.6	35	16.9	36	110.1	101.8–119.1
$AUC_{0\text{-inf}}$ (μg*h/ml)	18.6	35	16.9	36	110.1	101.8–119.1
C_{max} (μg/ml)	8.8	35	10.1	36	87.3	74.8–102.1

Note: Treatment B: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fasted conditions (test).

Treatment C: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fed conditions (test).

Parameters were ln-transformed prior to analysis.

Geometric LSMs were calculated by exponentiating the LSMs derived from the ANOVA.GMR = 100 × (test/reference).

Intra-subject CV% = 100 × (square root (exp[residual] − 1)), where residual = Residual variance for the treatment from ANOVA.

The assessment approach was two one-sided tests procedure, and the equivalence bound was 80% to 125%.

Data for one subject for treatment C were excluded because the subject vomited within two times the median T_{max}.

Abbreviations: ANOVA, analysis of variance; $AUC_{0\text{-}t}$, area under the concentration-time curve from time 0 to the last observed non-zero concentration calculated by the linear trapezoidal method; $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 extrapolated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; GMRs, geometric mean ratios; LSMs, least square means; PK, pharmacokinetic; TBP, tebipenem pivoxil; TBP-PI-HBr, tebipenem pivoxil hydrobromide; T_{max}, time to maximum plasma concentration.

observed in a prior study with the clinical development formulation.[2]

The 300 mg TBP-PI-HBr registration tablet evaluated in this study is intended as the marketed single-unit tablet strength. The 600 mg dose selected for this study was administered as a single dose of 2 × 300 mg tablets orally in each dosing period, which is the currently proposed therapeutic dose regimen of 600 mg TBP-PI-HBr every 8 h in patients with normal renal function or mild renal impairment (creatinine clearance >50 ml/min). The same dose of TBP-PI-HBr was used in a pivotal phase III study of patients with complicated urinary tract infections including acute pyelonephritis. Thus, the study design and dose used in this study provide adequate characterization of the TBP PK profile, consistent with recommendations in the FDA guidance.[7]

TABLE 5 Incidence of adverse events by treatment sequence (safety population)

	TBP-PI-HBr formulation		
	Number (%) of subjects		
Adverse events	A combined ($n = 36$)	B ($n = 36$)	C ($n = 36$)
Number with any TEAEs	3 (8%)	2 (6%)	1 (3%)
Abdominal discomfort	1 (3%)	0	0
Constipation	1 (3%)	0	0
Diarrhea	1 (3%)	0	0
Hematochezia	1 (3%)	0	0
Nausea	1 (3%)	0	1 (3%)
Salivary hypersecretion	0	0	1 (3%)
Vomiting	1 (3%)	0	1 (3%)
Arthralgia	0	1 (3%)	0
Back pain	0	1 (3%)	0
Presyncope	0	1 (3%)	0

Note: A combined: 600 mg (2 × 300 mg tablets) TBP-PI-HBr clinical study tablet administered B: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fasted conditions.

C: 600 mg (2 × 300 mg tablets) TBP-PI-HBr registration tablet administered at hour 0 on day 1, under fed conditions.

Abbreviations: TBP-PI-HBr, tebipenem pivoxil hydrobromide; TEAEs, treatment-emergent adverse events.

The results of this study demonstrated that the clinical and registration tablet formulations of TBP-PI-HBr were BE and that oral administration of the registration tablet with food had no clinically relevant effect on TBP PK profile. The most common TEAEs were of the gastrointestinal system, which is consistent with the carbapenem class of drugs.[12] TEAEs were all mild in severity and resolved after single doses, which is consistent with findings from other phase I studies of TBP-PI-HBr.[2,5] Thus, oral TBP-PI-HBr can be administered without regard to meals when administered to patients for the treatment of serious bacterial infections.

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CONFLICT OF INTEREST

Leanne Gasink is a consultant to Spero Therapeutics, Inc. Gina Patel is the principal with Patel Kwan Consultancy LLC, Madison, WI. All other authors were paid employees of Spero Therapeutics, Cambridge, MA, at the time of this study.

AUTHOR CONTRIBUTIONS

All authors were involved in designing the study, performed the research, analyzed the data, and writing the manuscript.

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