Bioequivalence of Two Oral Formulations of Tebipenem-Pivoxil Hydrobromide in Healthy Subjects

IDWeek 2021
Sept. 29-Oct. 3, 2021
Abstract #1121

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INTRODUCTION

- Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is a novel orally bioavailable carbapenem prodrug in development for treatment of serious bacterial infections (e.g., complicated urinary tract Infections).
- TBP, the active moiety, exhibits *in vitro* activity against gram-positive and gram-negative pathogens, including extended-spectrum-β-lactamase (ESBL)-producing and fluoroquinolone-resistant Enterobacterales (Jain et al, 2018).
- In a single- and multiple-ascending dose study of TBP-PI-HBr, plasma exposure of TBP increased in a linear and dose proportional manner (Eckburg et al, 2019).
- Plasma concentrations of TBP after single doses of TBP-PI-HBr 300 mg or 600 mg were similar under fed and fasted conditions, suggesting TBP-PI-HBr could be administered with or without food.

OBJECTIVE

- To establish the bioequivalence (BE) of the reference (clinical) and the test (registrational) drug product formulations of TBP-PI-HBr in healthy subjects and to assess the effect of food on the TBP PK profile.

METHODS

Study Design

- Open-label, randomized, single-dose, semi-replicate, 3-sequence, 4-period crossover, BE (under fasted conditions) and food-effect study.
- A replicate design was used where the reference product was repeated in two treatment periods (FDA Guidance, 2019) with a reference-scaled BE limit to be used for AUC or C_{max}.
- Subjects were randomized to one of three sequences.
  - In Periods 1 through 3, subjects received a single 600 mg oral dose (2 x 300 mg tablets) of TBP-PI-HBr, as either the reference clinical study drug product (Treatment A) or the test registration drug product (Treatment B) in alternating sequence, under fasted conditions.
  - In Period 4, subjects received a single 600 mg oral dose (2 x 300 mg tablets) of TBP-PI-HBr as the registration drug product under fed conditions (Treatment C).
- Each subject received Treatment A twice and Treatment B once, in alternating sequence while fasting, and Treatment C once while fed.
- A washout period of at least 7 days between each dose/period.
- On Day 1 of Treatments A and B, subjects fasted overnight for at least 10 hours prior to dosing and continued fasting for at least 4 hours post dose.
- On Day 1 of Treatment C, subjects fasted overnight for at least 10 hours until 30 minutes prior to their scheduled dose, when they were given a high fat/high calorie breakfast.

Pharmacokinetic Analysis

- Whole blood samples were collected to determine TBP concentrations pre-dose (0) and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post dose using validated LC-MS/MS assay.
- PK parameters were calculated using noncompartmental methods based on plasma TBP concentrations.

Statistical Analysis

- To assess BE between the test and reference PK parameters (AUC_{0-t}, AUC_{0-inf}, and C_{max},), ANOVA model with fixed effects of sequence, treatment and period and a random effect of subject was performed with a no diagonal factor analytic covariance structure.
- To assess the potential food-effect, ANOVA was performed on the ln-transformed AUC_{0-t}, AUC_{0-inf}, and C_{max}, which included treatment as a fixed effect (for Treatments B and C only) and subject as a random effect.
- Point estimates and 90% confidence intervals (CI) were constructed for the relevant contrasts from the ANOVA models.
- To assess BE, estimated geometric means were presented for each treatment, and ratios were expressed as a percentage of registrational relative to the clinical study treatment.
- To assess food effect, estimated geometric means were presented for the fed and fasted state expressed as a percentage relative to the fasted state (Treatment B).
- Bioequivalence was demonstrated if the 90% CIs for the geometric mean ratios for AUC_{0-t}, AUC_{0-inf}, and C_{max} fell within the established 80% to 125% BE limits (FDA Guidance 2019).

RESULTS

- 36 subjects were enrolled, and all were included in PK and safety analyses.
- Baseline demographics are presented in Table 1. Most subjects were male (69%), white (92%), with Hispanic/Latino ethnicity (72%); and mean age of 41 years.

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/m² [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 (0)	2 (17)	1 (8)
Hispanic or Latino, n (%)	8 (67)	9 (75)	9 (75)

[a] Mean ± standard deviation
Treatment A1: First administration of 600 mg (2 x 300 mg tablets) TBP-PI-HBr clinical study drug product administered at Hour 0 on Day 1, under fasted conditions
Treatment A2: Second administration of 600 mg (2 x 300 mg tablets) TBP-PI-HBr clinical study drug product administered at Hour 0 on Day 1, under fasted conditions
Treatment B: 600 mg (2 x 300 mg tablets) TBP-PI-HBr registration drug product administered at Hour 0 on Day 1, under fasted conditions
Treatment C: 600 mg (2 x 300 mg tablets) TBP-PI-HBr registration drug product administered at Hour 0 on Day 1, under fed conditions

Pharmacokinetics

- Mean peak plasma TBP concentrations were comparable following single doses of the clinical product and the registration product under fasted conditions (Figure 1).
- Geometric mean AUC_{0-t}, AUC_{0-inf}, and C_{max} values were comparable for the clinical product (Treatment A) and the registration product (Treatment B).
- Median T_{max} was 1 hour (range: 0.5 to 2 h) for the clinical product and 1.3 hours (range: 0.5 to 2.0 h) for the registration product (Table 2).
- Similarly, mean t½ values were comparable (range: 1.1 to 1.2 h) between the clinical product and the registration product under fasted conditions.
- Geometric mean AUC_{0-t} and AUC_{0-inf} values were comparable for the registration product under fasted (Treatment B) and fed (Treatment C) conditions (Table 2).
- The geometric mean C_{max} was lower under fed relative to fasted conditions (% change: 11% vs. 16%).
- Median T_{max} was slightly delayed to 1.5 hours (range: 0.7 to 4.0 h) for the registration product under fed conditions (Treatment C) relative to fasted conditions (Treatment B).
- Mean t½ was generally similar for the registration product under fasted and fed conditions.

Table 2. Pharmacokinetic parameters

Parameter	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-t} µg*h/mL	16.2 (28.3)	16.9 (38.0)	16.9 (34.3)	18.8 (39.6)
AUC_{0-inf} µg*h/mL	16.2 (28.3)	16.9 (38.1)	16.9 (34.3)	18.8 (39.5)

Data for one subject for Treatment C were excluded because the subject vomited within 2 times the median T_{max}
AUC and C_{max} values are geometric mean (geometric CV%).
T_{max} values are median (minimum, maximum).
$t_{½}$ values are arithmetic mean ± standard deviation.

- Based on the statistical comparisons of ln-transformed plasma TBP AUC_{0-t}, AUC_{0-inf}, and C_{max}, (Table 3) the test registration drug product was demonstrated to be statistically bioequivalent to the reference clinical drug product formulation administered under fasted conditions
- 90% CIs for the geometric mean ratios for each parameter fell within the 80% to 125% bioequivalence limits (with intra-subject CV% <30% in the reference formulation for each parameter).
- The geometric mean ratios were close to unity at approximately 102% for AUC and 96% for C_{max}.
- Following registration product administration under fed versus fasted conditions, food had no meaningful effect on overall TBP exposure (AUC) as the 90% CIs of the geometric mean ratios for AUC_{0-t} and AUC_{0-inf} were within the standard equivalence limits of 80% to 125%.
- Administration with food decreased TBP C_{max} by approximately 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. However, this decrease in C_{max} was not considered clinically meaningful as the primary PK/PD driver associated with TBP efficacy is plasma AUC.

REFERENCES
Eckburg PB, et al. Safety, Pharmacokinetics, and food effect of tebipenem pivoxil hydrobromide after single and multiple ascending oral doses in healthy adult subjects. Antimicrob Agents Chemother. 2019;63(9):e00618-19.
Jain A, et al. Tebipenem, the first oral carbapenem antibiotic. Expert Rev Anti Infect Ther. 2018;16(7):513-522.

Figure 1. Arithmetic mean plasma TBP concentrations following a 600 mg dose of clinical study drug product (A1 and A2) and registration drug product (B) fasted (LEFT) and with Treatments B and C fed vs. fasted (RIGHT).

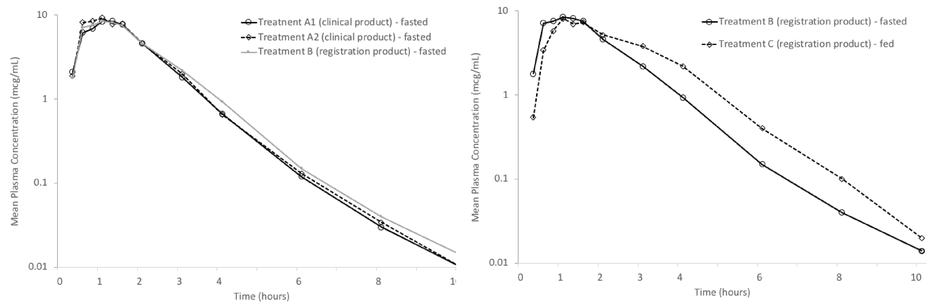

Table 3. Statistical comparisons of plasma TBP PK parameters following administration of registration vs. clinical study product during fasting and for fed vs. fasted conditions.

Registration (Treatment B) vs. Clinical Study Product (Treatment A)							
	Treatment B		Treatment A				Intra-subject CV%
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% CI	Treatment A
AUC_{0-t} (µg*h/mL)	16.9	36	16.5	72	102.1	96.9 - 107.6	20.8
AUC_{0-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
Fed (Treatment C) vs. Fasted (Treatment B)							
	Treatment C		Treatment B				
Parameter	Geometric LSMs	n	Geometric LSMs	n	GMR (%)	90% CI	
AUC_{0-t} (µg*h/mL)	18.6	35	16.9	36	110.1	101.8 - 119.1	
AUC_{0-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	

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) were calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (test/reference)
Intra-subject CV% = 100 x (square root (exp[residual]-1)), where residual = Residual variance for the treatment from ANOVA.
BE assessment was two one-sided tests procedure, and the BE acceptance bound was 80% to 125% when the reference formulation intra-subject CV% was <30%.
Data for one subject for Treatment C were excluded because the subject vomited within 2 times the median Tmax.

Safety/Tolerability

- 12 treatment-emergent adverse events (TEAEs) were reported in five (14%) subjects (Table 4), most commonly gastrointestinal in nature; all TEAEs were mild in severity and resolved during the study period.
- No deaths, serious adverse events or discontinuations due to TEAEs were reported.
- No clinically significant ECG, vital signs or clinical laboratory abnormalities were observed

Table 4. Incidence of Adverse Events by Treatment (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
Diarrhoea	1 (3%)	0	0
Haematochezia	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

SUMMARY

- Results of this study demonstrated the BE of the clinical and registration drug product oral tablet formulations of TBP-PI-HBr.
- Administration of the registration tablet with food had no clinically relevant effect on the PK profile, suggesting that TBP-PI-HBr may be administered without regard to meals when administered to patients for the treatment of serious bacterial infections
- TBP-PI-HBr was well tolerated at the proposed dose (600 mg) for the treatment of patients with serious bacterial infections

Funded by Spero Therapeutics, Inc., Cambridge, MA. Clinicaltrials.gov: NCT04421885