ECCMID 9-12 July 2021
Abstract # 00660

Pharmacokinetics of Oral Tebipenem Pivoxil Hydrobromide in Subjects with Varying Degrees of Renal Impairment

Gina Patel,1 Keith A. Rodvold,2 Vipul K Gupta,3 Jon Bruss,3 Leanne Gasink,3 Floni Bajraktari,3 Yang Lei,3 Akash Jain,3 Praveen Srivastava,3 Angela K. Talley3

1 Patel Kwan Consultancy LLC, Madison Wisconsin; 2 University of Illinois, Chicago, IL; 3 Spero Therapeutics Inc., Cambridge, MA

Spero Therapeutics
675 Massachusetts Ave
14th Floor
Cambridge, MA 02139
Phone: (303) 564-5139
atalley@sperotherapeutics.com

INTRODUCTION

- Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an oral carbapenem prodrug that is converted to TBP, the active moiety.
- TBP is active against multi-drug resistant (MDR) pathogens, including ESBL-producing Enterobacterales and gram-negative pathogens resistant to other antibiotic classes including fluoroquinolones.
- TBP demonstrated efficacy against ESBL-producing organisms in animal infection models, including the murine neutropenic thigh infection model and the murine ascending urinary tract infection (UTI) model.
- TBP-PI-HBr was development for treating complicated UTI and acute pyelonephritis.
- Because oral TBP-PI-HBr is eliminated primarily by renal excretion, it is expected that dosage adjustment will be needed in patients with severe RI.

OBJECTIVE

- Evaluate the PK, safety, and tolerability of TBP-PI-HBr in subjects with normal renal function, subjects with varying degrees of RI, and subjects with end-stage renal disease (ESRD) receiving hemodialysis (HD).

METHODS

- Phase 1, multi-center, open-label study
- Adult men or women at least 18 years of age
- Body mass index (BMI) ≥18.5 and ≤39.9 kg/m2 and body weight between 50.0 and 130.0 kg.
- Medically stable without clinically significant acute or chronic illness.
- Subjects were categorized into Cohorts at screening using estimated glomerular filtration rate (eGFR) calculated with MDRD.
  - Cohort 1 normal renal function (eGFR ≥90 mL/min/1.73m^2)
  - Cohort 2 eGFR of 60 to <90 mL/min/1.73m^2
  - Cohort 3 eGFR of 30 to <60 mL/min/1.73m^2
  - Cohort 4 eGFR <30 mL/min/1.73m^2
- Cohort 5 ESRD on HD ≥3 times per week for ≥3 months at screening.
- Cohorts 1-4: single dose of oral TBP-PI-HBr 600 mg
- Cohort 5 received a single dose of oral TBP-PI-HBr 600 mg
  - Within 2 (±1) hours after completion of regularly scheduled HD on Day 1 (Period 1)
  - A second dose 1 hour prior to their regularly scheduled HD on Day 5 (Period 2)

Study Assessments

- Physical examinations, vital signs, 12-lead ECG, clinical laboratory tests (hematology, biochemistry, coagulation and urinalysis), adverse events (AEs), and PK analysis

Statistical Analysis

- Estimation of PK parameters for RI subjects (Cohort 2-5) compared to Cohort 1 used an ANOVA model with log-transformed values of AUC0–last, AUC0-∝, Cmax, and CL/F as the response variables and with the fixed-effect term of Cohort as a categorical variable.
- Mean difference and 90% confidence interval (CI) were calculated for each RI group (vs. healthy subjects) and were back transformed to provide geometric mean ratios and 90% CIs for each comparison.
- To evaluate the effect of dialysis on TBP, log-transformed PK parameters (AUC0–last, AUC0-∝, Cmax, and CL/F) obtained with dosing before HD (test) versus dosing after HD (reference) in ESRD subjects were evaluated using an ANOVA model with period as the factor, body weight at the baseline, age, and sex as covariates, and subject as the random effect.
- A 2-sided 90% CI for the estimated ratio of the effect was calculated for all PK parameters (AUC0–last, AUC0-∝, Cmax, and CL/F).
- The ratio of the geometric means and their CI was obtained by back transforming the estimated mean difference and its corresponding CI.

RESULTS

Table 1. Baseline characteristics

	Estimated Glomerular Filtration Rate (mL/min/1.73m^2)				
	Normal eGFR ≥90 (n=7)	Mild eGFR 60-<90 (n=8)	Moderate eGFR 30-<60 (n=8)	Severe eGFR <30 (n=8)	ESRD (n=8)
Age, years [a]	62 ± 5.0	69 ± 5.4	69 ± 8.8	64 ± 9.3	58 ± 7.9
Age range, years	56 – 71	62 – 76	52 – 80	53 – 77	42 – 68
Female, n (%)	3 (42.9)	3 (37.5)	4 (50.0)	6 (75.0)	6 (75.0)
Weight, kg [a]	79.9 ± 9.4	71.7 ± 12.2	78.3 ± 12.1	81.2 ± 8.8	98.8 ± 16.0
BMI, kg/m^2 [a]	27.7 ± 2.4	26.7 ± 3.7	28.3 ± 3.8	27.3 ± 3.5	32.1 ± 4.6
Race, n (%)					
White	2 (28.6)	6 (75.0)	8 (100)	8 (100)	0
Black or African American	5 (71.4)	2 (25.0)	0	0	8 (100)
Hispanic or Latino, n (%)	0	5 (62.5)	6 (75.0)	5 (62.5)	0
eGFR, mL/min/1.73m^2 [a]	101 ± 8.4	73 ± 5.7	47 ± 9.5	17 ± 8.5	Not applicable

Pharmacokinetics

- For Cohorts 1-4, mean plasma TBP concentrations reached a peak within approximately 1.5 hours and then declined over time (Figure 1).
- For Cohorts 1-3, plasma TBP concentrations were not measurable after 16 hours. In Cohort 4 (severe RI), plasma concentrations were measurable at 48 hours post dose.
- With increasing RI, elimination t1/2 and AUC increased and CL/F decreased (Table 2).
- Apparent CL/F correlated (R2 = 0.585) with CL_{CR} for Cohorts 1-4 (Figure 2).
- A correlation (R2 = 0.771 and 0.712) existed between and CL_R and CL_{CR} (Figure 2).
- All cohorts with RI exhibited higher exposure (C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}\infty}$) to TBP compared to healthy subjects (Cohort 1).
- Compared to healthy subjects, geometric LS mean ratios of $AUC_{0\text{-}\infty}$ for TBP were approximately 1.4, 2.2, and 4.5 times higher in Cohorts 2, 3 and 4, respectively.
- C_{max} was 1.3 times higher for Cohorts 3 and 4 compared to healthy subjects (Cohort 1).

Table 2. Pharmacokinetic parameters

Parameter	Cohort 1 Normal (N=7)	Cohort 2 Mild RI (N=8)	Cohort 3 Moderate RI (N=8)	Cohort 4 Severe RI (N=8)	Cohort 5 Period 1 (N=8)	Cohort 5 Period 2 (N=8)
C_{max} (µg/mL)	14.1 (67.1)	14.8 (34.0)	18.4 (14.9)	18.8 (50.8)	14.0 (50.4)	11.7 (39.1)
T_{max} (h)	1.5 (0.5, 2.0)	1.5 (1.0, 2.0)	1.5 (0.5, 4.0)	1.5 (1.0, 4.0)	4.0 (1.5, 6.0)	3.0 (1.5, 3.0)
$AUC_{0\text{-last}}$ (µg·h/mL)	21.1 (40.2)	28.8 (37.1)	46.0 (29.4)	95.6 (75.4)	149 (35.6)	90.8 (16.3)
$AUC_{0\text{-}\infty}$ (µg·h/mL)	21.2 (40.2)	28.8 (37.1)	46.2 (29.9)	95.8 (75.3)	152 (35.6)	93.0 (17.4)
$t_{1/2}$ (h)	1.1 ± 0.23	1.2 ± 0.14	1.3 ± 0.15	3.6 ± 1.8	7.9 ± 1.9	8.0 ± 2.1
CL/F (L/h)	21.9 (40.2)	16.1 (37.1)	10.0 (29.9)	4.83 (75.3)	3.04 (35.6)	4.97 (17.4)
V_Z/F (L)	33.3 (30.0)	27.4 (36.2)	19.0 (26.7)	21.8 (45.0)	33.5 (44.2)	55.0 (22.7)

Geometric mean (CV%) is presented for C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, CL/F and V_Z/F
Arithmetic mean (± SD) is presented for $t_{1/2;}$
Median (minimum, maximum) is reported for T_{max}

- Cohort 4 (severe RI) displayed a wide range of plasma TBP concentration-time profiles.
- At a CL_{CR} <20 mL/min, the apparent CL/F of TBP was lower (mean: 3.3 L/h) compared to subjects with CL_{CR} ≥20 mL/min (mean: 8.0 L/h) (Table 3).
- TBP t1/2, $AUC_{0\text{-inf}}$, and CL_R were prolonged in subjects with an CL_{CR} <20 mL/min compared to subjects with an CLCR ≥20 mL/min.
- For Cohort 5 (ESRD), mean plasma TBP concentrations were lower post-HD relative to pre-dialysis and measurable for up to 48 hours (Figure 1).
- In Cohort 5, TBP C_{max} was similar to other Cohorts, but t1/2, T_{max}, and AUC were markedly higher, and CL/F was markedly lower in both Period 1 (post-dialysis) and Period 2 (pre-dialysis) (Table 2).
- Compared to dosing in Period 1, geometric mean plasma CL/F and Vz/F for TBP increased, and C_{max} and $AUC_{0\text{-}\infty}$ decreased in Period 2.
- In Cohort 5, after a 4-hour HD session, TBP exposure (ANOVA of log-transformed $AUC_{0\text{-}\infty}$) decreased from 152.0 µg*h/mL (Period 1) to 92.8 µg*h/mL (Period 2), a mean decrease of approximately 40%.
- A slight decrease in arithmetic mean value of Cmax from 14.7 µg/mL to 11.7 µg/mL was observed after a 4-hour HD session.

Table 3. Arithmetic mean (min, max) PK parameters for Cohort 4 subjects with CL_{CR} <20 mL/min and ≥20 mL/min

PK Parameter	Cohort 4 CL_{CR} <20 mL/min (N=4)	Cohort 4 CL_{CR} ≥20 mL/min (N=4)
$AUC_{0\text{-}\infty}$ (µg·h/mL)	183.0 (111.0, 389.0)	60.5 (49.4, 82.8)
$t_{1/2}$(h)	5.1 (4.2, 6.5)	2.0 (1.5, 2.6)
CL/F (L/h)	3.3 (1.2, 4.2)	8.0 (5.6, 9.4)
CL_R (L/h)	0.9 (0.3, 1.5)	3.9 (2.5, 5.1)

Figure 2. Plasma concentrations over time for TBP for Cohorts 1-4 and Cohort 5.

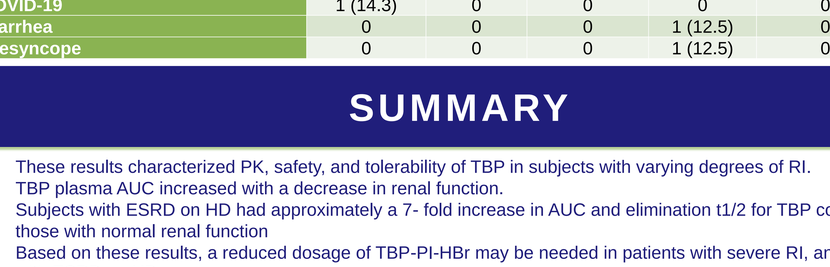

Figure 2. Apparent total body clearance vs. estimated creatinine clearance renal clearance vs. creatinine clearance of TBP for Cohorts 1 to 4.

Safety/Tolerability

- Four (10.3%) subjects reporting 5 TEAEs of mild severity; all resolved without intervention (Table 4).
- No serious AEs or deaths occurred.
- No clinically significant abnormalities in the clinical laboratory results, ECG findings or physical examination were reported.

Table 4. Incidence of Adverse Events (AE) Occurring in Each Cohort

	Number (%) of Subjects				
	Normal eGFR (n=7)	Mild eGFR (n=8)	Moderate eGFR (n=8)	Severe eGFR (n=8)	ESRD (n=8)
Any treatment emergent AE	1 (14.3)	0	0	2 (25.0)	1 (12.5)
Any treatment related AE	0	0	0	1 (12.5)	0
Abdominal pain	0	0	0	1 (12.5)	0
Arteriovenous fistula	0	0	0	0	1 (12.5)
COVID-19	1 (14.3)	0	0	0	0
Diarrhea	0	0	0	1 (12.5)	0
Presyncope	0	0	0	1 (12.5)	0

SUMMARY

- These results characterized PK, safety, and tolerability of TBP in subjects with varying degrees of RI.
- TBP plasma AUC increased with a decrease in renal function.
- Subjects with ESRD on HD had approximately a 7- fold increase in AUC and elimination t1/2 for TBP compared to those with normal renal function
- Based on these results, a reduced dosage of TBP-PI-HBr may be needed in patients with severe RI, and in patients with ESRD on HD.
- Population PK modeling, along with other studies in healthy subjects and infected patients, will be used to develop dosing recommendation for patients with various degrees of renal impairment, including ESRD on HD.
- The safety and tolerability profile of TBP-PI-HBr was not impacted by the degree of RI in this population of otherwise healthy subjects.

Funded by Spero Therapeutics, Inc., Cambridge, MA. Clinicaltrials.gov: NCT04178577