Pharmacokinetics-Pharmacodynamics Evaluation of Tebipenem Pivoxil Hydrobromide Using the 10-Day Hollow-Fiber *In Vitro* Infection Model

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INTRODUCTION

- Tebipenem pivoxil hydrobromide, an orally (PO) bioavailable prodrug of tebipenem, is currently in development for the treatment of complicated urinary tract infections (cUTI).
- The emergence of extended-spectrum β-lactamase (ESBL) and Amp C-β-lactamases among organisms common to cUTI has led to diminished activity of the PO cephalosporins and other PO agents [1, 2].
- The spectrum of tebipenem activity against Enterobacterales including ESBL- and AmpC-producing organisms, is consistent with intravenous carbapenems, such as ertapenem and meropenem [3].
- As described herein, a series of hollow-fiber *in vitro* infection model studies were designed to evaluate the efficacy of tebipenem and to determine the exposure that prevented on-therapy resistance to tebipenem. The tebipenem dosing regimen evaluated in the recently-completed cUTI Phase 3 study [4], 600 mg administered every eight hours (q8h) over 7-10 days, was among those evaluated.

OBJECTIVE

- The goal of the hollow-fiber *in vitro* infection model studies undertaken was to determine the tebipenem exposure required to prevent on-therapy resistance and to evaluate the tebipenem regimen evaluated in the recently-completed Phase 3 clinical trial.

METHODS

Antimicrobial Agent and Challenge Isolates

- A panel of three *Escherichia coli* isolates were selected based upon their known resistance mechanisms and tebipenem minimum inhibition concentration (MIC) values. All isolates were either purchased from JMI Laboratories (North Liberty, IA) or provided by the National Collection of Type Cultures (**Table 1**).
- Tebipenem was provided by Spero Therapeutics (Cambridge, MA). Ertapenem was purchased from Henry Schein (Melville, NY).

Table 1. Known resistance mechanisms and tebipenem modal MIC values of isolates utilized in the hollow-fiber *in vitro* infection model studies

Isolate	Known resistance mechanisms	Tebipenem modal MIC* (mg/L)	
		Microtiter	Agar
E. coli 998822	CTX-M-15, OXA-1, OXA-30 (ST-131 O25b)	0.03	0.015
E. coli NCTC 13441	CTX-M-15, Sequence Type-131 (ST-131)	0.015	0.03
E. coli 4643	CTX-M-15, OXA1/30	0.008	0.015

*All MICs performed using CLSI methodologies [5] and presented as the modal value.

Hollow-Fiber *In Vitro* Infection Model

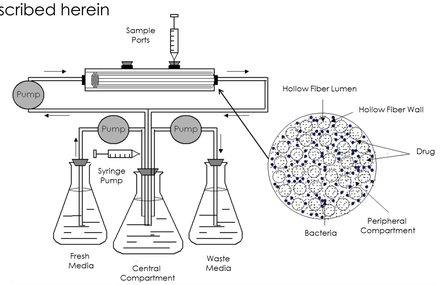
- 10 mL of each *E. coli* isolate were inoculated into the hollow-fiber *in vitro* infection model cartridges (Fibercell Systems, Frederick, MD) at an inoculum of 1.0 x 10^8 colony forming units (CFU)/mL using Mueller-Hinton broth medium (**Figure 1**).
- Each challenge isolate was subjected to concentration-time profiles simulating free-drug plasma concentrations observed after tebipenem PO administration in healthy volunteers, assuming a protein binding value of 45% [6].

METHODS

Hollow-Fiber *In Vitro* Infection Model

- A series of 10-day dose-ranging studies were completed using two isolates (*E. coli* 998822 and NCTC 13441) exposed to tebipenem regimens of 4.69 to 1200 mg q8h, linearaly scaled from the tebipenem 600 mg q8h regimen evaluated in healthy volunteers.
- A third isolate (*E. coli* 4643) was evaluated over a 10-day period using only the 600 mg q8h regimen evaluated in the Phase 3 trial.
- For each study, samples were collected for the enumeration of the total and resistant bacterial populations, for samples obtained at 0 and 5 hours after start of the experiment, and on Days 1, 2, 3, 4, 6, 8, and 10.
- Samples for bacterial enumeration were washed twice with sterile normal saline, serially diluted and plated on both drug-free and agar supplemented with tebipenem concentrations representing four-times the baseline agar MIC.
- MIC values were determined for a subset of isolates found in the drug-supplemented agar plates.
- 1 mL samples were collected for the evaluation of the simulated pharmacokinetic profile via liquid chromatography-tandem mass spectrometry on a Sciex 5500 with an Exion LC AC front-end.
- All hollow-fiber *in vitro* infection model studies were completed in duplicate and compared to a no-treatment control.

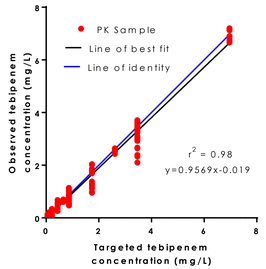
Figure 1. Schematic of the hollow-fiber *in vitro* infection models utilized in the studies described herein



RESULTS

Figure 2. The relationship between targeted and observed tebipenem concentrations simulated in the hollow-fiber *in vitro* infection models

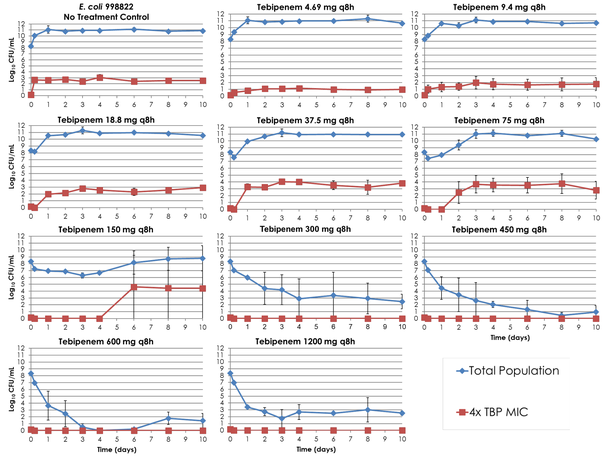
- The targeted concentration-time profiles for tebipenem were well simulated in the hollow-fiber *in vitro* model for all dosing regimens.
- The above-described agreement was supported by the coefficient of determination (r^2) of 0.98 and a slope value of 0.96, representing a deviation from 1 to 4% for the agreement between observed and targeted concentration-time profiles.



RESULTS

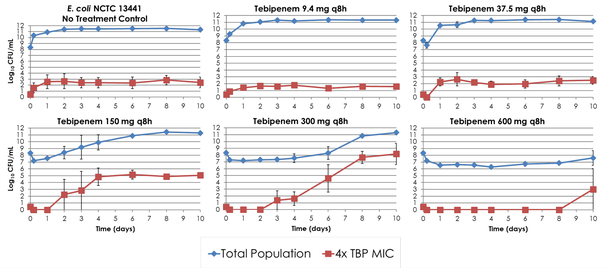
- A full dose response, ranging from treatment failure to reductions in bacterial burden from baseline, was observed in the 10-day HFIM dose-ranging studies for *E. coli* 998822 and NCTC 13441 as shown in **Figure 3** and **4**, respectively. A summary of the results is provided below:
  - For *E. coli* 998822 shown in **Figure 3**, amplification of resistant subpopulations to densities greater than that observed in the no-treatment control was observed for tebipenem doses ranging from 37.5 mg to 150 mg q8h.
  - Tebipenem 600 mg q8h successfully reduced the bacterial burden to ≤ 3-$\log_{10}$ CFU/mL with no amplification of resistance over the 10-day duration of the study.

Figure 3. Average *E. coli* 998822 total and drug-resistant subpopulations observed in the 10-day hollow-fiber *in vitro* infection model dose-ranging studies



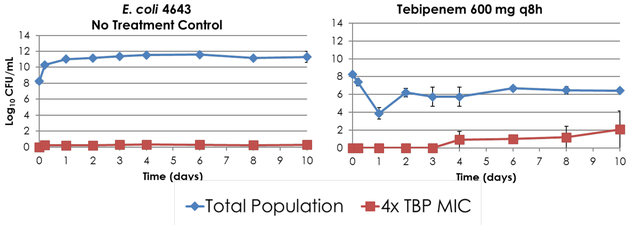
  - For *E. coli* NCTC 13441 shown in **Figure 4**, amplification of resistant subpopulations was observed for tebipenem dosing regimens of 150 and 300 mg q8h.
  - Tebipenem 600 mg q8h suppressed the growth of *E. coli* NCTC 13441 with an average bacterial burden between 6 and 8-$\log_{10}$ CFU/mL over the 10-day period, with amplification of the resistant population only seen in one replicate on Day 10.

Figure 4. Average *E. coli* NCTC 13441 total and drug-resistant subpopulations observed in the 10-day hollow-fiber *in vitro* infection models dose-ranging studies



- As shown in **Figure 5** for *E. coli* 4643, a 2-$\log_{10}$ CFU/mL reduction over the course of the 10-day period, with amplification of resistance only occurring in one of two replicates, was observed after administration of tebipenem 600 mg q8h.

Figure 5. Average *E. coli* 4643 total and drug-resistant subpopulations observed in the 10-day hollow-fiber *in vitro* infection models based on the study for tebipenem 600 mg q8h dose



- Tebipenem MIC values for isolates collected from the drug-supplemented agar plates used to evaluate the density of the drug-resistant subpopulations observed for each *E. coli* isolate ranged from 0.06 to 0.25 mg/L.

CONCLUSIONS

- The ability of tebipenem 600 mg q8h, the dosing regimen studied in a Phase 3 study of patients with cUTI [4], to suppress the amplification of a pre-existent drug-resistant *E. coli* subpopulation was evaluated over 10 days in a study conducted using a hollow-*fiber in vitro* infection model.
- When challenged with a bacterial inoculum of 1 × 10^8 CFU/mL, tebipenem exposures representing 600 mg q8h reduced bacterial burdens below that of the initial inoculum over a 10-day study period, with intermittent amplification of pre-existing drug-resistant subpopulations toward the end of study duration.
- These data support the selection of tebipenem 600 mg q8h dosing regimen that minimizes the potential for on-therapy drug-resistance amplification against *E. coli* bacterial burdens larger than those typically observed in patients with cUTI [7, 8].

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