Characterization of Tebipenem Pharmacokinetics-Pharmacodynamics for Efficacy Against Enterobacteriaceae in a One-Compartment *In Vitro* Infection Model

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INTRODUCTION

- Tebipenem (SPR859) is the active form of the orally bioavailable prodrug tebipenem pivoxil (SPR994).
- Tebipenem pivoxil is an oral carbapenem with broad-spectrum *in vitro* activity against Gram-positive, and -negative bacteria and is being developed as an oral option for the treatment of patients with complicated urinary tract infections (cUTI).
- The goal of the studies described herein was to characterize the pharmacokinetics-pharmacodynamics (PK-PD) of tebipenem against a diverse panel of Enterobacteriaceae isolates using a one-compartment *in vitro* infection model. Specific objectives included the following:
  - To carry out dose-fractionation studies to identify the PK-PD index most associated with efficacy of tebipenem against Enterobacteriaceae; and
  - To carry out dose-ranging studies to determine the magnitude of the PK-PD index most associated with efficacy that is required for various levels of bacterial reduction for a panel of Enterobacteriaceae isolates.

METHODS

Antimicrobial Agent and Challenge Isolates

- Tebipenem was provided by Spero Therapeutics (Cambridge, MA).
- A panel of 13 Enterobacteriaceae isolates were supplied from the American Type Culture Collection (ATCC), National Collection of Type Cultures (NCTC) and JMI Laboratories (North Liberty, IA).

In Vitro Susceptibility Testing

- In accordance with Clinical Laboratory Standards Institute (CLSI) guidelines [1], susceptibility studies were completed in triplicate over a two-day period to determine the tebipenem minimum inhibitory concentration (MIC) associated with each Enterobacteriaceae isolate in the challenge panel.

One-Compartment *In Vitro* Infection Model Dose-Fractionation Studies

- A series of 24-hour dose-fractionation studies were completed using a single *Escherichia coli* isolate (ATCC 25922).
- Bacteria (1 x 10^6 colony forming units [CFU]/mL) were exposed to tebipenem concentrations that mimicked human healthy volunteer free-drug plasma concentration-time profiles following oral drug administration.
- Seven tebipenem total daily dose levels (24-hour area under the concentration-time curve [free-drug AUC] range, 0.11 to 19.0 mg•h/L) were fractionated in equal divided doses administered every 4, 8, or 12 hours (q4h, q8h, and q12h, respectively).
- Samples were collected for the evaluation of pharmacokinetic (PK) profiles, and enumeration of bacterial burden over the course of the study.

One-Compartment *In Vitro* Infection Model Dose-Ranging Studies

- In the dose-ranging studies, 13 clinical Enterobacteriaceae isolates were exposed to tebipenem doses ranging from 4.69 to 1200 mg administered q8h (24-hour free-drug AUC ranging from 0.14 to 37.2 mg•h/L).

METHODS

Pharmacokinetic-Pharmacodynamic Analysis

- PK models were fit to the samples collected for the evaluation of the drug concentration profile.
- Data from the dose-fractionation studies were evaluated using Hill-type models and non-linear least squares regression. Relationships between change in $\log_{10}$ CFU/mL from baseline at 24 hours and each of the following tebipenem PK-PD indices were characterized:
  - Free-drug maximum concentration (C_{max}) to MIC ratio (C_{max}:MIC ratio), minimum concentration (C_{min}) to MIC ratio (C_{min}:MIC ratio), percent time above MIC (%T>MIC), and AUC:MIC ratio, with and without adjustment for dosing interval tau for the latter (AUC:MIC ratio•1/dosing interval tau [τ]).
- Hill-type models and non-linear least squares regression were also used to evaluate the data from the dose-ranging studies for the PK-PD index most associated with tebipenem efficacy.

RESULTS

In Vitro Susceptibility Testing

- The known resistance mechanisms and tebipenem MIC values of 0.008 to 0.25 mg/L for the isolates evaluated in the *in vitro* infection models are provided in **Table 1**.

Table 1. Tebipenem MIC values and known resistance mechanisms for the isolates evaluated within the one-compartment *in vitro* infection model dose-fractionation and dose-ranging studies

Isolate	Known resistance mechanisms	Tebipenem MIC (mg/L)
E. coli ATCC 25922[a]	Wild type ATCC reference strain	0.015
E. coli NCTC 13441	CTX-M-15, Sequence Type-131 (ST-131)	0.015
E. coli 4643	CTX-M-15, OXA1/30	0.008
E. coli 13319	CTX-M-15, TEM-1,AcrAB-TolC overexpression OmpC, OmpF porin deficient	0.015
E. coli 872217	CMYII	0.25
E. coli 845741	CTX-M-15, OXA-1, SHV-12, (ST-131)	0.03
Klebsiella pneumoniae 25021	CTX-M-15, TEM-1, OXA-2	0.03
K. pneumoniae 604	CTX-M-15, OXA1/30, SHV-1	0.06
K. pneumoniae ATCC 43816	Wild type ATCC reference strain	0.015
K. pneumoniae 632346	CTX-M-15, OXA-1/30, SHV-5	0.125
K. pneumoniae 934954	CTX-M-15, OXA-1, SHV-28, TEM-1	0.125
P. mirabilis ATCC 29906	Wild type ATCC reference strain	0.015
P. mirabilis ATCC BAA-2791	TEM-1, CMY-4	0.25

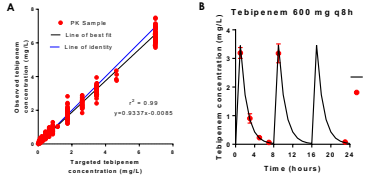
a. Isolate utilized for the dose-fractionation studies.

One-Compartment *In Vitro* Infection Model Studies

- As evidenced by the agreement between targeted and observed tebipenem concentrations shown in **Figure 1**, the targeted free-drug plasma concentration-time profiles were well simulated for all tebipenem dosing regimens studied in the *in vitro* infection model.

RESULTS

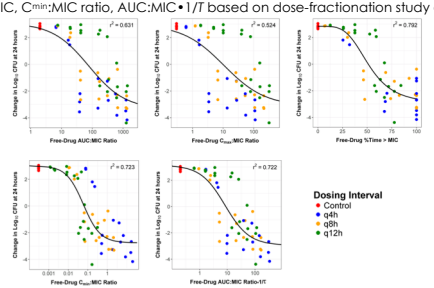
Figure 1. Relationship between all targeted and observed tebipenem concentrations simulated in the one-compartment *in vitro* infection model (A) and the average concentration-time profile for the tebipenem 600 mg q8h regimen (B)



One-Compartment *In Vitro* Infection Model Dose-Fractionation Studies

- Results of dose-fractionation study data shown in **Figure 2** demonstrated the activity of tebipenem to be time-dependent, with free-drug C^{min}:MIC ratio, %T>MIC and AUC:MIC ratio•1/τ similarly describing the PK-PD of tebipenem based on r^2 values.
  - Free-drug %T>MIC failed to describe the data well as evidenced by the pooling of data at 100% free-drug %T>MIC, effects ranging from net bacterial stasis to a 4 $\log_{10}$ CFU reduction from baseline.
  - Free-drug C^{min}:MIC ratio failed to describe the *in vitro* activity of tebipenem well as evidenced by the layering of activity by dosing interval, with larger exposures required when tebipenem was administered more frequently.
  - Free-drug AUC:MIC ratio•1/τ was considered to be the PK-PD index most associated with tebipenem efficacy.

Figure 2. Relationships between change in $\log_{10}$ CFU/mL from baseline at 24 hours and each of free-drug tebipenem AUC:MIC ratio, C^{max}:MIC ratio, %T>MIC, C^{min}:MIC ratio, AUC:MIC•1/τ based on dose-fractionation study data

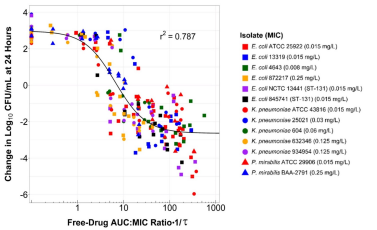


RESULTS

One-Compartment *In Vitro* Infection Model Dose-Ranging Studies

- The relationship between change in $\log_{10}$ CFU/mL from baseline at 24 hours and tebipenem free-drug AUC:MIC ratio•1/τ based on data from the dose-ranging studies is shown in **Figure 3**.
- The magnitude of free-drug AUC:MIC ratio•1/τ associated with achieving net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline based on data for the panel of 13 Enterobacteriaceae isolates was 7.23, 13.1, and 32.4, respectively.

Figure 3. Relationship between the change in $\log_{10}$ CFU/mL from baseline at 24 hours and tebipenem free-drug AUC:MIC ratio•1/τ based on data for 13 Enterobacteriaceae isolates evaluated in the dose-ranging studies



CONCLUSIONS

- The results of dose-fractionation studies demonstrated that free-drug AUC:MIC ratio•1/τ was the PK-PD index most associated with tebipenem efficacy.
- Based upon data for 13 Enterobacteriaceae isolates evaluated in the dose-ranging studies, the magnitude of tebipenem free-drug AUC:MIC ratio•1/τ associated with net bacterial stasis and 1- and 2-$\log_{10}$ CFU reductions from baseline was 7.23, 13.1, and 32.4, respectively.
- These data will be useful to design other pre-clinical studies and support tebipenem dose selection for clinical studies in patients with cUTI.

REFERENCES

1. Clinical and Laboratory Standards Institute. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved standard, 10th edition. CLSI document M07-A10. Clinical and Laboratory Standards Institute, Wayne, PA. 2015.

ACKNOWLEDGEMENTS

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