Pharmacokinetic-Pharmacodynamic Evaluation of Sulopenem Using a Five-Day Hollow-Fiber *In Vitro* Infection Model

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INTRODUCTION

- Sulopenem etzadroxil, the oral (PO) prodrug of the active moiety sulopenem, is a thiopenem in development for the treatment of uncomplicated urinary tract infections.
- Oral sulopenem is a bilayer tablet composed of sulopenem etzadroxil and probenecid, an organic anion transport inhibitor that delays renal excretion of sulopenem.
- The goal of the studies described herein was to determine whether the chosen sulopenem clinical PO dosing regimen of 500 mg administered every 12 hours (q12h), would induce resistance amplification in a hollow-fiber *in vitro* infection model over a clinically relevant time period.

METHODS

Antimicrobial Agent and Challenge Isolates

- Sulopenem was provided by Iterum Therapeutics (Old Saybrook, CT).
- A panel of four *Escherichia coli* clinical isolates (fluoroquinolone-resistant, ESBL producing, Sequence Type 131, sulopenem MIC 0.03 to 0.125 mg/L) were supplied from the 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 sulopenem minimum inhibitory concentration (MIC) associated with each *E. coli* challenge isolate.

Hollow-Fiber *In Vitro* Model Evaluating the Sulopenem Clinical Dose

- A series of duplicate, five-day, hollow-fiber *in vitro* infection model studies, evaluating the sulopenem oral clinical dose of 500 mg (q12h), were conducted against the panel of four *E. coli* isolates.
- Bacteria (1 x 10^6 colony forming units [CFU]/mL) were exposed to sulopenem concentration time profiles representing total-drug urine profiles following a 500 mg oral dose administered twice daily (q12h).
- Each sulopenem regimen was compared against a no-treatment control regimen and two active control compounds simulated using free-drug plasma values following intravenous (IV) administration (meropenem 2 g administered every 8 hours [q8h], and levofloxacin 750 mg administered every 24 hours [q24h]).
- Samples were collected over the five-day period for the enumeration of total bacterial burdens and observation of simulated pharmacokinetic (PK) profiles via qualified liquid chromatography tandem mass-spectrometry (LC-MS/MS).

Analytical Method

- An analytical method was developed for the determination of sulopenem, meropenem and levofloxacin unknown pharmacokinetic samples in cation adjusted Mueller Hinton broth by LC-MS/MS on a Sciex 5500 with an ExionLC AC front-end.

RESULTS

In Vitro Susceptibility Testing

- Known resistance mechanisms, sequence types and sulopenem MIC values for isolates evaluated in the *in vitro* infection models are provided in **Table 1**.
  - Sulopenem MIC values ranged from 0.03 to 0.125 for the four *E. coli* isolates evaluated.

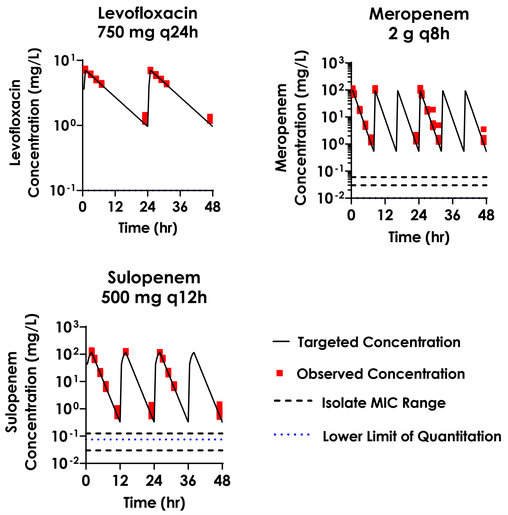
Table 1. Sulopenem MIC values, known resistance mechanisms and sequence types for the isolates evaluated in the five-day hollow-fiber *in vitro* infection model

Isolate	Known resistance mechanisms (Sequence Type)	Sulopenem MIC (mg/L)
E. coli NCTC 13441	CTX-M-15, (ST-131)	0.125
E. coli 1031823	CTX-M-14, TEM-1 (ST-131, O25b)	0.06
E. coli 845741	CTX-M-15, OXA-1, SHV-12 (ST-131, O25b)	0.06
E. coli 992013	CTX-M-27, TEM-1 (ST-131, O25b)	0.03

Hollow-Fiber *In Vitro* Model Evaluating the Sulopenem Clinical Dose

- As evidenced by the agreement between targeted and observed sulopenem, meropenem and levofloxacin concentrations shown in **Figure 1**, concentration-time profiles for each compound were well simulated in the hollow-fiber infection *in vitro* model.

Figure 1. Concentration-time profiles of the levofloxacin 750 mg q24h, meropenem 2 g q8h, and sulopenem q12h regimens evaluated in the five-day hollow-fiber *in vitro* infection model studies

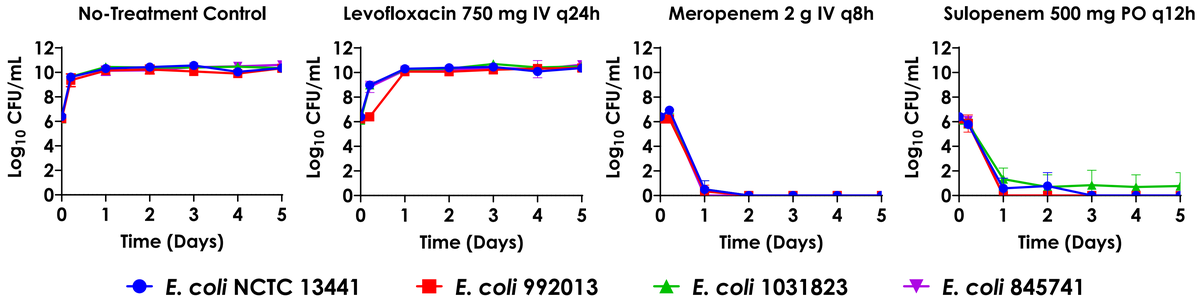


RESULTS

Hollow-Fiber *In Vitro* Infection Model Evaluating the Sulopenem Clinical Dose

- The sulopenem 500 mg q12h regimen repeatedly reduced the bacterial density of the total population from the initial burden of 1.0 x 10^6 CFU/mL to those below 1 $\log_{10}$ CFU/mL, and prevented amplification of drug-resistant subpopulations over the five-day period for each of the four isolates evaluated in the system (**Figure 2**).
- The bactericidal activity observed for the sulopenem 500 mg q12h regimen simulating urine concentrations was similar to that of the meropenem positive control regimen simulating free-drug plasma values.
- The levofloxacin 750 mg q24h negative control regimens failed to provide any antimicrobial activity across the isolate panel, as would be expected for fluoroquinolone-resistant isolates.

Figure 2. Hollow-fiber *in vitro* infection model study results of the four *E. coli* isolates exposed to sulopenem 500 mg q12h, meropenem 2 g q8h, levofloxacin 750 mg q24h, and no-treatment control regimens over a five-day period.



CONCLUSIONS

- The five-day hollow-fiber *in vitro* infection model studies simulating urine concentration time profiles of a sulopenem 500 mg PO q12h regimen provided insight into the regimens ability to prevent on-therapy resistance over a clinically relevant period of time.
- The sulopenem 500 mg q12h clinical regimen was able to repeatedly reduce the bacterial density of the total population from the initial burden of 1.0 x 10^6 CFU/mL to those below 1 $\log_{10}$ CFU/mL over the clinically relevant study duration, as well as prevent amplification of drug-resistant subpopulations over the five-day period for each isolate evaluated.
- The meropenem active control successfully reduced burdens across the entire challenge isolate panel while the levofloxacin negative control failed to provide any antimicrobial activity as expected for a panel of isolates that are resistant to fluoroquinolones.
- The activity observed in the sulopenem 500 mg q12h clinical regimen simulating urine concentration time profiles observed following oral dosing was similar to that observed in the meropenem 2 g q8h positive control regimen simulating free-drug plasma profiles following intravenous administration.
- The data described herein provides confidence into the ability of the sulopenem etzadroxil/probenecid 500 mg/500 mg PO q12h clinical regimen to successfully reduce bacterial burdens below 1 $\log_{10}$ CFU/mL as well as prevent the amplification of drug-resistant populations over the five-day period, for a panel of clinically relevant *E. coli* isolates.

REFERENCES

1. Clinical Laboratory Standards Institute. Methods for Dilutional Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. 11th edition. CLSI supplement M07; 2018

ACKNOWLEDGEMENTS

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