**INTRODUCTION**

- Tebipenem (SPR859) is a carbapenem that is active against a range of Enterobacteriaceae with a variety of resistance mechanisms. Tebipenem is the microbiologically active form of an orally administered pivalox pro-drug SPR949, that is currently under development for complicated urinary tract infections (cUTI).
- The pharmacokinetic and pharmacodynamics (PK-PD) of tebipenem has been well characterised in the neutropenic mouse thigh model of infection, and the PK driver is best described by AUC/MIC*1/Tau.
- Here, further work in a hollow fibre infection model is described to support the identification of PK index and magnitude that best links drug exposure with antibacterial efficacy for multidrug resistant Enterobacteriaceae.

**METHODS**

**Hollow Fibre Infection Model**

- An ESBL-producing *Escherichia coli* (SPT719) with a tebipenem MIC of 0.03 mg/L was used as the challenge strain. Active drug (tebipenem) was used for all experiments.
- The simulated PK profile was based on Phase I human PK data.
- Dose ranging studies were performed to identify informative parts of the exposure-response relationships.
- Bacterial killing and the emergence of resistance were used as experimental endpoints, using drug-free Mueller Hinton agar and drug containing agar with a concentration of active drug of 0.125 mg/L.
- Dose fractionation studies were performed using an isodos experiment with q6h, q8h, q12h and q24h schedules of administration.
- The pharmacokinetic and pharmacodynamic PK-PD data were modelled using a population methodology to identify drug exposures that resulted in bacterial killing and the emergence of resistance.

**RESULTS**

- The MIC of tebipenem against SPT719 was 0.03 mg/L. The fT>MIC for each regimen ranged from 28% to 100%. More fractionated regimens produced more antibacterial effect and suppressed the emergence of resistance. Logarithmic killing and the prevention of emergence of resistance was achieved with a fT>MIC 54-76%.

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>Notes</th>
<th>Test Article</th>
<th>Mode MIC (mg/L)</th>
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<tbody>
<tr>
<td><em>E. coli</em> strain SPT-719</td>
<td></td>
<td>SPR859 (tebipenem)</td>
<td>0.03</td>
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<tr>
<td></td>
<td>ESBL+</td>
<td>Ertapenem</td>
<td>0.125</td>
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<td>Meropenem</td>
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**CONCLUSIONS**

- SPR859 exhibits time-dependent pharmacodynamics for both bacterial killing and the prevention of emergence of resistance.
- The pharmacodynamic targets in the hollow fibre infection model are comparable to those estimated from murine models.
- These data will be used to identify optimal dosing regimens for patients with cUTI.