INTRODUCTION

- Increasing prevalence of multi-drug resistant (MDR) bacteria is a serious threat to global health with limited treatment options.
- SPR994 is an orally bioavailable prodrug of Tebipenem, and is currently under development for complicated urinary tract infections.
- Tebipenem is active against a range of Enterobacteriaceae with a variety of resistance mechanisms.
- The pharmacokinetics and pharmacodynamics (PK-PD) of SPR994 for gram-negative pathogens is poorly described.
- Dose finding, dose fractionation, and pharmacokinetic studies were performed to determine the PK-PD of SPR994 that best links drug exposure with antimicrobial activity.
- All experiments were performed under a UK Home Office License with local ethical committee clearance at the University of Liverpool.

METHODS

Mouse Models
- Neutropenic thigh mouse model against a well characterised wild-type challenge strain of *Escherichia coli* ATCC 25922 was used.
- Male CD-1 mice weighing 25-30 grams.
- Endpoint of studies was average CFU/g of both thighs or drug concentrations in plasma.

Dose Finding Studies
- Treatment started 2 hours post inoculation. SPR994 was administered via oral gavage every 6, 12, or 24 hours.
- Inhibitory Sigmoid $E_{max}$ model was fitted.
- Further pharmacodynamics were examined in a range of wild-type and ESBL-producing *E. coli* and Klebsiella pneumoniae.

Dose Fractionation Study
- $EC_{50}$, $EC_{90}$, $EC_{95}$, and $EC_{99}$ of SPR994 was administered orally every 6, 12, or 24 hours ($q8h$, $q12h$, or $q24h$) for dose fractionation studies.
- Difference in groups were compared using ANOVA and non-linear regression.

Pharmacokinetics (PK)
- PK of SPR994 was estimated using 3.33, 8.33, 16.67, and 33.33mg/kg administered q8h.
- Drug concentrations in mouse plasma were measured using LC/MS/MS.
- Results were mathematically modelled using Pmetrics.

RESULTS

1. Pharmacokinetics showed SPR994 is orally bioavailable and has linear PK.

2. Wild-type & non-wild-type strains of *E. coli* & *K. pneumoniae*, molecular information, ESBL content, and MICS against SPR994 are poorly described.

- Several PK-PD parameters were explored (figures 3 to 6).
- The use of the traditional index $T>MIC$ for carbapenems couldn’t be used as the data clump at 100% $T>MIC$ (figure 5).
- The pharmacodynamics of SPR994 were comparable across the various strains and were independent of the presence of ESBL. A dose of SPR994 6.67mg/kg q8h was required to achieve stasis in mice.
- The PK-PD index in mice for SPR994 is $AUC:MIC*1/Tau$ (figures 7-10) and these data will be used in part as an index to help identify dosing regimens for patients.

CONCLUSIONS