Pharmacokinetics and Pharmacodynamics of Tebipenem for Multi-Drug Resistant Enterobacteriaceae

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INTRODUCTION

• Increasing prevalence of multi-drug resistant (MDR) bacteria is a serious threat to global health with limited treatment options
• Tebipenem pivoxil (TBPM-Pi, SPR994) is a new carbapenem that is orally bioavailable
• SPR994 is active against a range of Enterobacteriaceae with a variety of resistance mechanisms and is currently licensed for use in children in Japan
• The pharmacokinetics and pharmacodynamics (PK-PD) of SPR994 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 approval 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 hours (q6h), in a total of 3 studies.
• Inhibitory Sigmoid Emax model was fitted.
• Further pharmacodynamics were examined in a range of wild-type and ESBL-producing Escherichia coli and Klebsiella pneumoniae.

Dose Fractionation Study
• EC50, EC75, and EC90 of SPR994 was administered orally every 6, 12, or 24 hours (q6h, 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 orally.
• 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. Strains used, molecular information & MICs

<table>
<thead>
<tr>
<th>Organism</th>
<th>Strain</th>
<th>Known Molecular Information</th>
<th>MIC (ug/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>ATCC25922</td>
<td>QM strain</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>ATCC25923</td>
<td>TEM-1</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>NCTC13462</td>
<td>CTX-M2</td>
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<tr>
<td></td>
<td>SPT719</td>
<td>CP_SHV_ESBL_CP_TEM_WT</td>
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<tr>
<td></td>
<td>SPT720</td>
<td>MOX-1</td>
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<tr>
<td></td>
<td>SPT741</td>
<td>CP_CTX_M-Group1_CP_TEM_WT_ST131_O129 (clade)</td>
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<tr>
<td>K. pneumonia</td>
<td>ATCC43816</td>
<td>QM strain</td>
<td>0.015</td>
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<tr>
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<td>ATCC2776</td>
<td>TEM-1</td>
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<td>NCTC13469</td>
<td>CTX-M1</td>
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<td></td>
<td>SPT722</td>
<td>CTX-M915, OXA-1, SHV-24 TEM-1</td>
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<td>SPT725</td>
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</tr>
</tbody>
</table>

3. The dose fractionation study showed the fractionated schedules out performing the once daily dose, with ANOVA supporting this conclusion.

SPR994 exhibits time dependent PD which cannot be described with T>MIC (D), but is quantified using Cmin/MIC (Fig. 6) & AUC/MIC1/tau (Fig. 7).

4. Dose finding studies with 6 strains of E. coli supports the AUC>MIC*1/Tau PK-PD driver of SPR994

5. Dose finding studies with 6 strains of K. pneumoniae supports the AUC>MIC*1/Tau PK-PD driver of SPR994

6. E. coli & K. pneumoniae dose finding studies demonstrate minimal differences between species, wild-type, or ESBL-producers.

CONCLUSIONS

• Stasis, -1, and -2 log kill were demonstrated over 12 strains of E. coli and K. pneumoniae, with a dose of SPR994 6.67mg/kg q6h required to achieve stasis in mice.
• The pharmacodynamics of SPR994 were comparable across the various strains of E. coli and K. pneumoniae tested, and were independent of the presence of ESBL.
• The PK-PD driver in mice for SPR994 is AUC>MIC1/tau and these data will be used in part as an index to help identify dosing regimens for patients.