Dose Ranging and Dose Fractionation of Tebipenem-Pivoxil (SPR994) in Neutropenic Murine Thigh Models of Gram-Negative Bacterial Infection

1Evotec (UK) Ltd., Macclesfield, U.K., 2Spero Therapeutics, Cambridge, MA, USA

ABSTRACT

Background: SPR994 is tebipenem-pivoxil, an orally available carbapenem with broad-spectrum activity against extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae, currently under development for complicated urinary tract infections (cUTI). Herein, we assessed the efficacy of SPR994 in neutropenic murine models of thigh infection by Escherichia coli.

Methods: MIC assays were performed with SPR994, the microbiologically active form of SPR994, using CLSI methodology. Male ICR mice were rendered neutropenic using cyclophosphamide on days 4 and 1. Mice were infected by intramuscular injection into the lateral thigh muscle with E. coli ATCC 25922 (5×10^9 CFU/mL), or E. coli H44/9 (ESBL+; 1×10^10 CFU/mL) or E. coli ATCC 25922 (5×10^9 CFU/mL) in an ESBL-producing clinical isolate (ATCC 25922, bldt). Treatment initiated 1 h post infection. For dose-fractionation studies, SPR994 was administered as a single dose (30 mg/kg p.o. or q8h) or divided into three equal doses (10 mg/kg p.o. or q8h) on days 5-9 post infection. For dose-fractionation studies, mice were euthanized 25 h post infection, and thigh tissue quantitatively cultured, serially diluted, plated on appropriate media. Colony forming units were quantified following overnight incubation.

RESULTS

Figure 1. Structures of SPR859 and SPR994.

Table 1. MIC of test antibiotics. MEM, meropenem; TIG, teigacycline

<table>
<thead>
<tr>
<th>Bacterium</th>
<th>MIC (μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SPR859</td>
</tr>
<tr>
<td>E. coli ATCC 25922</td>
<td>0.03</td>
</tr>
<tr>
<td>E. coli H44/9</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Figure 2. Scatter plot of geometric mean bacterial burden (CFU/g) 25h following infection with E. coli H44/9, ATCC 25922 and treatment with test articles.

A. SPR994 PO dose-fractionation: q24h, q12h, and q6h administration.
- Maximum efficacy observed following administration of 5 mg/kg/day SPR994 q6h (2.2 log10 CFU/g reduction in burden of pre-treatment).
- Within the dose range of 10 to 15 mg/kg/day, q9h SPR994 was significantly more effective than q12h and q24h administration.
- In this study, at 20 mg/kg/day, the differences between dosing regimens were not significant.
- If mice were euthanized prior to the 25 h study endpoint (due to clinical condition), this time is indicated in brackets for the relevant group.

B. SPR994 PO dose-fractionation: q24h, q12h, q6h, q4h and q2h administration.
- Trend towards increasing efficacy with increasing fractionation of total daily dose of SPR994.
- Benefit of fractional dosing most evident in mice receiving 10 mg/kg/day SPR994.
- 10 mg/kg/day SPR994 administered q6h and q4h reduced bacterial burden by 1.4 and 1.8 log10 CFU/g, respectively, cf. pre-treatment.
- 20 mg/kg/day SPR994 q4h, q6h, or q8h reduced bacterial burden by 1.5 to 2.3 log10 CFU/g, cf. pre-treatment.

CONCLUSIONS

- Orally-administered SPR994 was effective at reducing the burden of E. coli in the thighs of mice in a dose-dependent fashion in in fractionalized doses of the antibiotic displayed a trend towards increasing efficacy.
- These results support the continued development of SPR994 as an oral option for the treatment of multidrug-resistant Gram-negative bacterial infections.

INTRODUCTION

SPR994 is tebipenem-pivoxil, an orally available carbapenem with broad-spectrum activity against extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria currently under development for the treatment of complicated urinary tract infections (cUTI). Herein, we assessed the efficacy of SPR994 in neutropenic murine models of thigh infection by Escherichia coli.

METHODS

Antimicrobial susceptibility testing was performed with SPR859, the microbiologically active form of SPR994, using CLSI methodology. Animal experiments were performed under UK Home Office Licence P237472, with local ethical committee clearance. Male ICR mice were rendered neutropenic using cyclophosphamide on days 4 & 1 (150 and 100 mg/kg, respectively). Mice were infected by intramuscular injection with either E. coli ATCC 25922 (5×10^9 CFU/mL), or E. coli H44/9 (ESBL+; 1×10^10 CFU/mL) for an intended model duration of 25 h. Treatment initiated 1 h post infection. For dose-fractionation studies, SPR994 was administered as a single oral dose (30 mg/kg PO). For dose-fractionation, PO doses between 1 and 30 mg/kg/day were administered on days 5-9 post infection. For dose-fractionation studies, mice were euthanized 25 h post infection, and thigh tissue quantitatively cultured, serially diluted, plated on appropriate media. Colony forming units were quantified following overnight incubation.

Dose Ranging and Dose Fractionation of Tebipenem-Pivoxil (SPR994) in Neutropenic Murine Thigh Models of Gram-Negative Bacterial Infection

1Evotec (UK) Ltd., Macclesfield, U.K., 2Spero Therapeutics, Cambridge, MA, USA