Background

• SPR206 is a novel polymyxin derivative with potent in vitro and in vivo activity against Acinetobacter baumanii, Pseudomonas aeruginosa, and multiple clinically important species of Enterobacteriaceae, including multidrug- and extensively drug-resistant strains.1-3

• Nonclinical toxicology studies in mice, rats, and nonhuman primates have demonstrated that SPR206 exhibits a lower risk for nephrotoxicity than colistin and polymixin B.4

• A first-in-human pharmacokinetic and safety study demonstrated no appreciable drug accumulation with repeated intravenous dosing and no evidence of nephrotoxicity observed over 14 days of 100 mg qd dosing regimen of SPR206.5

• Concentrations of antibiotics in epithelial lining fluid (ELF) and in alveolar macrophages (AM) are important for determining antibiotic activity and dosing in pneumonia.4,6

• This study was designed to determine the concentrations of SPR206 in the extravascular (ELF) and intracellular (AM) compartments of the lung to provide essential information for the development of SPR206 as an anti-infective agent for the treatment of lower respiratory tract infections.

Methods

• Phase 1, multiple-dose, open-label pharmacokinetic study in healthy adult male and female subjects. Safety assessments included physical exams, vital sign determination, standard clinical laboratory monitoring, ECG, and adverse event recording.

• Subjects were administered three intravenous doses of SPR206 as a 1-hr infusion of 100 mg every 8 hr.

• Blood samples for determining plasma SPR206 concentrations were collected within 60 minutes prior to the start of the first 3 doses and at 2, 3, 4, 6, and 8 hours after the start of the third intravenous infusion of SPR206.

• Each subject underwent one standardized bronchoalveolar and bronchoalveolar lavage (BAL) at 2, 3, 4, 6, or 8 hr after the start of the third intravenous infusion of SPR206.

• Plasma and BAL samples were obtained at each sampling time to determine SPR206 and urine concentrations by validated LC-MS/MS assays.

• ELF concentrations were calculated by urea dilution method.4,6,8

• AM concentrations were determined from cell pellet concentrations, cell count in BAL fluid and macrophage cell volume.9

• Noncompartmental pharmacokinetic analysis of SPR206 total plasma concentrations was performed using Phoenix WinNonLin software version 8.3. (Certara Inc.).

• Mean concentration value at each BAL sampling time was used to determine AUC₃ₐ₉ of SPR206 in plasma, ELF, and AM.

• ELF- and AM-to-plasma (total and unbound) ratios were determined with simultaneous drug concentrations at each BAL sampling time and with AUC₀₋₉ values.

• Unbound fraction value of 0.5±1 was used for SPR206 in plasma.

Objectives

The primary objective of this study was to evaluate the intra pulmonary pharmacokinetics, including ELF and AM concentrations, of SPR206 compared to plasma concentrations of SPR206 in healthy adult subjects.

The secondary objective of this study was to assess the safety and tolerability of SPR206 in healthy adult subjects.

Table 2. Ratios of ELF and AM concentrations to total and unbound plasma concentrations of SPR206 (Plasma and BAL pharmacokinetic populations)

<table>
<thead>
<tr>
<th>BAL sampling time</th>
<th>ELF to total plasma</th>
<th>ELF to unbound plasma</th>
<th>AM to total plasma</th>
<th>AM to unbound plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 hours</td>
<td>0.183 ± 0.032</td>
<td>0.208 ± 0.035</td>
<td>0.190 ± 0.036</td>
<td>0.226 ± 0.124</td>
</tr>
<tr>
<td>3 hours</td>
<td>0.199 ± 0.066</td>
<td>0.216 ± 0.072</td>
<td>0.184 ± 0.065</td>
<td>0.201 ± 0.071</td>
</tr>
<tr>
<td>4 hours</td>
<td>0.200 ± 0.067</td>
<td>0.208 ± 0.074</td>
<td>0.223 ± 0.089</td>
<td>0.244 ± 0.097</td>
</tr>
<tr>
<td>6 hours</td>
<td>0.428 ± 0.176</td>
<td>0.469 ± 0.192</td>
<td>0.519 ± 0.223</td>
<td>0.566 ± 0.244</td>
</tr>
<tr>
<td>8 hours</td>
<td>0.347 ± 0.138</td>
<td>0.380 ± 0.151</td>
<td>0.503 ± 0.192</td>
<td>0.550 ± 0.210</td>
</tr>
</tbody>
</table>

Table 3. Ratios of ELF and AM AUC₃ₐ₉ values to total and unbound plasma AUC₀₋₉ values of SPR206 (Plasma and BAL pharmacokinetic populations)

<table>
<thead>
<tr>
<th>Matrix</th>
<th>Ratio of AUC₀₋₉ of ELF to AUC₀₋₉ of total plasma</th>
<th>Ratio of AUC₀₋₉ of AM to AUC₀₋₉ of total plasma</th>
<th>Ratio of AUC₀₋₉ of ELF to AUC₀₋₉ of unbound plasma</th>
<th>Ratio of AUC₀₋₉ of AM to AUC₀₋₉ of unbound plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>0.328</td>
<td>0.300</td>
<td>0.256</td>
<td>0.242</td>
</tr>
<tr>
<td>AM</td>
<td>0.334</td>
<td>0.328</td>
<td>0.256</td>
<td>0.242</td>
</tr>
</tbody>
</table>

Conclusions and Summary

• The results of this study provided important information on pulmonary PK of SPR206 in healthy subjects. The estimated intrapulmonary SPR206 penetration ratios as measured by ratio of AUC₀₋₉ in ELF to am to unbound plasma SPR206 were 0.264 and 0.328, respectively.

• More than 33% of 3 doses of 100 mg IV qd was well tolerated and generally safe with no SAEs or deaths and no clinically significant abnormalities observed in laboratory parameters, vital signs, ECG assessments, and physical examinations.

References


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