SPR206 Pharmacokinetics (PK) in Plasma, Epithelial Lining Fluid (ELF), and Alveolar Macrophages (AM) in Healthy Adult Subjects

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Background

- SPR206 is a novel polymyxin derivative with potent *in vitro* and *in vivo* activity against *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and multiple clinically important species of *Enterobacterales*, 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 polymyxin B.[1,4]
- 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 q8h 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.[6,7]
- This study was designed to determine the concentrations of SPR206 in the extracellular (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.

Objectives

- The primary objective of this study was to evaluate the intrapulmonary 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.

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-hour infusion of 100 mg every 8 hours.
- Blood samples for determining plasma SPR206 concentrations were collected within 60 minutes prior to the 2nd and 3rd 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 bronchoscopy and bronchoalveolar lavage (BAL) at 2, 3, 4, 6, or 8 hours after the start of the third intravenous infusion of SPR206.
- Plasma and BAL samples were obtained at each sampling time to determine SPR206 and urea concentrations by validated LC-MS/MS assays.
- ELF concentrations were calculated by urea dilution method.[8,9]
- AM concentrations were determined from cell pellet drug 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 AUC_{0-8} 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 AUC_{0-8} values.
- Unbound fraction value of 0.914 was used for SPR206 in plasma.

Results

Table 1. Noncompartmental pharmacokinetic parameters in plasma, ELF, and AM after administration of the 3rd dose of SPR206 (Plasma and BAL pharmacokinetic populations[a,b])

Matrix	AUC_{0-8} (h·ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	t_{max} (h)
Plasma[a]	20120.7	4395.0	1409.9	2.1
ELF	4859.8	735.5	431.5	2.2
AM	6026.4	860.6	604.2	6.4

[a] Plasma pharmacokinetic population included all subjects enrolled (N=34).
[b] BAL pharmacokinetic population included 27 subjects.

Figure 1. Mean (SD) concentrations of SPR206 in plasma, ELF, and AM at BAL sampling time points.

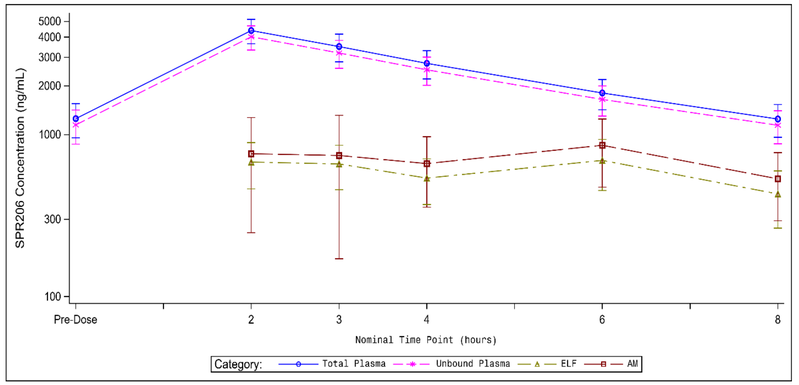

Table 2. Ratios of ELF and AM concentrations to total and unbound plasma concentrations of SPR206 (Plasma and BAL pharmacokinetic populations)

BAL sampling time	ELF to total plasma	ELF to unbound plasma	AM to total plasma	AM to unbound plasma
2 hours	0.183 ± 0.032	0.200 ± 0.035	0.206 ± 0.114	0.226 ± 0.124
3 hours	0.199 ± 0.066	0.218 ± 0.072	0.184 ± 0.065	0.201 ± 0.071
4 hours	0.190 ± 0.067	0.208 ± 0.074	0.223 ± 0.089	0.244 ± 0.097
6 hours	0.428 ± 0.176	0.469 ± 0.192	0.519 ± 0.223	0.568 ± 0.244
8 hours	0.347 ± 0.138	0.380 ± 0.151	0.503 ± 0.192	0.550 ± 0.210

Data expressed as arithmetic mean ± SD.

Table 3. Ratios of ELF and AM AUC_{0-8} values to total and unbound plasma AUC_{0-8} values of SPR206 (Plasma and BAL pharmacokinetic populations)

Ratio of AUC_{0-8} of ELF to AUC_{0-8} of total plasma	Ratio of AUC_{0-8} of ELF to AUC_{0-8} of unbound plasma	Ratio of AUC_{0-8} of AM to AUC_{0-8} of total plasma	Ratio of AUC_{0-8} of AM to AUC_{0-8} of unbound plasma
0.242	0.264	0.300	0.328

Safety

- Treatment with 3 doses of SPR206 100 mg IV q8h was safe and well tolerated in healthy adult subjects. No safety concerns were identified.
- Overall, 64.7% of subjects experienced at least 1 TEAE and 13 subjects (38.2%) experienced at least 1 study medication-related TEAE.
- The most frequently reported study medication-related TEAEs were oral paresthesia (29.4%) and nausea (5.9%).
- All paresthesia-like events were mild and resolved within the day of their occurrence in most cases. None of the paresthesia-like events led to discontinuation of study medication or study discontinuation.
- There were no SAEs, deaths, TEAEs leading to study medication, or study discontinuations during the study. No clinically significant abnormalities were noted related in safety clinical laboratory parameters including albumin, urea nitrogen, creatinine, and estimated creatinine clearance. No clinically meaningful changes were noted in vital signs, ECG assessments, and physical examinations.

Summary and Conclusions

- The results of this study provided important information on intrapulmonary PK of SPR206 in healthy subjects. The estimated intrapulmonary SPR206 penetration ratios as measured by ratio of AUC_{0-8} in ELF and AM to unbound plasma SPR206 were 0.264 and 0.328, respectively.
- Administration of 3 doses of SPR206 100 mg IV q8h was well tolerated and generally safe with no SAEs or deaths and no clinically significant abnormal abnormalities observed in laboratory parameters, vital signs, ECG assessments, or physical examination.

References

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