ABSTRACT

Background: SPR206 is a polymyxin analog with potent, broad-spectrum, direct antibacterial activity for the treatment of multi-drug resistant Gram-negative infections. The GLP 14-day toxicity assessment of SPR206 is reported here, including a CNS assessment.

Methods: SPR206 was assessed for toxicity in male and female cynomolgus monkeys at 15, 30, and 45 mg/kg/day delivered via three one-hour infusions (8 hours apart; TID) for 14 consecutive days. A 28-day recovery period also was included in the study design. Parameters assessed during the study included body weights, clinical observations, food consumption, neurological examinations, electrocardiography, ophthalmology, hematology, coagulation, serum chemistry, urinalysis, and urine and plasma toxicokinetics. Macroscopic findings, organ weights, and histopathology were performed on a full panel of tissues.

Results: The NOAEL of SPR206 following 14 days of TID dosing to cynomolgus monkeys was 30 mg/kg/day. There were no SPR206 related effects on food consumption, electrocardiography, or ophthalmology at any SPR206 dose. The target organ of toxicity for SPR206 in monkeys was the kidney. SPR206 at 45 mg/kg/day resulted in significant clinical observations, including one mortorbund female, and mild to moderate increases in blood urea nitrogen (BUN) and serum creatinine (Scr). Changes in BUN and Scr correlated with pale kidneys (one female), higher kidney weights, and histopathological changes in the kidney of tubular degeneration, degeneration/regeneration, casts, and dilation. The observed nephrotoxicity at 45 mg/kg/day was partially reversible following a 28-day recovery period. SPR206 was associated with sporadic hipoactivity, ataxia, and balance at x0 mg/kg/day, however, no neurological effects were evident at any dose level including the highest dose tested of 45 mg/kg/day. The toxicokinetics of SPR206 were dose proportional: the AUC of SPR206 at the NOAEL dose was 342 mg·h/mL.

Conclusions: In the current toxicology assessment, the target organ of toxicity for SPR206 in this study was the kidney. This toxicity is monitorable, reversible, and the NOAEL, AUC<sub>0-24</sub> exposure compares favorably to that of clinically validated comparator, SPR741. Therefore supporting advancement of SPR206 into Phase 1 studies. In other GLP safety testing, SPR206 was not genotoxic, and there were no significant deviations in cardiovascular or respiratory safety pharmacology parameters.

INTRODUCTION

SPR206 is a polymyxin analog with potent, broad-spectrum, direct antibacterial activity for the four major Gram-negative ESKEAPE pathogens (K. pneumoniae, A. baumannii, P. aeruginosa, and Enterobacter species), as well as E. coli, including those possessing prominent resistant mechanisms. SPR206 exhibits non-clinical efficacy at or superior to PMB and colistin and is being investigated for the treatment of serious Gram-negative hospital infections. SPR206 was assessed for potential target organs of toxicity, recovery of any toxicity, and biomarkers to monitor and potentiate safety in a GLP 14-day toxicology study in cynomolgus monkeys per ICH guidance to enable Phase 1 studies in normal healthy volunteers.

METHODS

SPR206 or control article/vehicle (0.9% Sodium Chloride Injection, USP) was administered by IV, 1-hour infusion through a chronic femoral IV catheter. Doses were administered three times per day (8 hours ± 30 minutes apart), for fourteen consecutive days. The dosing volume was constant among groups, at 10 mL/kg. The SPR206 dose levels in the current study were 15, 30, or 45 mg/kg/day. Parameters assessed during the study included weekly body weights, clinical observations (daily during the dosing period), food consumption, neurological examinations, electrocardiography, ophthalmology, clinical pathology (hematology, coagulation, serum chemistry including blood urea nitrogen and creatinine, urinalysis), and plasma toxicokinetics (TK). At necropsy, gross observations were recorded, organ weights were measured, and specific tissues were collected. Histopathologic assessment was conducted on tissue sections stained with hematoxylin and eosin (H&E).

RESULTS

The NOAEL of SPR206 following 14 days of repeated three times per day one hour infusions in male and female cynomolgus monkeys was 30 mg/kg/day based upon histopathological observations and accompanying and serum creatinine biomarker evaluations (Table 1). SPR206 at doses of ≤ 30 mg/kg/day was associated with non-adverse changes in tubular degeneration/regeneration and tubular necrosis with slight increases in renal biomarkers. At 45 mg/kg/day, SPR206 was associated with higher incidence and greater severity of tubular degeneration/regeneration and tubular necrosis with associated increases in renal biomarkers. Histopathological changes were partially reversible at 30 and 45 mg/kg/day doses.

CONCLUSIONS

As anticipated, the target organ of toxicity for SPR206 in this study is the kidney. The toxicity is monitorable and reversible. TK analysis at the NOAEL dose indicates high plasma exposure, consistent with a previously evaluated molecule, SPR741, that successfully completed Phase 1 evaluations. Additional toxicology and safety pharmacology studies of SPR206 reveal the risk for CNS, CV, pulmonary, genotoxic and metabolic issues is low. The totality of data supports advancement of SPR206 into clinical evaluation and we anticipate initiating Phase 1 studies around year end.

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