A GLP 28 Day Repeat Dose Toxicology Study of SPR720 in Monkeys

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ABSTRACT

Background: Non-tuberculous mycobacteria (NTM) are increasingly associated with a variety of debilitating infections. Current treatment is lengthy and variably effective, often leading to the emergence of resistance. As such, novel therapies are needed. SPR720 is an orally bioavailable prodrug of SPR719, an aminobenzimidazole inhibitor of guanine S-P-N-Kase with broad-spectrum antibacterial activity. Spero Therapeutics is developing SPR720 for the treatment of infections caused by non-tuberculous mycobacteria. The GLP 28-day toxicity assessment of SPR720 is reported here.

Methods: SPR720 was assessed for toxicity in male and female cynomolgus monkeys at 30, 100, and 300 mg/kg/day given by oral gavage for 28 consecutive days. A 28-day recovery period 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: There were no SPR720 related effects on mortality, body weights, food consumption, electrocardiography, ophthalmology, clinical pathology, or histopathology. Clinical signs included soft tissue edema, decreased activity, and anorexia, primarily during Week 1 of dosing. The no-observed-adverse-effect level (NOAEL) for SPR720 was 300 mg/kg/day. The AUC0-24h and Cmax exposures to SPR719 (active drug form) at the NOAEL on Day 28 were 32000 ng/mL and 4010 ng/mL, respectively. As expected, SPR720 exposures were less than 3% of those seen for SPR719.

Conclusions: The target organ of toxicity for SPR720 in this study was transient gastrointestinal upset. This toxicity is non-reversible; in other GLP safety testing, SPR720 was genotoxic, and there were no significant alterations in cardiovascular, central nervous system, or respiratory safety pharmacology parameters. Additionally, SPR720 successfully completed a GLP 31-day repeat dose toxicity studies in rats with SPR720 showed effects and exposure closely resembling those to that observed in monkey. These data collectively support advancement of SPR720 into Phase 1 clinical assessment.

INTRODUCTION

Non-tuberculous mycobacteria (NTM) infections are increasing in prevalence globally due to improved recognition and diagnosis. NTM, once thought to be strictly environmental species, are responsible for a wide range of infections that are generally difficult to treat due to high rates of resistance and poor tolerability to current therapeutic options. Therefore new agents are needed. SPR720 is an orally bioavailable phosphate prodrug of SPR719, a novel aminobenzimidazole which exhibits potent, broad-spectrum activity against NTM species. SPR720 was assessed for potential target organs of toxicity, recovery of any toxicity, and toxicokinetics (TK) in a GLP 28-day toxicity study in cynomolgus monkeys per ICH guidance to enable Phase 1 studies in normal healthy volunteers.

METHODS

SPR720 or control article/vehicle (0.5% methylcellulose 400 cps in deionized water) was administered by oral gavage. Doses were administered once per day for twenty eight consecutive days, and the study included animals in a twenty eight day recovery period. The dosing volume was constant among groups, at 5 mL/kg. The SPR720 dose levels in the current study were 30, 100, or 300 mg/kg/day. Parameters assessed during the in-life phase of the study included body weights, clinical observations food consumption, electrocardiography, ophthalmology, clinical pathology (hematology, coagulation, serum chemistry, urinalysis). 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

Oral gavage of SPR720 once daily for 28-days at doses of 30, 100, and 300 mg/kg/day in male and female cynomolgus monkeys resulted in non-adverse clinical observations and liver weight increases in females at 300 mg/kg/day. With the exception of soft tissue edema, SPR720 related findings demonstrated complete reversibility during the recovery period. There were no macroscopic or microscopic findings related to SPR720 and there was no impact on mortality, body weights, ophthalmology, ECGs, or clinical pathology endpoints. Therefore, the NOAEL for SPR720 in this study was 300 mg/kg/day.

Toxicokinetic analysis showed that Cmax and AUC0-24h of SPR720 increased with increasing dose in a greater than dose proportional and approximately dose proportional manner, respectively after oral dosing of SPR720. The Cmax and AUC0-24h of SPR719 increased with increasing dose in a greater than dose proportional manner after oral dosing of SPR720. Systemic exposure of SPR720 did not increase with repeated dosing, however systemic exposure of SPR719 did increase. The systemic exposure of SPR719 was approximately 182 to 376 times higher than SPR720. The AUC0-24h and Cmax for SPR720 and SPR719 at the NOAEL on Day 28 were 949 and 320000 ng/mL and 579 and 40100 ng/mL, respectively.

Figure 1. Structure of SPR720 (left) and SPR719 (right)

CONCLUSIONS

In this study there were no adverse events determined for SPR720 and the NOAEL was assigned to be the top dose studied of 300 mg/kg/day. The target organ for SPR720 in monkey is the gastrointestinal based on transient GI upset. TK analysis at the NOAEL dose indicates high plasma exposure of the active moiety, SPR719, and very low exposure of the administered prodrug, SPR720. Additional toxicology and safety pharmacology studies of SPR720 reveal the risk for CNS, CV/pulmonary, genotoxicity and metabolic issues is low. The totality of data supported advancement of SPR720 into clinical evaluation and a Phase 1 study assessing safety/tolerability and PK is currently ongoing.

Figure 2. Mean SPR719 Plasma Concentration-Time Profiles on Days 1 and 28 Following Oral Gavage Administration of 30, 100, and 300 mg/kg/day SPR720

In other GLP and non-GLP assessments, SPR720/SPR719 was determined to have no impact on pulmonary pharmacology and to be negative for chromosomal aberration, Ames, and micronucleus assays. SPR719 exhibited an IC50 of 19.1 μg/mL in GLP HERG assay. SPR720 is converted to SPR719 by human and non-human intestinal and liver S9 fractions with high Kp and Vmax. In vivo, SPR720 is rapidly and extensively converted to SPR719 in the gut and liver and oral bioavailability of SPR719 is ~70% across species. SPR719 and SPR720 are not significant direct, concentration-dependent or time-dependent inhibitors of human CYP isozymes (IC50>40 μM).