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Phase 1 First-in-Human Single- and Multiple-Ascending Dose Trial Demonstrates Pharmacokinetics and Tolerability of SPR720, an Oral DNA GyrB Inhibitor for Mycobacterial Infections

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BACKGROUND

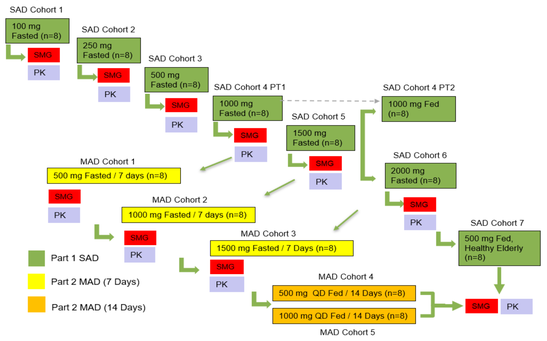
- Nontuberculous mycobacteria pulmonary disease (NTM-PD) is a chronic, progressive disease that occurs through inhalation of mycobacteria from environmental sources.
- Among numerous NTM species worldwide, NTM-PD is primarily caused by Mycobacterium avium complex (MAC) which includes *M. avium*, *M. intracellulare*, *M. chimaera* and several subspecies; *M. abscessus* and *M. kansasii*.
- No systemic oral antimicrobial agents are approved for the treatment of pulmonary nontuberculous mycobacteria infections.
- Increasing rates of resistance to current standard of care agents, along with tolerability issues, and high rates of clinical relapse, highlight the urgent need for new antimicrobials to treat NTM-PD.
- SPR720 (phosphate pro-drug of SPR719) is a novel aminobenzimidazole bacterial DNA gyrase (GyrB) inhibitor.
- SPR719 has broad-spectrum activity vs. clinically relevant mycobacteria in vitro (Abstract #1274) and in murine (Abstract #1637) and hollow fiber (HF) infection models (Abstract #1659).
- SPR720 is in clinical development as a new oral therapy for (NTM-PD) and pulmonary tuberculosis

OBJECTIVE

- Evaluate the safety, tolerability, and pharmacokinetics (PK) of SPR720/SPR719 in healthy volunteers in a single ascending dose (SAD) /multiple ascending dose (MAD) clinical trial.

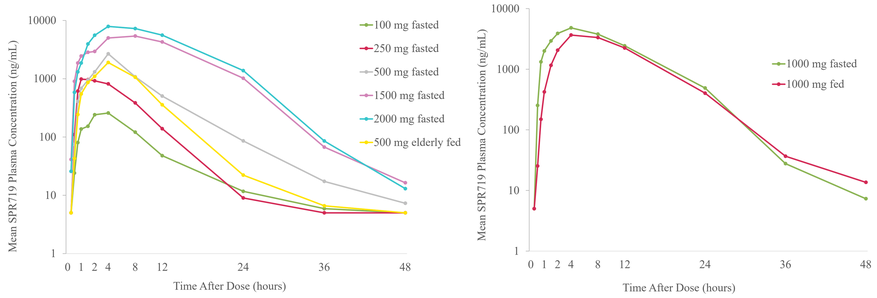
STUDY DESIGN

- Phase 1 randomized, double-blind, placebo-controlled trial
- 7 SAD cohorts (including a food effect cohort)
  - Oral SPR720 or placebo (n=8/cohort, 3:1 randomization)
  - Doses of 100 mg to 2000 mg
- 5 MAD cohorts
  - Total daily doses of 500 mg to 1500 mg for 7 or 14 days
- Safety monitoring and intensive PK sampling during the trial
- Plasma PK parameters calculated using non-compartmental analysis



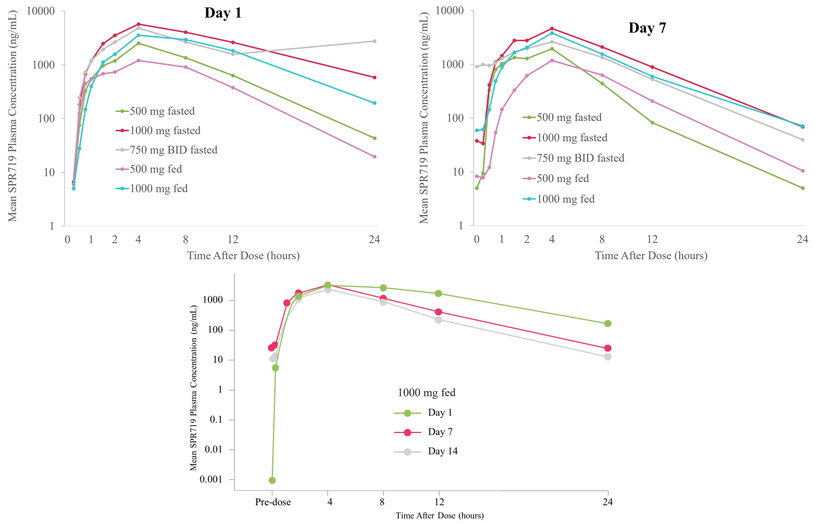
RESULTS

Figure 1 : Geometric Mean Plasma SPR719 Concentration-Time Curves Following (a) Single-ascending Doses (SAD) of SPR720 and (b) SP720 1000 mg During Fed and Fasting States



- Across SAD cohorts, a dose proportional and greater-than-dose proportional increase in plasma SPR719 C_{max} and AUC_{0-24}, respectively, was observed
- Following administration of a high-fat meal, a small decrease in plasma exposure was observed vs. the fasted state; this decrease was considered non-clinically significant
- The median T_{max} for SPR719 ranged from 2.75 hr to 8 hr across cohorts and the mean elimination half-life ($t_{1/2}$) ranged from 2.92 hr to 4.5 hr.
- Urinary excretion of SPR719 (0-24 hr) was low (0.5%)

Figure 2: Geometric Mean Plasma SPR719 Concentration-Time Curves Following Multiple Ascending Doses (MAD) of SPR720 on over 7 and 14 Days



- Across MAD cohorts, SPR719 plasma C_{max} and AUC both increased in a greater than dose proportional manner with increasing oral doses of SPR720.
- Repeated oral dosing of SPR720 in healthy human subjects resulted in a decrease (~40%) in plasma exposure of SPR719 at Day 7 relative to Day 1, suggesting induction of elimination pathways of SPR719.
- Plasma AUC_{0-24} was similar at Days 7 and 14 indicating that induction of elimination had stabilized by Days 7-14
- This conclusion is further supported by stable SPR719 trough concentrations by Day 7 (data not shown).

Table 1: Incidence of treatment-emergent adverse events in single-ascending dose cohorts

SAD Event	Number (%) of Subjects									
	Placebo Overall (N=14)	Cohort 1 100 mg (N=6)	Cohort 2 250 mg (N=6)	Cohort 3 500 mg (N=6)	Cohort 4 1000 mg Fasted (N=6)	Cohort 4 1000 mg Fed (N=6)	Cohort 5 1500 mg (N=6)	Cohort 6 2000 mg (N=6)	500 mg Elderly (N=6)	Overall SPR720 (N=42)
Nausea	0	0	0	0	0	0	4 (66.7)	5 (83.3)	0	9 (21.4)
Headache	1 (7.1)	0	0	0	1 (16.7)	0	3 (50.0)	3 (50.0)	0	7 (16.7)
Vomiting	0	0	0	0	0	0	3 (50.0)	5 (83.3)	0	8 (19.0)
Diarrhea	0	0	0	1 (16.7)	0	0	0	2 (33.3)	0	3 (7.1)

Table 2: Incidence of treatment-emergent adverse events in multiple-ascending dose cohorts

MAD Event	Number (%) of Subjects						
	Placebo Overall (N=10)	Cohort 1 500 mg 7 days (N=6)	Cohort 2 1000 mg 7 days (N=6)	Cohort 3 750 mg q12h 7 days (N=6)	Cohort 4 500 mg 14 days (N=6)	Cohort 5 1000 mg 14 days (N=6)	Overall MAD SPR720 (N=30)
Diarrhea	1 (10.0)	2 (33.3)	4 (66.7)	4 (66.7)	0	3 (50.0)	13 (43.3)
Headache	0	2 (33.3)	3 (50.0)	2 (33.3)	1 (16.7)	0	8 (26.7)
Nausea	0	2 (33.3)	1 (16.7)	3 (50.0)	0	1 (16.7)	7 (23.3)
Vomiting	0	1 (16.7)	2 (33.3)	1 (16.7)	0	0	4 (13.3)
Abdominal pain	0	0	2 (33.3)	1 (16.7)	0	0	3 (10.0)
Back pain	0	0	1 (16.7)	0	0	1 (16.7)	2 (6.7)

SAD Cohorts
- Of 42 subjects, 18 (42.9%) reported a total of 35 TEAEs; all were mild or moderate.
- More subjects reported TEAEs in the 1500 mg and 2000 mg cohorts (66.7% and 100%, respectively).

MAD Cohorts
- Of 30 subjects who received SPR720, 18 (60.0%) reported a total of 101 TEAEs; all were mild or moderate severity
- More subjects reported TEAEs in the 1000 mg or 1500 mg (750 mg q12h) cohorts (50.0% and 66.7%, respectively).
- One subject in MAD cohort 3 (750 mg q12h) discontinued study drug due to increased pancreatic enzymes; this was asymptomatic and resolved without interventional treatment.
  - This could be attributed to persistently high trough plasma concentrations of SPR719 >1000 ng/mL throughout the dosing period.
- Slight elevations in ALT (<3xULN) were observed over 14 days of dosing, which were asymptomatic and reversible; there were no cases of Hy's Law.

CONCLUSIONS

- SPR720 was well-tolerated at repeat daily oral doses up to 1000 mg over the maximum duration of 14 days.
- In SAD cohorts, C_{max} and AUC increased in a dose-proportional and greater than dose-proportional manner, respectively.
- In MAD cohorts, exposure declined between Days 1 and 7, but was similar at Days 7 and 14; urinary excretion of SPR719 was minimal
- Together with HF pharmacodynamic data (Abstract #1659), the human safety and PK data for SPR720 suggest that predicted therapeutic exposures can be attained with a well-tolerated once-daily dose.
- Further evaluation of SPR720 in a Phase 2 trial in patients with NTM-PD is planned.

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