### BACKGROUND

- Non tuberculosis 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 M. avium complex (MAC) which includes M. avium, M. intracellulare, M. chimaera and several sub-species; M. abscessus and M. kansasi.
- 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 and human 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=6/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

- Across SAD cohorts, a dose proportional and greater-than-dose proportional increase in plasma SPR719 Cmax and AUC0-24, 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 Tmax for SPR719 ranged from 2.75 hr to 8 hr across cohorts and the mean elimination half-life (t1/2) ranged from 2.92 hr to 4.5 hr.
- Urinary excretion of SPR719 (0-24 hr) was low (~40%) in plasma exposure of SPR719 at Day 7 relative to Day 1, suggesting induction of elimination pathways of SPR719.
- Plasma AUC0-24 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).

### SAFETY

- 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.
- Of 30 subjects who received SPR720, 18 (60.0%) reported a total of 101 TEAEs; all were mild or asymptomatic.
- More subjects reported TEAEs in the 1500 mg and 2000 mg cohorts (66.7% and 100%, respectively).
- Of 42 subjects, 18 (42.9%) reported a total of 35 TEAEs; all were mild or moderate.
- MAD Cohorts
  - More subjects reported TEAEs in the 1000 mg and 2000 mg cohorts (66.7% and 100%, 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 MAD cohorts, Cmax 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.