SPR720, A Novel Aminobenzimidazole Gyrase Inhibitor, Demonstrates Potent Efficacy Against Mycobacterium avium ATCC 700898 in a Chronic C3HeB/FeJ Mouse Infection Model

Deepshika Verma1, Chelsea Peterson1, Suzanne Stokes2, Nicole Cotroneo1, Diane Ordway1
1Colorado State University, Fort Collins, CO; 2Spero Therapeutics, Cambridge, MA

ABSTRACT

SPR720, a novel aminobenzimidazole gyrase inhibitor, was evaluated in a model of chronic nontuberculous mycobacterial (NTM) lung disease. NTM avium, avium, avium (NTM) infection was induced in C3HeB/FeJ mice by aerosol infection with Mycobacterium avium (ATCC 700898). Treatment with SPR720, 30 mg/kg QD, at 27 days post-infection, resulted in a ∼8-log10 CFU/lung reduction compared to untreated controls. Treatment with SPR720, 30 mg/kg QD, and rifabutin (RFB) 100 mg/kg QD to day 60 treatment as well as with SPR720, 30 mg/kg QD, plus ethambutol (EMB) 30 mg/kg QD to day 60 treatment, significantly enhanced the activity of SPR720. The combination of SPR720, 30 mg/kg QD, plus rifabutin (RFB) 100 mg/kg QD to day 60 treatment was statistically superior to any of the single-agent treatments and a statistically significant reduction compared to untreated controls. These results provide preclinical support for combination therapy with SPR720, a novel aminobenzimidazole inhibiting NTM infections.

RESULTS

Figure 1: Pulmonary Bacterial Burden (log10 CFU/lung) after Treatment with SPR720 Alone and in Combination with Clarithromycin, Rifabutin, and or Ethambutol

Table 1: Bacterial Burden (log10 CFU/organ) in Lung, Spleen and Liver

CONCLUSIONS

• The oral administration of SPR720 demonstrated a statistically significant reduction in the bacterial burden in all tissues with concomitant improvement in lung pathology, both alone and in combination with standard of care agents.

• These data support the further clinical development of SPR720 as an oral option for the treatment of pulmonary NTM infections in humans.

REFERENCES

1. CLSI standard M24, 3rd ed., Wayne, PA.

INTRODUCTION

Nontuberculous mycobacterial (NTM) pulmonary infection is a chronic, progressive disease that occurs through inhalation of mycobacteria from environmental sources. NTM are found worldwide and NTM pulmonary infections are primarily due to Mycobacterium avium complex (MAC). M. africanum, and M. kansasi (FDA 2016). There are currently no systemic antimicrobial agents specifically approved for the treatment of pulmonary NTM infections, and no formal FDA guidance for the clinical development of drugs for this indication. Thus, there is an urgent need for the introduction of new agents the treatment of pulmonary NTM disease (NTM-PD). The increasing resistance and risk of poor tolerability to current standard of care (SoC) agents, as well as the high relapse and mortality rates, highlight the unmet need and priority for development of new agents for NTM-PD.

METHODS

The minimum inhibitory concentration (MIC) of SPR719 was determined using methods established by the CLSI. The efficacy of SPR720 was evaluated in a 60-day chronic C3HeB/FeJ mouse infection model, a model which was developed to be representative of non-tuberculosis mycobacterial (NTM) pulmonary infections (Verma et al 2019). C3HeB/FeJ mice were infected by aerosol delivery of 1×108 CFU/mL of Mycobacterium avium ATCC 700898, a broadly susceptible isolate with an SPR719 MIC of 2 μg/mL. These mice were sacrificed on Day 7 and Day 27 post-infection to determine bacterial uptake. On Day 28 post-infection, SPR720 was administered by oral gavage at 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day delivered every 24 hours (QD), and 50 mg/kg was delivered twice a day (BID) for a total of 100 mg/kg/day. Positive control clarithromycin was administered by oral gavage at 250 mg/kg/day. Ethambutol was administered by oral gavage at 100 mg/kg/day, and rifabutin was administered by oral gavage at 100 mg/kg/day in combination treatments. Animals were dosed from Day 26 to Day 61 consecutively. At the end of the dosing phase (Day 61), whole lung, spleen and liver were aseptically removed, processed, and plated on 7H11 agar plates for 21-25 days to determine bacterial burdens as colony forming units (CFUs).

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