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ABSTRACT

Background: Tebipenem-pivoxil (SPR994) is an orally available carbapenem with broad spectrum activity against extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae and is currently under development for complicated urinary tract infections (cUTI). Escherichia coli is the dominant species of bacteria causing UTIs and is becoming increasingly resistant to existing antibiotics, therefore new treatment options are needed. The efficacy of SPR994 was assessed in an acute murine thigh model using E. coli ATCC 25922, E. coli ATCC BAA-2523 (OXA-48 expressing) or K. pneumoniae NR-48977 (carbapenemase expressing).

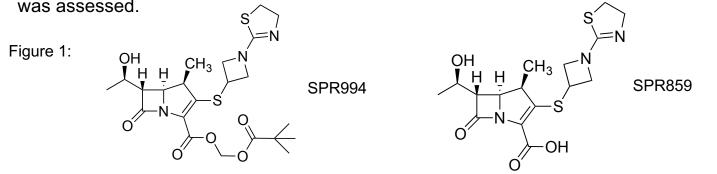
Methods: : Minimum Inhibitory Concentration (MIC) were performed performed on SPR859, the microbiologically active form of SPR994, using CLSI methodology. Neutropenia was induced in CD-1 female or male mice by administering cyclophosphamide by intraperitoneal injection on days -4 and -1 (150 and 100 mg/kg, respectively). Mice were infected by intramuscular injection into the lateral thigh muscles with either E. coli ATCC 25922, E. coli ATCC BAA-2523 or K. pneumoniae NR-48977. SPR994 was dosed at various concentrations either orally once or three times per day. Mice were euthanized at 24 h or 25 h post infection. Thigh muscle was homogenized, serially diluted, plated on permissive media with colony forming units (CFU) counted after overnight incubation.

Results: The MIC values of SPR859 were 0.015 mg/L, 0.5 mg/L and >128 mg/L for *E. coli* ATCC 25922, ATCC BAA-2523 and K. pneumoniae NR-48977, respectively. All strains displayed robust *in vivo* growth (1.8-4.5 log₁₀ CFU/g thigh tissue) between 2 h and 24 h. Relative to the pre-treatment control group at 2h, 1 log reductions were achieved with administration of SPR994 at 10 mg/kg/day against E. coli ATCC 25922, while a dose of 500mg/kg/day was required against E. coli ATCC BAA-2523. SPR994 did not produce a reduction in burden against K. pneumoniae at any dose assessed up to a maximum dose of 900 mg/kg/day.

Conclusions: Treatment with SPR994 resulted in a reduction of E. coli ATCC 25922 and E. coli ATCC BAA-2523 burden in thigh tissue, but as expected due to the high MIC value, no reduction of *K. pneumoniae* NR-48977 burden in thigh tissue was observed. The difference in dose levels required to achieve 1 log reduction in burden between of E. coli ATCC 25922 and E. coli ATCC BAA-2523 are consistent with the divergence of MICs between the isolates. These studies support continued clinical development of SPR994 as the first oral carbapenem for the treatment of serious Gram-negative infections.

INTRODUCTION

- Escherichia coli is the dominant species of bacteria causing UTIs and is becoming increasingly resistant to existing antibiotics, therefore new treatment options are needed
- SPR994 is an orally available carbapenem with broad spectrum activity against ESBL producing Enterobacteriaceae
- In these studies, the efficacy of SPR994 in an acute neutropenic murine thigh infection model was assessed.



METHODS

- Neutropenia was induced in CD-1 mice by administering cyclophosphamide by intraperitoneal (IP) injection on days -4 and -1 (150 and 100 mg/kg, respectively)
- Either female or male mice were infected by intramuscular (IM) injection into the lateral thigh muscles with either E. coli ATCC 25922 (female; Study #1), ATCC BAA-2523 (female; study #2) or K. pneumoniae NR-48977 (male; Study #3)
- SPR994 was dosed orally (PO) at various concentrations and intervals as noted in Tables 2, 3
- Mice were euthanized 24h post infection and the thigh muscle quantitatively cultured, serially diluted and plated on appropriate media and CFUs were counted after overnight incubation
- MIC data was performed using SPR859, the microbiologically active form of SPR994, using CLSI methodology

RESULTS

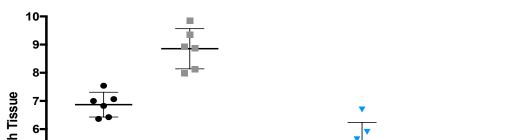
Table 1: *In vitro* potency against organisms used in the studies

Isolate	MIC (μg/mL)			
	SPR859	Levo	Tigecycline	Meropenem
E. coli ATCC 25922	0.015	0.125	n/a	n/a
E. coli ATCC BAA-2523	0.5	0.125-0.5	n/a	n/a
K. pneumoniae NR-48977	>128	n/a	1	>128

Study #1: Mean E. coli ATCC 25922 bacterial titers in thigh tissue following administration of SPR994 orally in the murine thigh infection model.

Table 2: Study design, burden and log change compared to 2h pre-treatment for E. coli ATCC 25922

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Study Group	Dose Level (mg/kg/day)	Regimen (Hours Post-Infection)	Mean Log ₁₀ CFU/g	Log Change vs. 2h Control				
2hr			6.86					
Vehicle 24hr		2	8.85	2.0				
Levofloxacin	120	2	3.49	-3.4				
SPR994	10	2	5.58	-1.3				
SPR994	30	2	4.92	-1.9				
SPR994	100	2	4.48	-2.4				



Levo 120mg/kg

Dose Level

(mg/kg/day)

200

30

100

300

500

in the murine thigh infection model.

Study Group

2hr

Vehicle 24hr

Levofloxacin

SPR994

SPR994

SPR994

SPR994

SPR994 vs. E. coli 25922

Figure 2:

Monotherapy of SPR994

SPR994, mg/kg, PO, QD

Regimen

(Hours Post-Infection)

2, 10, 18

2, 10, 18

2, 10, 18

2, 10, 18

2, 10, 18

Study #2: Mean *E. coli* ATCC BAA-2523 bacterial titers in thigh tissue following administration of SPR994 (PO)

Table 3: Study design, burden and log change compared to 2h pre-treatment for *E. coli* ATCC BAA-2523

10mg/kg/day dose shows a 1.3 Log₁₀cfu/g reduction compared to the 2hr control

Robust growth of *E.coli* isolate 25922 was observed between 2 and 24h post-infection

Mean

Log₁₀CFU/g

6.63

9.74

5.18

9.50

9.24

8.12

5.37

Log Change vs.

2h Control

3.1

-1.5

2.9

2.6

1.5

-1.3

SPR994 (mg/kg; PO; TID) Monotherapy of SPR994 500mg/kg/day dose shows a 1.2 Log₁₀cfu/g reduction compared to the 2hr control • Robust growth of *E.coli* isolate ATCC 25922 was observed between 2 and 24h post-infection

SPR994 vs. E. coli ATCC BAA-2523

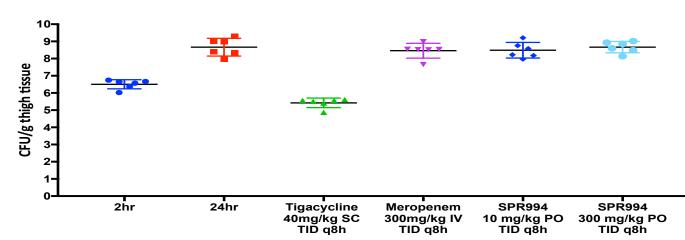
Study #3: Mean K. pneumoniae NR-48977 bacterial titers in thigh tissue following administration of SPR994 (PO) in the murine thigh infection model

Table 4: Study design, burden and log change compared to 2h pre-treatment for *K. Pneumoniae NR-48977*

Study Group	Dose Level (mg/kg/day)	Regimen (Hours Post-Infection)	Mean Log ₁₀ CFU/g	Log Change vs. 2h Control
2hr			6.52	
Vehicle 24hr		2, 10, 18	8.77	2.3
Tigecycline	120	2, 10, 18	5.45	-1.1
Meropenem	900	2, 10, 18	8.60	2.1
SPR994	30	2, 10, 18	8.54	2.0
SPR994	900	2, 10, 18	8.70	2.2

Figure 4:

Figure 3:



- Monotherapy of SPR994 at 900mg/kg/day dose shows no Log₁₀cfu/g reduction compared to the 2hr control
- Robust growth of *K. pneumoniae* isolate NR-48977 was observed between 2 and 24h post-infection

CONCLUSIONS

- Treatment of SPR994 shows correlation between MIC and in vivo efficacy
- These studies support continued clinical development of SPR994 as the first oral carbapenem for the treatment of serious Gram-negative infections.