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In Vivo Characterization of Tebipenem-Pivoxil (SPR994) in a Murine Ascending *Escherichia coli* Urinary Tract Infection Model

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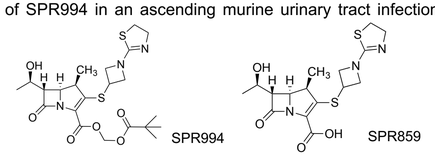
ABSTRACT

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). The dominant species that cause cUTI is *E. coli*, and some of these isolates are increasing in resistance to currently used antibiotics. In these studies, we assessed the efficacy of SPR994 in a murine ascending *E. coli* UTI model.
Methods: MICs were performed on SPR859, the microbiologically active form of SPR994, levofloxacin (LEVO), and ciprofloxacin (CIP) using CLSI methodology. Female C3H/HeN mice were infected via transurethral catheter with either *E. coli* ATCC 700928 or UTI89. Beginning 24 hours after infection, SPR994, levofloxacin or ciprofloxacin was dosed orally (PO) once per day (QD) for 3 days. Mice infected with ATCC 700928 were euthanized 24 hours following the final dose of SPR994 and kidneys, bladder, and urine were collected aseptically and quantitatively cultured. Mice infected with UTI89 were euthanized 24 hours after the final dose of SPR994 and their kidneys were collected aseptically and quantitatively cultured.
Results: The SPR859 and LEVO MIC values were 0.015 mg/L and 0.03 mg/L against *E. coli* ATCC 700928, respectively. The SPR859 and CIP MIC values were both 0.015 mg/L against UTI89. *In vivo* growth of ATCC 700928 between 24 hours and 96 hours post-infection was typical for these matrices and strains in this model. PO administration of SPR994 (up to 30 mg/kg/day) displayed a dose dependent reduction in burden against *E. coli* ATCC 700928 (1.4 – 3.9 Log_{10}CFU/g kidney tissue; 2.9 – 4.1 Log_{10}CFU/g bladder tissue; 0.3 – 2.2 Log_{10}CFU urine) and significant reduction in burden against *E. coli* UTI89 (2.7 – 3.0 Log_{10}CFU/g kidney tissue) compared to the pre-treatment control group. SPR994 was more potent than LEVO clearing ATCC 700928 from kidney and bladder tissue and urine at a dose of 3 mg/kg/day (PO; QD) compared to LEVO dose of 20 mg/kg/day (PO; QD) and more potent than CIP clearing UTI89 from kidney tissue at a dose of 1 mg/kg/day compared to CIP dose of 20 mg/kg/day.
Conclusions: In these dose-ranging studies, SPR994 resulted in a significant reduction in *E. coli ATCC* 700928 burden in kidney tissue, bladder tissue, and urine and *E. coli* UTI89 burden in kidney tissue as measured by CFU counts compared to the 24-hour vehicle control. These studies support continued development of SPR994 as the first and only oral carbapenem for MDR G- UTIs.

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 ascending murine urinary tract infection model was assessed.



METHODS

- All mice were placed on 5% glucose solution *ad libitum* 5 days prior to infection.
- Mice were infected transuretherally with either *E. coli* ATCC 700928 or *E. coli* UTI89.
- SPR994 was dosed orally (PO) at various concentrations once per day (QD) for 3 days.
- Mice were euthanized 24 hours after the final dose and the kidneys, bladder, and urine were collected and quantitatively cultured, serially diluted, and plated on appropriate media and CFUs were counted after overnight incubation.
- All studies were approved by Spero institutional Animal Care and Use Committee (IACUC) (Study #1) and University of Manchester Animal Welfare and Ethics Committee (Study #2).

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

Isolate	MIC (µg/mL)		
	SPR859	LEVO	CIP
E. coli ATCC 700928	0.015	0.03	--
E. coli UTI89	0.015	--	0.015

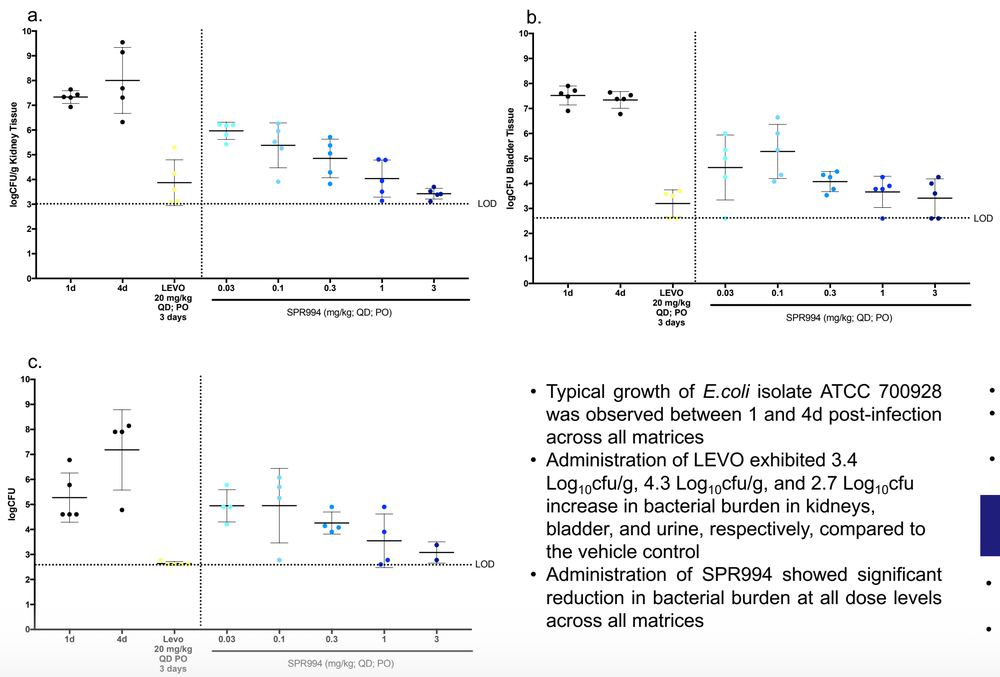
RESULTS

Study #1: Mean *E. coli* (ATCC 700928) bacterial titers in kidney and bladder tissue and urine following administration of SPR994 (PO) in the murine UTI model.

Table 2: Study design, burden and log change compared to 1d pre-treatment for *E. coli* ATCC 700928

Study Group	Dose Level (mg/kg/day)	Regimen (Days Post-Infection)	Kidney		Bladder		Urine	
			Mean Log_{10}CFU/g	Log Change vs. 1d Control	Mean Log_{10}CFU/g	Log Change vs. 1d Control	Mean Log_{10}CFU	Log Change vs. 1d Control
1d	--	--	7.3	--	7.5	--	5.3	--
Vehicle 4d	--	1, 2, 3	8.0	0.7	7.4	-0.1	7.2	1.9
Levofloxacin	20	1, 2, 3	3.9	-3.4	3.2	-4.3	2.6	-2.7
SPR994	0.03	1, 2, 3	6.0	-1.3	4.6	-2.9	4.9	-0.4
	0.1	1, 2, 3	5.4	-1.9	5.3	2.2	5.0	-0.3
	0.3	1, 2, 3	4.9	-2.4	4.1	-3.4	4.3	-1.0
	1	1, 2, 3	3.9	-3.4	3.7	-3.8	3.5	-1.8
	3	1, 2, 3	3.4	-3.9	3.4	-4.1	3.1	-2.2

Figure 1: Burdens for *E. coli* ATCC 700928 in Kidney (a.), Bladder (b.), and Urine (c.)



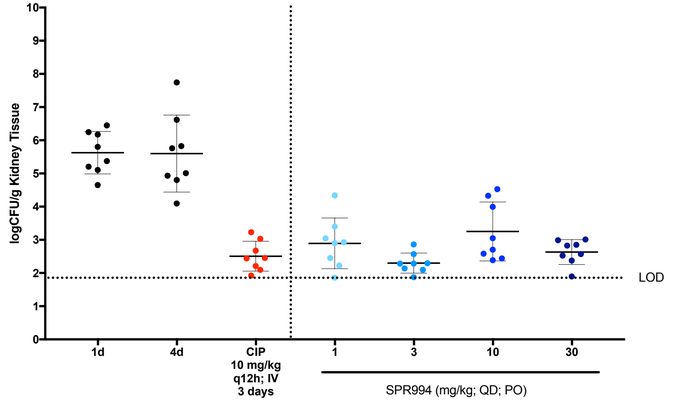
- Typical growth of *E.coli* isolate ATCC 700928 was observed between 1 and 4d post-infection across all matrices
- Administration of LEVO exhibited 3.4 Log_{10}cfu/g, 4.3 Log_{10}cfu/g, and 2.7 Log_{10}cfu increase in bacterial burden in kidneys, bladder, and urine, respectively, compared to the vehicle control
- Administration of SPR994 showed significant reduction in bacterial burden at all dose levels across all matrices

Study #2: Mean *E. coli* (UTI89) bacterial titers in kidney tissue following administration of SPR994 (PO) in the murine UTI model.

Table 3: Study design, kidney burden and log change compared to 1d pre-treatment for *E. coli* UTI89

Study Group	Dose Level (mg/kg/day)	Regimen (Days Post-Infection)	Mean Log_{10}CFU/g	Log Change vs. 1d Control
1d	--	--	5.6	--
Vehicle 4d	--	1, 2, 3	5.6	0.0
Ciprofloxacin	10	1, 2, 3	2.5	-3.1
SPR994	1	1, 2, 3	2.9	-2.7
	3	1, 2, 3	2.3	-3.3
	10	1, 2, 3	3.3	-2.3
	30	1, 2, 3	2.6	-3.0

Figure 2: Burdens for *E. coli* UTI89 in Kidney Tissue



- Typical growth of *E.coli* isolate UTI89 was observed between 1 and 4d post-infection
- Administration of CIP exhibited 3.1 Log_{10}cfu/g increase in bacterial burden compared to vehicle control
- Administration of SPR994 showed significant reduction in bacterial burden

CONCLUSIONS

- Administration of SPR994 demonstrates significant reduction of bacterial burden of *E. coli* 700928 and *E. coli* UTI89.
- These studies support continued clinical development of SPR994 as the first oral carbapenem for the treatment of serious Gram-negative infections.