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Single- and multiple-ascending dose (SAD/MAD) study demonstrates the human pharmacokinetics (PK) and tolerability of SPR994 (tebipenem pivoxil hydrobromide), an oral carbapenem (CP), at the predicted therapeutic dose

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BACKGROUND

SPR994 is an orally available prodrug of tebipenem (TBPM), a CP with activity versus MDR Gram-negative pathogens, including quinolone-resistant and ESBL-producing *Enterobacteriaceae*. It is under development as an oral alternative to IV antibiotic therapy. We report safety and PK results of the first-in-human SAD/MAD study of SPR994 in healthy adult volunteers.

METHODS

Study Design: This was a double-blind, placebo controlled, ascending dose, multi-cohort trial, performed at a single investigative site in Australia. All subjects signed written informed consent, and were screened within 28 days of randomization.

TBPM pivoxil hydrobromide (SPR994 tablets), TBPM pivoxil free base (Orapenem® fine granules), or placebo (PBO) was administered (n=8/cohort, 3:1 randomization) at a single dose of 100-900 mg in varying immediate and extended release formulations (14 SAD cohorts, including immediate release [IR], 2H, 4H, 6H, and 12H release in fed and fasted states) and 300-600 mg q8h for 14 days (2 MAD cohorts, IR formulation).

Key inclusion criteria: Healthy adult males and females (of non-child bearing potential); ages 18 to 55 years; BMI ≥ 18.5 and ≤ 29.9 (kg/m2); medically healthy without clinically significant abnormalities at screening.

Key exclusion criteria: Significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic or neurological disease, including any acute illness or surgery within the past three months determined by the PI to be clinically relevant, including history of *C. difficile* infection (CDI).

PK & Safety Assessments: Concentrations of TBPM in plasma and urine were measured by validated LC-MS/MS methods. Plasma PK parameters were determined using non-compartmental methods. Safety assessments included physical exams, electrocardiograms, and serum and urine laboratory tests.

RESULTS

SAD Safety: TEAEs were reported for 20/75 SPR994 subjects (27%), 5/8 Orapenem subjects (63%), and 10/25 placebo subjects (40%), with a total of 58 TEAEs. Most TEAEs were classified as mild (55/58, 95% of all TEAEs); 2 TEAE were moderate (conjunctivitis, unrelated to study drug [SPR994 12H 600 mg] and ALT increased, probably related to study drug [Orapenem]) and 1 TEAE was severe (ALT increased, probably related to study drug [Placebo]). The most common TEAEs were diarrhea (6 [8%] SPR994, 1 [4%] placebo) and headache, (3 [4%] SPR994, 2 [25%] Orapenem), all mild.

MAD Safety: TEAEs were reported for 12/12 SPR994 subjects and 4/4 placebo subjects, with a total of 34 TEAEs. Most TEAEs were mild (33/34, 97% of all TEAEs) in severity, with 1 TEAE classified as moderate (ALT increased, ALT increased in SPR994 300 mg cohort). No TEAEs were classified as severe. TEAEs deemed to be related to study drug administration (possibly, probably) were reported in 11/12 SPR994 subjects (92%) and 2/4 placebo subjects (50%) (Table 1). There were no SAEs or premature discontinuations of study drug.

Table 1. Summary of Related TEAEs by MedDRA Preferred Term in MAD.

	Number (%) of Subjects with TEAEs			
Preferred Term	SPR994 300 mg TID (n=6)	SPR994 600 mg TID (n=6)	Total Active (n=12)	Placebo (n=4)
Headache	1 (17%)	1 (17%)	2 (17%)	-
Abdominal discomfort	1 (17%)	-	1 (8%)	-
Abdominal distension	-	-	-	1 (25%)
Abdominal pain	1 (17%)	1 (17%)	2 (17%)	1 (25%)
Abdominal pain upper	-	2 (33%)	2 (17%)	-
Diarrhea*	2 (33%)	5 (83%)	7 (58%)	1 (25%)
Dry mouth	1 (17%)	-	1 (8%)	-
Nausea	-	1 (17%)	1 (8%)	1 (25%)
ALT increased**	2 (33%)	1 (17%)	3 (25%)	-
AST increased	1 (17%)	-	1 (8%)	-
Total	6 (100%)	5 (85%)	11 (92%)	2 (50%)

*Most diarrhea events were single episodes of loose stool on Day 1, which resolved with continued dosing; there were no cases of CDI.
**All increased ALT events were mild except 1 moderate event (SPR994 300 mg subject, peak ALT 142 U/L); this subject had 2 doses of study drug held on Day 8-9, and levels returned to normal despite restarting therapy.

SAD PK: SPR994 was rapidly metabolized to release TBPM, with levels of TBPM pivoxil below quantification in all samples. For the IR, 2H and 4H formulations, TBPM AUC was similar for both fed and fasted dose administrations. In fed condition, the fraction of dose excreted in urine was approximately 50% for all formulations over the 0-4 h collection period.

MAD PK: TBPM T_{max} was ≤1.5 h of administration on both Day 1 and Day 14, with a median T_{max} of <1 hour. TBPM AUC for 600 mg was more than twice the AUC for 300 mg on Day 1 (2.7 fold) and Day 14 (2.5 fold). Cmax was dose proportional on Day 1, and also higher than dose proportional (2.7 fold) on Day 14 for 600 mg compared with 300 mg dose level. There was no accumulation with dosing; TBPM $AUC_{0\text{-}8h}$ was similar for the first and last doses, consistent with the short $t_{½}$ of <1 h. More than half (57% for 300 mg and 66% for 600 mg) of the administered dose was excreted in urine on Day 1 (0-8 h).

Table 1. Mean Plasma PK Parameters of TBPM in MAD.

	Median (Range)	**Arithmetic Mean (% Coefficient of Variation)**				
Cohort (n)	T_{max} (hr)	C_{max} (ng/mL)	$AUC_{0\text{-}8h}$ (hr*ng/mL)	$t_{½}$ (hr)	CL/F (L/hr)	Vd/F (L)
SPR994-IR 300mg q8h, Day 1 (n=6)	0.50 (0.25-1.00)	7759 (50.7)	7726 (27.2)	0.82 (26.9)	32.4 (35.6)	37.0 (28.2)
SPR994-IR 300mg q8h, Day 14 (n=6)	0.63 (0.47-1.50)	6493 (61.5)	7484 (36.5)	0.72 (16.0)	34.8 (39.3)	36.5 (47.8)
SPR994-IR 600mg q8h, Day 1 (n=6)	0.88 (0.50-1.50)	13428 (31.9)	20592 (19.3)	0.79 (12.1)	23.2 (19.5)	26.2 (19.2)
SPR994-IR 600mg q8h, Day 14 (n=6)	0.63 (0.50-1.50)	15090 (30.8)	17924 (25.4)	0.83 (20.0)	27.5 (30.1)	31.8 (21.4)

CONCLUSIONS

- SPR994 was well tolerated at the predicted therapeutic dose and exposure levels
  - Gastrointestinal events were the most common types of TEAEs, all mild and consisted primarily of loose stools on Day 1
- Predictable PK characteristics allow for q8h oral dosing without regard to meals
- Further evaluation of SPR994-IR 600 mg q8h in a Phase 3 cUTI trial is ongoing