PB Eckburg
24 April 2018
Abstract number: 5544
Poster number: P2206

Safety of SPR741, a Novel Polymyxin Potentiator, in Healthy Adults Receiving Single- and Multiple-Dose Intravenous Administrations

PB Eckburg[1]*, N Farinola[2], L Utley[1], S Walpole[1], T Keutzer[1], E Kopp[1], S Coleman[1], J Tomayko[3]

[1]Spero Therapeutics, Cambridge MA, USA; [2]CMAX Clinical Research, Adelaide, Australia, [3]Anti-Infectives, Pfizer, Groton CT, USA

Paul Eckburg, MD
+1-650-888-3475

ABSTRACT

Background: SPR741 is a novel, synthetic polymyxin analog that enhances the potency of existing antimicrobials against multidrug-resistant (MDR) Gram-negative bacteria. The first-in-human Phase 1 study SPR741-101s was completed, and its primary objective of assessing safety and tolerability of SPR741 after single- and multiple-dose IV administrations to healthy adult subjects is summarized here.

Methods: This was a double-blind, placebo-controlled, multi-cohort trial. In the single ascending dose (SAD) part, 8 cohorts of 8 subjects each (6 active: 2 placebo) received study drug at single doses ranging from 5 mg to 800 mg. In the multiple ascending dose (MAD) part, 4 cohorts of 8 subjects each (6 active: 2 placebo) received study drug q8h IV for 14 days (50 mg, 150 mg, 400 mg, and 600 mg). Standard safety assessments were performed, including plasma and urine renal function tests.

Results : All 96 subjects completed the study; 2 MAD subjects were prematurely withdrawn from study drug due to treatment-emergent adverse events (TEAEs) (tachycardia in placebo subject, mild atrial fibrillation in SPR741 150 mg subject). Most TEAEs were mild in severity (98% SAD, 84% MAD subjects); 1 serious AE (atrial fibrillation) and no severe TEAEs or deaths occurred. Commonly-occurring TEAEs (≥10% SPR741 subjects) in MAD included headache, creatinine clearance (CrCl) decreased, and infusion site reactions; 7 subjects, all SPR741 subjects, had abnormal renal lab TEAEs (6 CrCl decreased and 1 glomerular filtration rate decreased, 4 of which occurred in the highest dose cohort [600 mg]). All abnormal renal test TEAEs resolved or were resolving at the end of the study. No other clinically significant changes in vital signs, physical examinations, or laboratory findings were reported.

Conclusion: SPR741 administered up to q8h for 14 days was generally well tolerated in daily doses up to 1,800 mg in healthy subjects. Observed TEAEs, including decreased CrCl, were consistent with known effects of the polymyxin class. These data support further clinical development of SPR741 in humans for the treatment of serious infections caused by MDR pathogens.

INTRODUCTION

The emergence and spread of multidrug-resistant (MDR) strains of *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*, has revealed shortcomings in the current antibiotic armamentarium for treating infections caused by these bacteria. Such infections result in significant morbidity and mortality and incur substantial economic costs. There is a lack of new antibiotics with potential activity against MDR Gram-negative pathogens currently in clinical development. Spero Therapeutics has identified a series of novel polymyxin analogs of which SPR741 is a candidate. SPR741 lacks significant direct antibacterial activity against Gram-negative organisms (MIC >16 µg/mL for relevant target pathogens). When combined with antibiotics that have limited or no antibacterial activity against Gram-negative pathogens, SPR741 can expand the spectrum of the partner antibiotic to include MDR Gram-negative species.

METHODS

Study Design: This was a double-blind, placebo controlled, ascending dose, multi-cohort trial, performed at a single investigative site in Australia. The study was conducted in two parts (SAD and MAD). All subjects signed written informed consent, and were screened for eligibility within 28 days of study entry. SAD cohorts were dosed at 5, 15, 50, 100, 200, 400, 600, and 800 mg; MAD cohorts were dosed at 50, 150, 400, and 600 mg q8h for 14 days.

Key inclusion criteria:

- Healthy adult males and/or females (of non-child bearing potential), 18 to 55 years of age (inclusive) at the time of screening.
- BMI ≥ 18.5 and ≤ 29.9 (kg/m^2) .
- Medically healthy without clinically significant abnormalities at screening or Day -1.

Key exclusion criteria:

- History or presence of 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.

Safety assessments:

- Incidence and severity of adverse events (AEs); vital signs; physical exam findings; electrocardiogram (ECG) parameters; clinical laboratory parameters (serum chemistry, haematology, coagulation, urinalysis).
- For MAD only: in addition to the above, changes in 24-hour CrCl based on plasma and urine creatinine concentration measured at baseline and following the last dose on Day 14.

RESULTS

SAD (Tables 1 and 2): Most TEAEs were mild in severity (33/34 [97%]); 1 TEAE was moderate in severity (arthralgia in a placebo subject). No TEAEs were severe or serious. There was no apparent treatment or dose-related trend in the severity of TEAEs. The most common TEAEs were headache (8% active; 6% placebo) and PK catheter site pain (6% active, 0 placebo). No subject experienced a TEAE classified as a renal or urinary disorder, and no subject had an abnormal serum creatinine value.

Table 1: Overall Summary of TEAEs in SAD

	Number (%) of Subjects with TEAEs [Number of TEAEs Reported]									
	SPR741									Placebo
	5 mg (n=6)	15 mg (n=6)	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)	600 mg (n=6)	800 mg (n=6)	Total Active (n=48)	(n=16)
TEAEs	-	-	4 (67%) [7]	4 (67%) [9]	1 (17%) [2]	3 (50%) [7]	2 (33%) [3]	1 (17%) [1]	15 (31%) [29]	5 (31%) [5]
Related TEAEs	-	-	1 (17%) [1]	2 (33%) [3]	-	2 (33%) [2]	1 (17%) [2]	-	6 (13%) [8]	2 (13%) [2]
At least Moderate TEAEs	-	-	-	-	-	-	-	-	-	1 (6%) [1]
SAEs	-	-	-	-	-	-	-	-	-	-
TEAEs leading to premature discontinuation of study drug	-	-	-	-	-	-	-	-	-	-

Table 2: Summary of TEAEs by System Organ Class (SOC) in SAD.

	Number of Subjects (>2%) with at least one Treatment-Emergent AE [Number of TEAEs]									
	SPR741									Placebo
SOC	5 mg (n=6)	15 mg (n=6)	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)	600 mg (n=6)	800 mg (n=6)	Total Active (n=48)	(n=16)
All TEAEs	-	-	4 (67%) [7]	4 (67%) [9]	1 (17%) [2]	3 (50%) [7]	2 (33%) [3]	1 (17%) [1]	15 (31%) [29]	5 (31%) [5]
Nervous system	-	-	2 (33%) [2]	-	1 (17%) [1]	2 (33%) [4]	1 (17%) [1]	-	6 (13%) [8]	2 (13%) [2]
Eye	-	-	1 (17%) [1]	-	-	1 (17%) [1]	-	-	2 (4%) [2]	-
Respiratory	-	-	1 (17%) [1]	2 (33%) [2]	-	-	-	1 (17%) [1]	4 (8%) [4]	-
Gastrointestinal	-	-	1 (17%) [1]	1 (17%) [1]	-	-	-	-	2 (4%) [2]	1 (6%) [1]
Skin and subcutaneous tissue	-	-	-	-	-	1 (17%) [1]	1 (17%) [1]	-	2 (4%) [2]	-
Musculoskeletal	-	-	1 (17%) [1]	2 (33%) [3]	1 (17%) [1]	-	-	-	4 (8%) [5]	1 (6%) [1]
General and administration site	-	-	1 (17%) [1]	3 (50%) [3]	-	1 (17%) [1]	1 (17%) [1]	-	6 (13%) [6]	-

MAD (Tables 3, 4 and 5): Most TEAEs were mild (234/241 [97%]); 7 TEAEs were moderate in severity. No TEAEs were severe. TEAEs reported in >10% of subjects included headache (33% active; 38% placebo), diarrhoea (13% active; 0 placebo), contact dermatitis (29% active; 50% placebo), administration site reactions (92% active; 88% placebo), and CrCl decreased (6 [25%] active vs. 0 placebo; Table 5). Two subjects experienced a TEAE classified as a renal and urinary disorder (dysuria in 1 SPR741 600 mg subject and bladder discomfort in 1 placebo subject), 6 TEAEs of CrCl decreased occurred in 6 SPR741 subjects in MAD, half of which occurred in the highest dose cohort (600 mg IV q8h for 14 days). With the exception of the 2 subjects lost-to-follow-up beyond Day 16, all CrCl decreases improved and were mild in severity, except 1 moderate TEAE in an SPR741 600 mg subject (CrCl decreased from 110 mL/min at baseline to 65 mL/min on Day 16). One additional SPR741 600 mg subject had a related TEAE of glomerular filtration rate decreased.

Table 3: Overall Summary of TEAEs in MAD

	Number (%) of Subjects with TEAEs [Number of TEAEs Reported]					
	SPR741					Placebo
	50 mg (n=6)	150 mg (n=6)	400 mg (n=6)	600 mg (n=6)	Total Active (n=24)	(n=8)
TEAEs	6 (100%) [23]	6 (100%) [45]	6 (100%) [42]	6 (100%) [68]	24 (100%) [178]	8 (100%) [63]
Related TEAEs	5 (83%) [8]	6 (100%) [12]	5 (83%) [22]	4 (67%) [48]	20 (83%) [90]	7 (88%) [31]
Moderate TEAEs	-	1 (17%) [1]	-	1 (17%) [1]	2 (8%) [2]	3 (38%) [5]
SAEs	-	1 (17%)* [1]	-	-	1 (4%) [1]	-
TEAEs leading to premature discontinuation of study drug	-	1 (17%)* [1]	-	-	1 (4%) [1]	1 (13%) [1]

*The SPR741 150 mg subject with premature discontinuation of study drug developed an SAE of atrial fibrillation on Day 11, which was brief, transient, and occurred in a subject with unrecognized cardiac abnormalities at the time of enrolment (e.g., PVCs, atrial dilatation, mitral regurgitation).

Table 4: Summary of TEAEs by SOC in MAD

	Number of Subjects (%) with at least one Treatment-Emergent AE [Number of TEAEs]					
	SPR741					Placebo
	50 mg (n=6)	150 mg (n=6)	400 mg (n=6)	600 mg (n=6)	Total Active (n=24)	(n=8)
All TEAEs	*6 (100%) [23]*	*6 (100%) [45]*	*6 (100%) [42]*	*6 (100%) [68]*	*24 (100%) [178]*	*8 (100%) [63]*
Infections and infestations	-	-	1 (17%) [1]	3 (50%) [5]	4 (17%) [6]	2 (25%) [4]
Metabolism and nutrition	-	-	-	1 (17%) [1]	1 (4%) [1]	-
Nervous system	2 (33%) [2]	4 (67%) [5]	1 (17%) [1]	3 (50%) [6]	10 (42%) [14]	4 (50%) [6]
Eye	-	1 (17%) [1]	1 (17%) [1]	-	2 (8%) [2]	-
Ear and labyrinth	-	-	-	1 (17%) [1]	1 (4%) [1]	-
Cardiac	-	1 (17%) [1]	-	-	1 (4%) [1]	1 (13%) [1]
Vascular	-	2 (33%) [2]	-	-	2 (8%) [2]	2 (25%) [2]
Respiratory	-	1 (17%) [2]	-	1 (17%) [1]	2 (8%) [3]	2 (25%) [2]
Gastrointestinal	2 (33%) [3]	2 (33%) [3]	1 (17%) [3]	1 (17%) [6]	6 (25%) [15]	2 (25%) [4]
Skin and subcutaneous tissue	3 (50%) [3]	3 (50%) [3]	1 (17%) [1]	3 (50%) [4]	10 (42%) [11]	4 (50%) [5]
Musculoskeletal	3 (50%) [3]	2 (33%) [3]	-	1 (17%) [4]	6 (25%) [10]	3 (38%) [4]
Renal and urinary	-	-	-	1 (17%) [1]	1 (4%) [1]	1 (13%) [1]
General and administration site*	5 (83%) [11]	6 (100%) [24]	6 (100%) [32]	5 (83%) [34]	22 (92%) [101]	7 (88%) [34]
Investigations	1 (17%) [1]	1 (17%) [1]	2 (33%) [2]	4 (67%) [4]	8 (33%) [8]	-
Injury and procedural complications	-	-	1 (17%) [1]	1 (17%) [1]	2 (8%) [2]	-

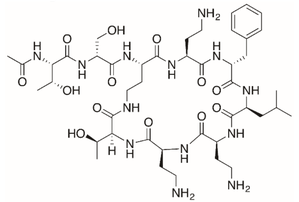
*The most common TEAE by SOC in both treatment groups consisted of PK sampling catheter reactions and study drug infusion site reactions. All study drug infusion site reactions (e.g., bruising, erythema, pain, phlebitis and swelling) were mild, and there was no apparent dose-related increase in reactions. Of note, 6 placebo subjects reported infusion site reactions deemed related to study treatment.

Table 5: SPR741 Subjects with TEAEs of Decreased CrCl in MAD

Subject	SPR741 Dosage	Severity	Predose & D16[a] CrCl (mL/min)	Relationship to Study Drug	Action Taken with Study Drug
R09006[b]	50 mg q8h x 14 d	Mild	63, 52	Possible	None
R10005	150 mg q8h x 14 d	Mild	212, 64	Unlikely	None
R11008[b]	400 mg q8h x 14 d	Mild	182, 82	Possible	None
R12006	600 mg q8h x 14 d	Mild	109, 85	Probable	None
R12007	600 mg q8h x 14 d	Moderate	110, 65	Probable	None
R12008	600 mg q8h x 14 d	Mild	168, 101	Probable	None

[a] Subjects with CrCl decreased on Day 16 had repeated, unscheduled CrCl and serum creatinine assessments until they returned to normal, near-normal, or baseline values. [b] Two subjects were lost to follow-up prior to return of CrCl to baseline values.

Figure 1. Structure of SPR741



CONCLUSIONS

- Overall, SPR741 was well tolerated as single or multiple ascending doses administered for up to 14 days duration.
  - Most TEAEs were mild in both SAD and MAD parts of the study.
  - There were no severe TEAEs, no deaths, and 1 SAE (atrial fibrillation, described above).
- PK catheter site and study drug administration site reactions were common in both parts of the study. None of the TEAEs associated with PK catheter site reactions were deemed related to study treatment. Nearly all of the study drug infusion site reactions occurred in MAD; however, infusion site phlebitis and thrombosis were uncommon (3 and 2 SPR741 subjects, respectively), all infusion site reactions were mild, and no infusion site reactions led to premature discontinuation of study drug.
- No renal-associated TEAEs occurred in any subject in the SAD part of the study; however, there was a dose-related trend in CrCl decreased in subjects who received multiple doses of SPR741, with 3 subjects who received the highest dose of SPR741 (600 mg) reporting this TEAE. With the exception of the 2 subjects lost-to-follow-up beyond Day 16, all CrCl decreases improved and were mild in severity except 1 moderately severe TEAE in an SPR741 600 mg subject. CrCl decrease is a known effect of the polymyxin antibiotic class.
- Summaries of TEAEs by severity and relationship showed no apparent differences between treatments (SPR741 or placebo) and no dose-related trends in subjects who received SPR741 in either the SAD or MAD parts of the study.
- These safety data support further development of this novel polymyxin potentiator.