Determination of the pharmacokinetics of single (SAD) and multiple ascending doses (MAD) of SPR741 in healthy volunteers

L Utley1, T Lister1, S Coleman2, PB Eckburg2

1Spero Therapeutics, Cambridge, MA, USA; 2Acceleor Pharma, Cambridge MA

ABSTRACT

Background: SPR741 is a novel polymyxin B derivative with minimal intrinsic activity and potent post-antimicrobial activity against a broad spectrum of Gram-negative pathogens. The study was conducted to support the development of SPR741 after single- and multiple-dose intravenous (IV) administrations to healthy adult subjects.

Materials and Methods: This was a double-blind, placebo-controlled, multi-center trial conducted in normal healthy volunteers. SPR741 or placebo was administered as a single 1-hour infusion at doses of 5.0 mg/kg, 10.0 mg/kg, and 50.0 mg/kg to 14 healthy adult volunteers (including 7 males and 7 females). SPR741 concentrations in plasma and urine were determined using validated LC-MS methods. Plasma pharmacokinetic parameters were determined using non-compartmental analysis.

Results: The study was well tolerated. No serious adverse events were reported. The most common adverse event was rash, reported in 3 out of 14 subjects. Mean t1/2 was 741.0 minutes for 37.9 mg/mL peak concentration of SPR741 in the urine at the first post-dose collection. Renal clearance ranged 0.747–1.87 L/hr and was constant at doses above 100 mg.

Methods: Methodology described above.

Results: Table 1 displays the mean PK parameters for each dose group. The MAD showed increased accumulation with repeated dosing, which was consistent with dose above 100 mg.

RESULTS (continued)

Figure 1: Mean plasma concentration of SPR741 vs time after a 1-hour infusion

Figure 3: Mean trough concentrations, days 2-13.

Table 2: Mean PK Parameters by Cohort in MAD.

Table 3: Mean PK Parameters by Cohort in MAD.

Conclusions: SPR741 administered up to 500 mg (1.0 mg/kg) did not cause an increase in plasma concentration or renal clearance. renal clearance was significantly decreased in the same time frame after a 1-hour infusion at 500 mg (1.0 mg/kg) and 100 mg (0.5 mg/kg) for two dose levels. These results support further clinical development of SPR741 in humans.

METHODS

Material and Methods: The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All subjects signed informed consent prior to study entry. Subjects were discontinued from the study if any adverse event, any laboratory abnormality, or any deviation from protocol.

RESULTS

RESULTS

Table 1: Mean PK Parameters by Cohort in SAD.

Table 2: Mean PK parameters by cohort in MAD.

Table 3: Mean PK parameters by cohort in MAD.

Introduction: The emergence and spread of multidrug-resistant (MDR) strains of E. coli, K. pneumoniae, and A. 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 classes of antibiotics with potential activity against MDR Gram-negative pathogens. Spero Therapeutics has identified a novel polymyxin analog of SPR741 as a lead candidate. This study was conducted to support the development of SPR741 after single- and multiple-dose intravenous (IV) administrations to healthy adult subjects.

INTRODUCTION

RESULTS

CONCLUSIONS

Figure 1: Mean plasma concentration of SPR741 vs time after a 1-hour infusion

Figure 3: Mean trough concentrations, days 2-13.

Table 2: Mean PK Parameters by Cohort in MAD.

Table 3: Mean PK parameters by cohort in MAD.

Introduction: This is a double-blind, placebo-controlled, ascending dose, multi-center trial, performed at 60 centers in 5 countries to assess the safety, tolerability, and pharmacokinetics of SPR741 in healthy adult subjects. The study was conducted in normal healthy volunteers. SPR741 was administered as a single 1-hour infusion at doses of 5.0 mg/kg, 10.0 mg/kg, and 50.0 mg/kg to 14 healthy adult volunteers (including 7 males and 7 females). SPR741 concentrations in plasma and urine were determined using validated LC-MS methods. Plasma pharmacokinetic parameters were determined using non-compartmental analysis.

RESULTS

RESULTS

Table 1: Mean PK Parameters by Cohort in SAD.

Table 2: Mean PK parameters by cohort in MAD.

Table 3: Mean PK parameters by cohort in MAD.

Conclusions: The study was well tolerated. No serious adverse events were reported. The most common adverse event was rash, reported in 3 out of 14 subjects. Mean t1/2 was 741.0 minutes for 37.9 mg/mL peak concentration of SPR741 in the urine at the first post-dose collection. Renal clearance ranged 0.747–1.87 L/hr and was constant at doses above 100 mg.

Methods: Methodology described above.

Results: Table 1 displays the mean PK parameters for each dose group. The MAD showed increased accumulation with repeated dosing, which was consistent with dose above 100 mg.

Table 1: Mean PK Parameters by Cohort in SAD.

Table 2: Mean PK parameters by cohort in MAD.

Table 3: Mean PK parameters by cohort in MAD.

Conclusion: SPR741 administered up to 500 mg (1.0 mg/kg) did not cause an increase in plasma concentration or renal clearance. renal clearance was significantly decreased in the same time frame after a 1-hour infusion at 500 mg (1.0 mg/kg) and 100 mg (0.5 mg/kg) for two dose levels. These results support further clinical development of SPR741 in humans.

Introduction: This is a double-blind, placebo-controlled, ascending dose, multi-center trial, performed at 60 centers in 5 countries to assess the safety, tolerability, and pharmacokinetics of SPR741 in healthy adult subjects. The study was conducted in normal healthy volunteers. SPR741 was administered as a single 1-hour infusion at doses of 5.0 mg/kg, 10.0 mg/kg, and 50.0 mg/kg to 14 healthy adult volunteers (including 7 males and 7 females). SPR741 concentrations in plasma and urine were determined using validated LC-MS methods. Plasma pharmacokinetic parameters were determined using non-compartmental analysis.

Results: The study was well tolerated. No serious adverse events were reported. The most common adverse event was rash, reported in 3 out of 14 subjects. Mean t1/2 was 741.0 minutes for 37.9 mg/mL peak concentration of SPR741 in the urine at the first post-dose collection. Renal clearance ranged 0.747–1.87 L/hr and was constant at doses above 100 mg.

Methods: Methodology described above.

Results: Table 1 displays the mean PK parameters for each dose group. The MAD showed increased accumulation with repeated dosing, which was consistent with dose above 100 mg.

Table 1: Mean PK Parameters by Cohort in SAD.

Table 2: Mean PK parameters by cohort in MAD.

Table 3: Mean PK parameters by cohort in MAD.

Conclusion: SPR741 administered up to 500 mg (1.0 mg/kg) did not cause an increase in plasma concentration or renal clearance. renal clearance was significantly decreased in the same time frame after a 1-hour infusion at 500 mg (1.0 mg/kg) and 100 mg (0.5 mg/kg) for two dose levels. These results support further clinical development of SPR741 in humans.

Introduction: This is a double-blind, placebo-controlled, ascending dose, multi-center trial, performed at 60 centers in 5 countries to assess the safety, tolerability, and pharmacokinetics of SPR741 in healthy adult subjects. The study was conducted in normal healthy volunteers. SPR741 was administered as a single 1-hour infusion at doses of 5.0 mg/kg, 10.0 mg/kg, and 50.0 mg/kg to 14 healthy adult volunteers (including 7 males and 7 females). SPR741 concentrations in plasma and urine were determined using validated LC-MS methods. Plasma pharmacokinetic parameters were determined using non-compartmental analysis.