A Phase 1 Study of the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of the Lipopeptide QPX9003 in Healthy Adult Subjects

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Abstract

Introduction: QPX9003 is a fully synthetic lipopeptide with potent activity against MDR Pseudomonas and Acinetobacter spp. This report describes the safety and pharmacokinetics of QPX9003 following single and multiple doses.

Methods: Twelve healthy subjects were enrolled in 2 cohorts of up to 8 subjects (each cohort randomized to have up to 6 active and 2 placebo) each in the multiple ascending dose phase (100 or 200 mg every 6 hrs). Subjects received a single dose of QPX9003 followed by 48 hours of washout, then were administered QPX9003 q6h for 7 days. All infusions were administered over 1 hour. Intensive plasma sampling was obtained after dosing and assayed for QPX9003 content using validated HPLC/MS methods.

Results: Single and multiple dose QPX9003 pharmacokinetic parameters (mean +/- SD) are shown below:

Parameter	Single Dose	Last Dose of MD	Single Dose	Last Dose of MD
	100 mg	100 mg q6h	200 mg	200 mg q6h
	N = 6	N = 6	N = 6	N = 5
C_{max} (mg/L)	5.9 ± 1.1	8.1 ± 1.0	12.6 ± 3.0	18.3 ± 4.2
AUC_{0-6} (mg·h/L)	17.7 ± 3.0	29.0 ± 4.5	36.3 ± 8.9	62.2 ± 15.8
AUC_{0-inf} (mg·h/L)	27.4 ± 6.0	NA	51.4 ± 12.0	NA
Clearance (L/h)	3.8 ± 0.9	3.5 ± 0.6	4.1 ± 1.0	3.4 ± 1.0
Vss (L)	19.5 ± 3.4	24.2 ± 3.1	17.8 ± 4.6	20.8 ± 4.7
Half-Life (h)	4.5 ± 0.9	7.4 ± 1.4	4.1 ± 1.2	7.6 ± 0.9

No subjects discontinued due to AEs and no SAEs were observed. There was no evidence of increasing numbers or severity of AEs with increasing dose, and all AEs were mild or moderate in severity.

Conclusion: QPX9003 was safe and well tolerated at all doses tested. QPX9003 plasma AUC and Cmax increased with increasing dose. QPX9003 plasma exposure accumulated ~ 1.5 fold over 7 days of q6h dosing consistent with its plasma half-life. Based on the PK and safety profile, QPX9003 produces plasma exposures that exceed the PK-PD target safely and warrants further clinical development.

Introduction

- Multi-drug resistant gram-negative organisms are a global threat associated with high morbidity and mortality and new antimicrobial agents are needed.
- QPX9003 is a new lipopeptide antibiotic with improved potency and safety in preclinical species compared to polymyxin B and colistin.
- QPX9003 is in development as intravenous (IV) therapy for the treatment of serious infections due to *Acinetobacter baumannii* complex and *P. aeruginosa*.
- This poster describes the safety and pharmacokinetic data of multiple doses in normal healthy human subjects.

Results

Table 1: Mean ± Standard Deviation QPX9003 Pharmacokinetic Parameters Following the First dose and at Steady-State in Normal Healthy Volunteers

Parameter	QPX9003 100 mg q6h by 1-hour IV infusion for 7 days		QPX9003 150 mg q6h by 1-hour IV infusion for 7 days		QPX9003 200 mg q6h by 1-hour IV infusion for 7 days	
	First Dose	Steady State	First Dose	Steady State	First Dose	Steady State
# of subjects	6	6	5	5	6	5
Dose (mg)	100	100	150	150	200	200
Cmax (mg/L)	5.9 ± 1.1	8.1 ± 1.0	8.7 ± 1.2	11.7 ± 1.5	12.6 ± 3.0	18.3 ± 4.2
First dose $AUC_{0-\infty}$ (mg*h/L)	27.4 ± 6.0	NA	34.2 ± 6.1	NA	51.4 ± 12.0	NA
Steady State AUC_{0-tau} (mg*h/L)	NA	29.0 ± 4.5	NA	37.2 ± 4.4	NA	62.2 ± 15.8
Cl (L/h)	3.8 ± 0.9	3.5 ± 0.6	4.5 ± 0.7	4.1 ± 0.5	4.1 ± 1.0	3.4 ± 1.0
V_{ss} (L)	19.5 ± 3.4	24.2 ± 3.1	18.6 ± 4.2	20.8 ± 5.2	17.8 ± 4.6	20.8 ± 4.7
$T_{1/2}$ (h)	4.5 ± 0.9	7.4 ± 1.4	3.6 ± 0.8	5.1 ± 1.6	4.1 ± 1.2	7.6 ± 0.9

Table 2: Mean ± Standard Deviation QPX9003 Pharmacokinetic Parameters Following the First and at Steady-State in Normal Healthy Volunteers

Parameter	QPX9003 150 mg q6h by 1-hour IV infusion for 14 days	
	First Dose	Steady State
# of subjects	10	10
Dose (mg)	150	150
Cmax (mg/L)	9.3 ± 1.2	12.7 ± 1.8
First Dose $AUC_{0-\infty}$ (mg*h/L)	32.3 ± 3.9	NA
Steady-State AUC_{0-tau} (mg*h/L)	NA	40.4 ± 7.2
Cl (L/h)	4.7 ± 0.7	3.8 ± 0.7
V_{ss} (L)	ND	19.3 ± 3.4
$T_{1/2}$ (h)	ND	6.3 ± 0.5

Table 4. Adverse Events Observed in Two or More Subjects Receiving QPX9003 or Placebo for 14 Days

Adverse Event Preferred Terms	Pooled Placebo N=2 n (%) E*	Cohort 11 (150 mg q6h x 14 days) N=10 n (%) E
Subjects with AEs	**2 (100.0) 7**	**5 (50.0) 11**
Decreased appetite	1 (50.0) 1	2 (20.0) 2
Paraesthesia	1 (50.0) 1	2 (20.0) 2
Headache	0	2 (20.0) 2
Nausea	1 (50.0) 1	1 (10.0) 1
Rash	1 (50.0) 1	1 (10.0) 1

Figure 1: Mean ± Standard Deviation QPX9003 Pharmacokinetic Parameters Following the First dose then 7 days of QID dosing to Healthy Volunteers

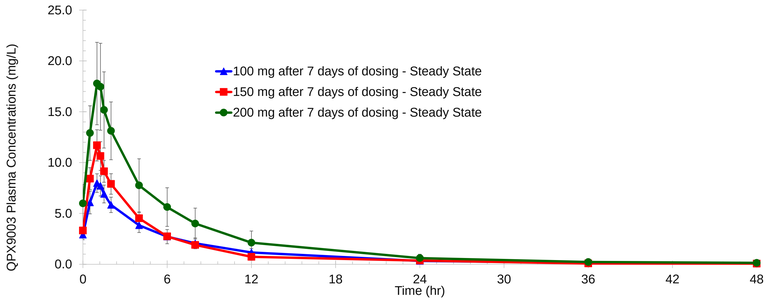

Table 3. Adverse Events Observed in Subjects Receiving QPX9003 or Placebo for 7 Days

Adverse Events	Pooled Placebo N=6 n (%) E*	Cohort 8 (100 mg q6h x 7d) N=6 n (%) E	Cohort 9 (150 mg q6h x 7d) N=5 n (%) E	Cohort 10 (200 mg q6h x7d) N=6 N (%) E	Pooled QPX9003 N=17 n (%) E
Subjects with AEs	**3 (50.0) 7**	**2 (33.3) 3**	**0**	**3 (50.0) 4**	**5 (29.4) 7**
Constipation	0	2 (33.3) 3	0	0	2 (11.8) 2
Abdominal pain	0	1 (16.7) 1	0	0	1 (5.9) 1
Abdominal pain upper	1 (16.7) 1	0	0	0	0
Nausea	2 (33.3) 2	0	0	0	0
Vomiting	2 (33.2) 2	0	0	0	0
Administration site reaction	0	0	0	1 (16.7) 1	1 (5.9) 1
Feeling abnormal	1 (16.7) 1	0	0	0	0
Headache	0	0	0	1 (16.7) 1	1 (5.9) 1
Epistaxis	0	0	0	1 (16.7) 1	1 (5.9) 1
Nasal congestion	1 (16.7) 1	0	0	0	0
Pruritus allergic	0	0	0	1 (16.7) 1	1 (5.9) 1

Materials and Methods

- Twenty-three healthy subjects were enrolled in 3 cohorts of up to 8 subjects (each cohort randomized to have up to 6 active and 2 placebo) each in the multiple ascending dose phase (100, 150 and 200 mg Q6H for 7 days) of the study. All infusions were administered over 1 hour. Following review of the safety and PK data in the 7-day dosing cohorts a single cohort of twelve healthy subjects (10 active and 2 placebo) to receive 150 mg Q6H for 14 days was enrolled. Intensive plasma sampling was obtained after the first and the last dose of multiple dosing and the samples were analyzed using a validated bioanalytical method with a range of 0.05 to 50 µg/mL.

Summary

Safety Summary

- QPX9003 was well tolerated in single dose escalation studies up to 400 mg (data not shown see ECCMID 2022), and multiple doses for 7 days up to 200 mg Q6H
- No evidence of increasing incidence/severity of AEs with increasing single doses
- In the 200 mg Q6H x 7-day cohort, 2 subjects met the RIFLE “risk” criteria of > 1.5 x increase in creatinine
- QPX9003 was well tolerated at 150 mg Q6H x 14 days
- All AEs were mild in severity

Pharmacokinetic Summary

- Overall, QPX9003 plasma concentrations increased with increasing dose
- Separate studies showed that QPX9003 41.1% bound to human plasma proteins. Using this value, the average 24h free QPX9003 AUC is estimated to be 68, 95 and 147 mg*h/L for 100, 150, or 200 mg doses administered every 6 hours, respectively.
- Based on the microbiological surveillance (MIC_{90}s for *A. baumannii* and *P. aeruginosa* are 1 mg/L and 0.25 mg/L, respectively), these Phase 1 clinical data, and target 24h free plasma QPX9003 AUC:MIC ratios of 73 and 115 (see Poster # 616), a QPX9003 dosage regimen of 400 mg/day or greater in humans would provide at least 1-log of bacterial killing for > 90% of isolates of *A. baumannii* and *P. aeruginosa*.
- Continued development of QPX9003 for the treatment of serious infections due to MDR *A. baumannii* and *P. aeruginosa* is warranted.

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