Pharmacodynamics (PD) of the Lipopeptide QPX9003 Against *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in the Neutropenic Mouse Thigh Infection Model

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Abstract

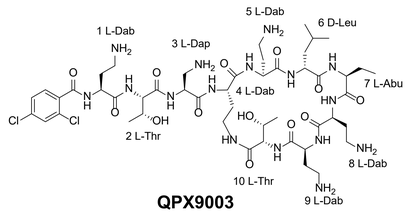
Background: *Acinetobacter baumannii* and *Pseudomonas aeruginosa* are important pathogens in hospital-acquired infections and can be resistant to multiple classes of antibiotics. QPX9003 is a novel synthetic lipopeptide that is highly active in vitro against MDR *Acinetobacter sp.* and *P. aeruginosa*. The purpose of these studies was to determine the pharmacodynamic parameter that best described the bacterial killing of QPX9003 in vivo.

Methods: Seven *A. baumannii* and six *P. aeruginosa* isolates were used in these studies. Swiss-Webster mice were rendered neutropenic by 150 mg/kg IP injections of cyclophosphamide 4 and 1 days prior to infection. The bacterial inoculum was prepared from an overnight culture adjusted to 10^8 CFU/mL then further diluted for inoculation into the thighs. Various dose and dose regimens of QPX9003 were administered by the IP route starting 2 hours post infection and continuing for 24 hours. Untreated control groups were sacrificed at the start of treatment. Treated and untreated control groups were sacrificed 24 hours after the start of treatment, thighs harvested, homogenized and plated to determine colony counts. PK was conducted in neutropenic, infected mice at doses ranging from 3 to 50 mg/kg administered by the IP route. The relationship between PK-PD parameters and the reduction in the log number of CFU per thigh between time zero and 24 h after the start of treatment were analyzed by using the sigmoid maximum reduction (Emax) PD model.

Results: The activity of QPX9003 was best described by the 24h free AUC/MIC ratio, with stasis and 1 log kill targets of 47.1 and 67.1 for *A. baumannii* and 96.1 and 117 for *P. aeruginosa*, respectively.

Organism	MIC (mg/L)	24h Free AUC/MIC		
		R^2	Stasis	1-log Kill
A. baumannii (7 strains)	0.5 – 1	0.89	47.1	67.1
P. aeruginosa (6 strains)	0.5 – 2	0.94	96.1	117

Conclusion: The PD of QPX9003 was best described by the 24h free AUC/MIC ratio. Based on the QPX9003 MIC_{90} for *P. aeruginosa* (0.25 mg/L) and *A. baumannii* (1 mg/L), 24h free AUCs between 30 and 67 mg*h/L will produce 1-log of bacterial killing for ~90% of *P. aeruginosa* and *A. baumannii* strains, respectively. QPX9003 is a potentially useful treatment for infections due to *P. aeruginosa* and *A. baumannii*, including MDR isolates, that is advancing in clinical studies.



QPX9003

Chemical Formula: $C_{48}H_{80}Cl_2N_{16}O_{13}$
Molecular Weight: 1160.15

Introduction

- Polymyxin B and colistin are often used against MDR gram-negative bacteria including *A. baumannii* and *P. aeruginosa*. These agents have limited efficacy and poor tolerability, with up to 60% of patients developing nephrotoxicity during treatment.
- MICs for QPX9003 were found to be ~4-fold lower than polymyxin B against MDR isolates of *P. aeruginosa*, *A. baumannii*, and Enterobacterales and QPX9003 was found to be less acutely toxic, less nephrotoxic and more efficacious than polymyxin B in animal studies.
- This poster describes studies to determine the PK-PD index that best describes bacterial killing of QPX9003 in the neutropenic mouse thigh infection model.

Methods

Mouse Pharmacokinetics

- Neutropenic, infected, female Swiss-Webster mice were administered single doses ranging from 3 to 50 mg/kg by the intraperitoneal route. Additional studies assessed drug accumulation using doses of 3 and 30 mg/kg administered every 6 hours for 5 total doses.
- Blood samples (N = 3/timepoint) were collected at various timepoints over 24 hours.
- Plasma levels were determined using an LC-MS/MS method and the data were fit to a non-compartmental model (WinNonlin).

Mouse Thigh Infection Model

- Female Swiss-Webster mice were used.
- Mice were rendered temporarily neutropenic by the administration of 150 mg/kg of cyclophosphamide (Baxter, IL) on days −4 and −1 prior to infection.
- Infection was initiated (under isoflurane anesthesia) *via* an intramuscular injection of 0.1 mL of inoculum (~ 10^6 CFU/thigh).
- Treatment was initiated 2 h post-infection and QPX9003 was administered every 2, 3, 4, 6, 8,12, or 24 hours by the intraperitoneal route.
- Controls were euthanized at the start of treatment while treated animals were euthanized 24 hours post-treatment using CO_2; thighs were removed aseptically, homogenized in 5 mL of saline, and plated on Mueller-Hinton Agar.

Pharmacodynamic Modeling

- The relationship between the PD indices and the change in log CFU compared to the start of treatment were fitted using the following inhibitory effect (Emax) model (Phoenix 64; Certara, Princeton, NJ):

$$Emax = E0 - (Imax \times X\gamma)/(X\gamma + IC50\gamma)$$

where E0 is the effect when X is equal to 0 (i.e., for the untreated control animals), Imax is the maximum reduction in the log number of CFU/lung, X is the PD index, IC50 is the PD parameter (X) corresponding to 50% of the maximum bacterial reduction, and γ is the steepness of the curve.

Results

Figure 1. Determination of the Pharmacodynamic Index that Best Describes Bacterial Killing by QPX9003 against Seven Different *Acinetobacter baumannii* Isolates

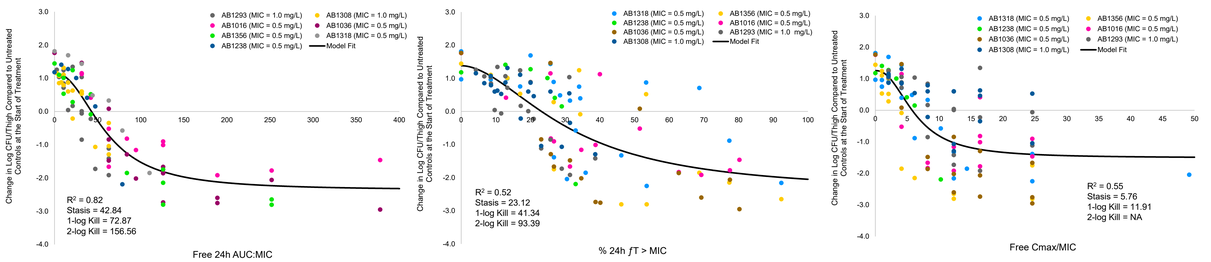


Figure 2. Determination of the Pharmacodynamic Index that Best Describes Bacterial Killing by QPX9003 against Six Different *Pseudomonas aeruginosa* Isolates

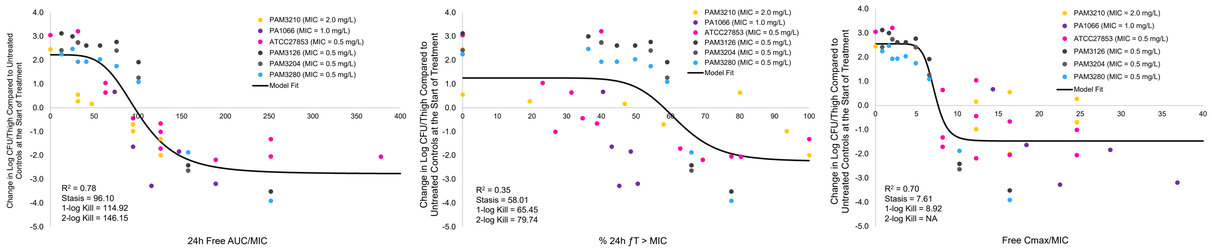


Table 1. Susceptibility Profile of Strains Used in PD Studies

Strain	QPX9003 MIC (mg/L)	PMB MIC (mg/L)
A. baumannii AB1293	1	1
A. baumannii AB1308	1	2
A. baumannii AB1016	0.5	1
A. baumannii AB1036	0.5	0.5
A. baumannii AB1356	0.5	2
A. baumannii AB1318	0.5	1
A. baumannii AB1238	0.5	1
P. aeruginosa PAM3210	2	2
P. aeruginosa PA1066	1	1
P. aeruginosa ATCC 27853	0.5	1
P. aeruginosa PAM3126	0.5	1
P. aeruginosa PAM3204	0.5	1
P. aeruginosa PAM3280	0.5	1

Table 2. Single Dose Pharmacokinetics of QPX9003 in Mice

Dose (mg/kg)	Cmax (mg/L)	CL (L/h/kg)	AUC (mg*h/L)	Free AUC (mg*h/L)
3	7.1	0.75	4.0	2.5
10	14.2	0.76	13.1	8.4
20	34.8	0.76	26.1	16.7
30	65.1	0.62	48.6	31.1
50	75.2	0.41	121	77.5

Table 3. QPX9003 Pharmacodynamic Indices

Organism	24h ƒAUC/MIC			%24h ƒ T > MIC			ƒ Cmax/MIC		
	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill	R^2	Stasis	1-log Kill
A. baumannii (7 strains)	0.82	43	73	0.52	23	41	0.55	5.8	12
P. aeruginosa (6 strains)	0.78	96	115	0.35	58	65	0.7	7.61	8.92

Summary

- QPX9003 was more potent than PMB against the strains used in these studies (Table 1)
- The pharmacokinetic profile of QPX9003 is, roughly, proportional to dose up to 30 mg/kg (Table 2). When dosing at 3 or 30 mg/kg every 6 hours for 5 doses, there was no accumulation at either dose level (data not shown).
- The PK-PD index that best describes bacterial killing by QPX9003 in the neutropenic mouse thigh infection model against both *A. baumannii* and *P. aeruginosa* is 24h free QPX9003 plasma area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio. (Figures 1 and 2)
- The magnitude of the PK-PD index that best describes the activity of QPX9003 (Free 24h AUC/MIC) against *A. baumannii* was 42.8 for stasis and 72.9 for 1-log of bacterial killing (Table 3).
- The magnitude of the PK-PD index that best describes the activity of QPX9003 (Free 24h AUC/MIC) against *P. aeruginosa* was found to be 96.1 for stasis and 115 for 1-log of bacterial killing (Table 3).
- Based on the microbiological surveillance (MIC_{90}s for *A. baumannii* and *P. aeruginosa* are 1 mg/L and 0.25 mg/L, respectively), Phase 1 clinical data (IDWeek 2022, Abstract 217), and these PK-PD indices, 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.

Acknowledgments

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