

Pharmacokinetics of BWC0977 in Pulmonary Epithelial Lining Fluid and Efficacy in a Neutropenic Lung Infection Model in Rats

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Introduction

BWC0977, a novel bacterial topoisomerase inhibitor (NBTI) with broad-spectrum activity against ESBLs, AmpC, KPCs, and fluoroquinolone-resistant strains is currently progressing in phase 1 clinical trial. Here we describe the pharmacokinetic profile in the lung epithelial lining fluid (ELF) and the efficacy of BWC0977 in a rat lung infection model, thus indicating the potential to treat pneumonia. Here we describe the pharmacokinetics and pharmacodynamics (PK-PD) of BWC0977 assessed in neutropenic rats.

Methods

Pharmacokinetic (PK) study: 100 mg/kg 60min i.v. infusion dose was administered once to a neutropenic Lung Infection model in Rats infected with *P.aeruginosa* (ATCC27853) and plasma samples were taken at 2 min, 15 min, 30 min, 1h, 2h, 4h, 8h, and 24h post-dose. ELF was obtained by instilling 2ml of sterile saline into the lungs and removing saline from the lungs twice at 1h, 2h, and 4h post-dose. PK data analysis was done using WinNonlin[®] software.

Results

Figure-1: Mean (\pm SD) i.v. Pharmacokinetics of BWC0977 in Plasma and ELF

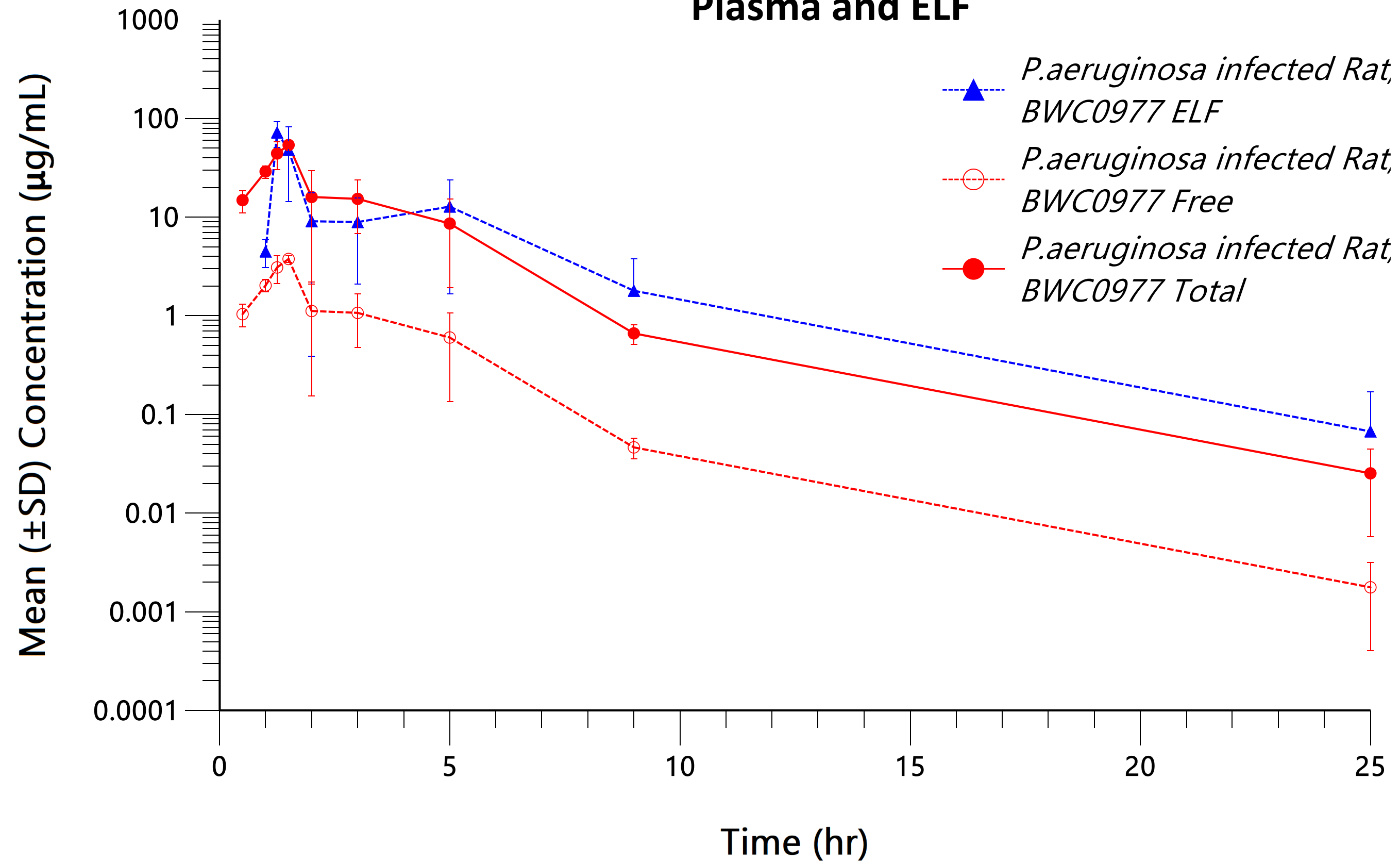


Table: NCA PK parameters of BWC0977 in plasma (Free and Total) and ELF of rats infected with *P.aeruginosa* (ATCC27853)

PK parameters (NCA)	ELF	Free _{plasma}	Total _{plasma}
Cmax (ug/mL)	81 \pm 11	2.7 \pm 0.24	54 \pm 4.8
AUC0-t (hr*ug/mL)	113 \pm 40	5.9 \pm 2.2	117 \pm 44
AUC0-inf (hr*ug/mL)	114 \pm 40	5.9 \pm 2.2	117 \pm 44
CL (mL/hr/kg)	955 \pm 321	19060 \pm 8186	953 \pm 409
Vss (mL/kg)	2875 \pm 543	45732 \pm 16729	2287 \pm 836
t1/2 (hr)	2.3 \pm 0.93	2.8 \pm 1.1	2.8 \pm 1.1
AUC _{ELF} /AUC _{plasma}	-	19.4	0.97
Cmax,ELF/Cmax,plasma	-	26.3	1.3

- BWC0977 was significantly higher (\sim 20X) exposures in the ELF in comparison to the free plasma level.
- Total plasma concentrations of BWC0977 could be representative of concentrations in ELF, the site of bacterial infection, in the lungs.

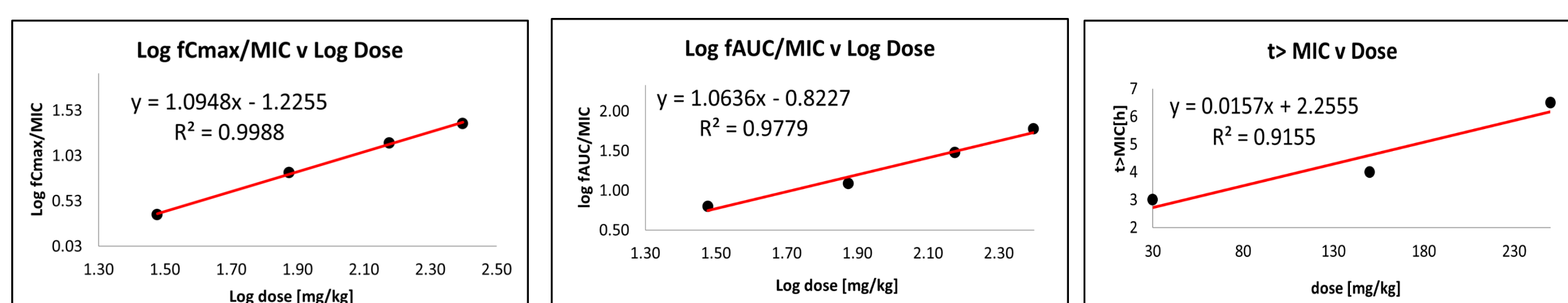
Design of Dose Fractionation Study

- Infecting Strain: *P. aeruginosa* ATCC27853; MIC 0.25 μ g/ml
- Dose route: IV infusion for 2 hours
- Duration of study = 24 h
- Plasma protein binding: 93%
- Design: Total doses of 450, 400, 350, 300, 150, 75, 40, 20, 10 & 5 mg/kg were fractionated as q24h, q12h, or q8h over a 24-h period and administered as a 2-hr intravenous infusion. Doses that were not tolerated were eliminated from the experiment

Dose [mg/kg]	Cmax (μ g/mL)	fCmax/MIC	Pred fCmax/MIC	AUC (ug/mL)	fAUC/MIC	Pred Log fAUC/MIC	T>MIC [h]	Pred t>MIC [h]
30	8.59	2.4	2.5	22.52	6.3	0.75	3	2.7
75	24.8	6.9	6.7	43.7	12.2	1.17	NE	NE
150	52.6	14.7	14.4	107	30.0	1.49	4	4.6
250	86.7	24.3	25.1	213	59.6	1.73	6.5	6.2

MIC *P.ae* 27853 = 0.25 μ g/mL; fu=0.07; NE: Not Estimated

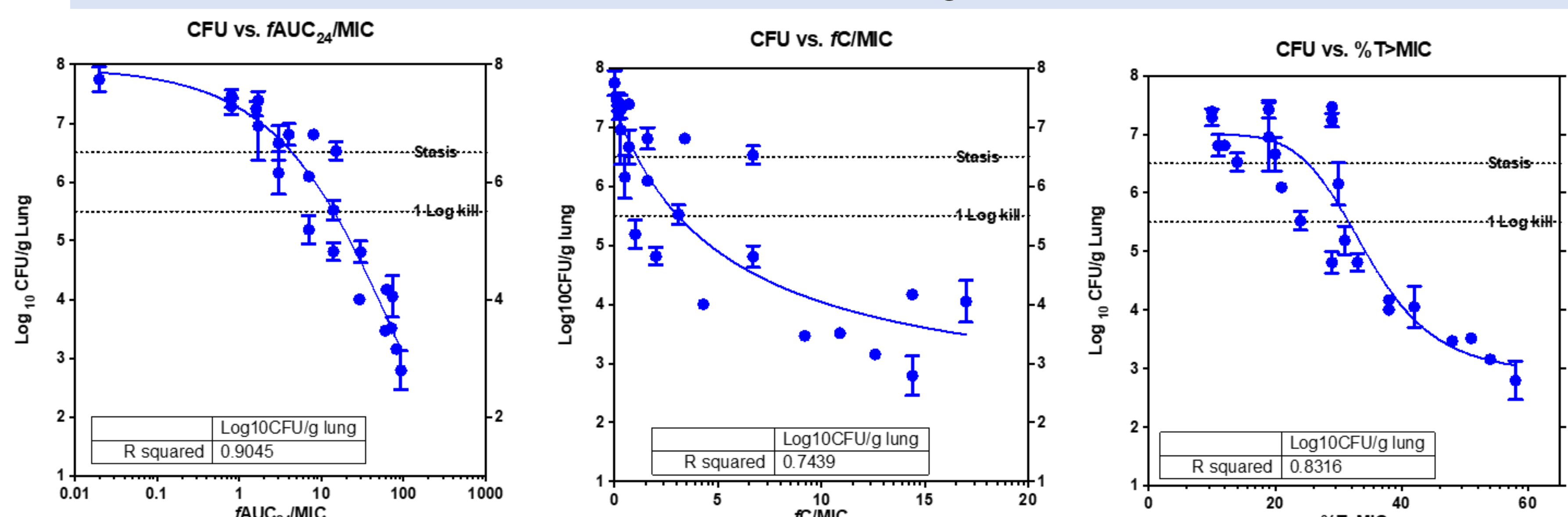
Linear Regression of Dose vs free PK Parameters/MIC



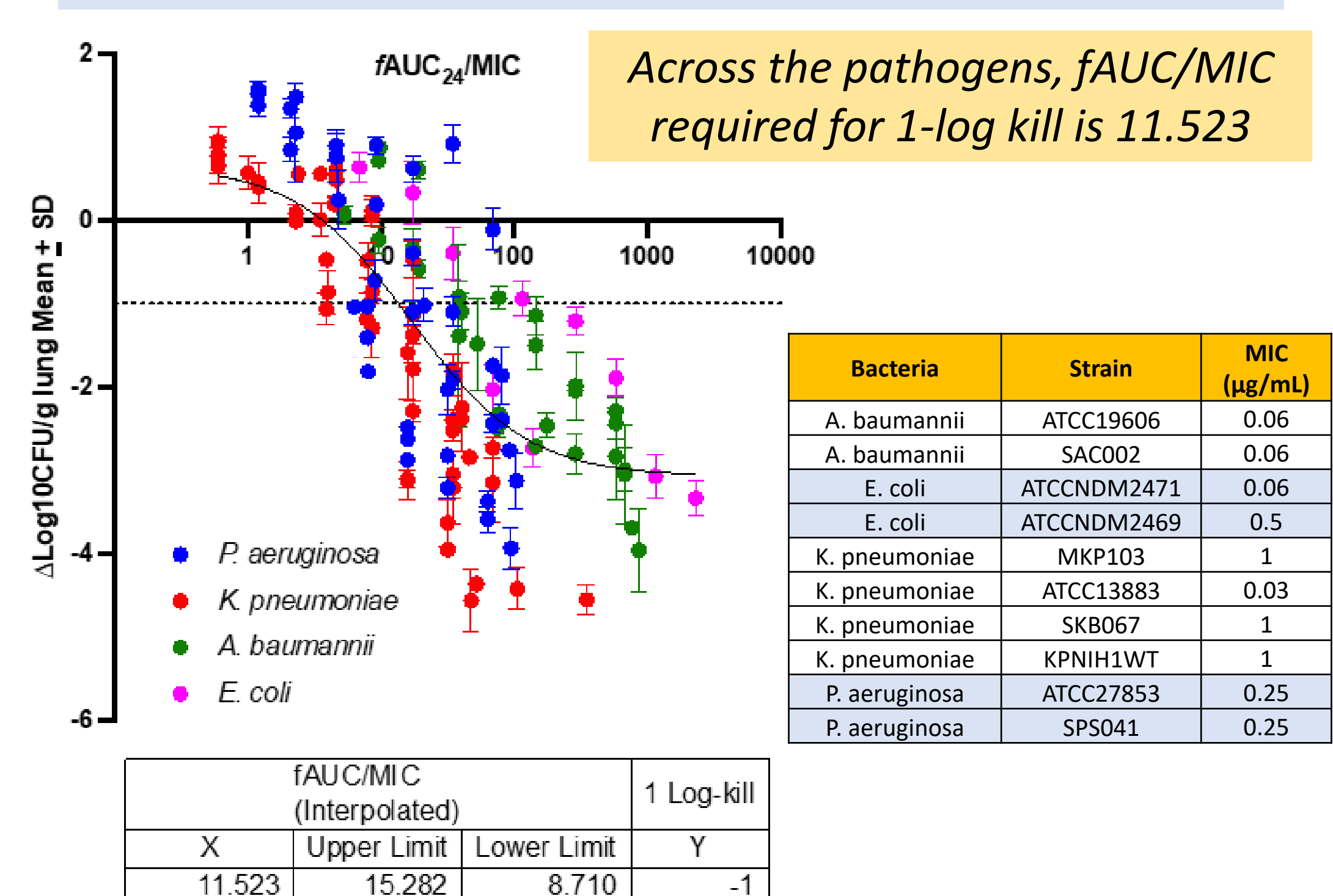
Total dose [mg/kg]	No of fractionated doses	dose [mg/kg]	regimen	Log fC/MIC	fC/MIC	Log fAUC/MIC	fAUC/MIC per dose	total fAUC/MIC	t>MIC [h]	total t>MIC[h]	%t>MIC
450	3	150	q8	1.16	14.4	1.49	31.0	93	4.6	13.8	58
400	3	133	q8	1.10	12.6	1.44	27.4	82	4.3	13.0	54
350	2	175	q12	1.23	17.0	1.56	36.6	73	5.0	10.0	42
350	3	117	q8	1.04	10.9	1.38	23.8	71	4.1	12.3	51
300	1	300	q24	1.49	30.7	1.81	64.9	65	7.0	7.0	29
300	2	150	q12	1.16	14.4	1.49	31.0	62	4.6	9.2	38
300	3	100	q8	0.96	9.2	1.30	20.2	60	3.8	11.5	48
150	1	150	q24	1.16	14.4	1.49	31.0	31	4.6	4.6	19
150	2	75	q12	0.83	6.7	1.17	14.8	30	3.4	6.9	29
150	3	50	q8	0.63	4.3	0.98	9.6	29	3.0	9.1	38
75	1	75	q24	0.83	6.7	1.17	14.8	15	3.4	3.4	14
75	2	37.5	q12	0.50	3.1	0.85	7.1	14	2.8	5.7	24
75	3	25	q8	0.30	2.0	0.66	4.6	14	2.6	7.9	33
40	1	40	q24	0.53	3.4	0.88	7.6	8	2.9	2.9	12
40	2	20	q12	0.20	1.6	0.56	3.6	7	2.6	5.1	21
40	3	13	q8	0.01	1.0	0.37	2.4	7	2.5	7.4	31
20	1	20	q24	0.20	1.6	0.56	3.6	4	2.6	2.6	11
20	2	10	q12	-0.13	0.7	0.24	1.7	3	2.4	4.8	20
20	3	7	q8	-0.32	0.5	0.05	1.1	3	2.4	7.1	30
10	1	10	q24	-0.13	0.7	0.24	1.7	1.7	2.4	2.4	10
10	2	5	q12	-0.46	0.3	-0.08	0.8	1.7	2.3	4.7	19
10	3	3	q8	-0.65	0.2	-0.27	0.5	1.6	2.3	6.9	29
5	1	5	q24	-0.46	0.3	-0.08	0.8	0.8	2.3	2.3	10
5	2	2.5	q12	-0.79	0.2	-0.40	0.4	0.8	2.3	4.6	19
5	3	1.7	q8	-0.98	0.1	-0.59	0.3	0.8	2.3	6.8	29

Results

PK/PD driver Vs *P.aeruginosa*



PK/PD driver Vs All pathogens tested



Conclusion

- In the neutropenic rat lung infection model, the PK/PD index that best described the *in vivo* efficacy of BWC0977 against *Pseudomonas aeruginosa* was AUC/MIC followed by % T>MIC
- Target free fraction exposure (fAUC/MIC) to cover *Pseudomonas aeruginosa* was estimated to be 11.523

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