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MOLECULAR TREATMENTS
FOR INFECTIOUS DISEASE

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PK-PD Relationship and PK Driver of Efficacy of the Novel Antibacterial Lysin Exebacase (CF-301) in Pre-Clinical Models

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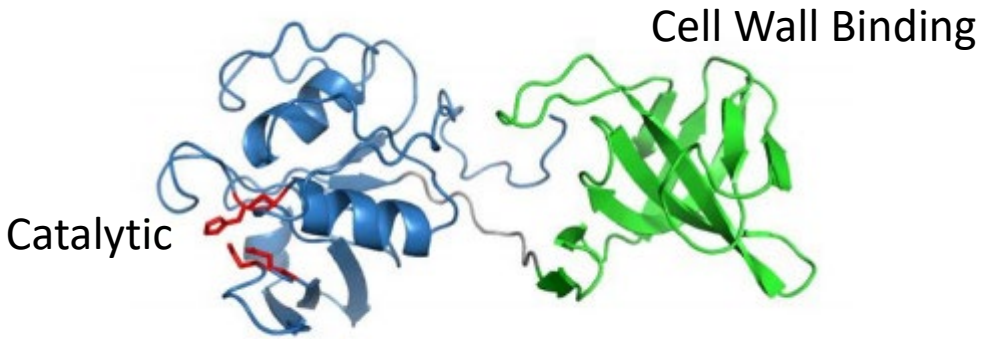
BACKGROUND

- Exebacase (CF-301) – a first in class bacteriophage-derived lysin
- Recombinant protein produced in E.coli
- Direct lytic agent
- Active against S. aureus
- Two functional domains



BACKGROUND – (cont'd)

- Specific features of exebacase include:
  - Novel MOA (cell wall hydrolase enzyme)
  - Bactericidal against resistant *S. aureus*
  - Fast, targeted action
  - Potent activity against biofilm
  - Synergy with standard of care antibiotics (e.g., daptomycin)
  - Low propensity for resistance
- Exebacase completed Phase 1 and Phase 2
- Encouraging clinical results in MRSA blood stream infections (BSI) with significant improvement about 43% higher than SoC alone

OBJECTIVES

The objectives of this project were:

a) To develop animal population PK model in NONMEM in animal species

b) Based on PK parameter estimates from the final population PK model, simulate animal exposure indices (AUC/MIC, C_{max}/MIC and T>MIC) for doses used in animal efficacy assessments

c) To perform PK-PD analyses to characterize the PK-efficacy relationship and determine the PK driver of efficacy in animal models

d) To guide selection of efficacious exposures and doses in humans

METHODS

Population PK analysis:

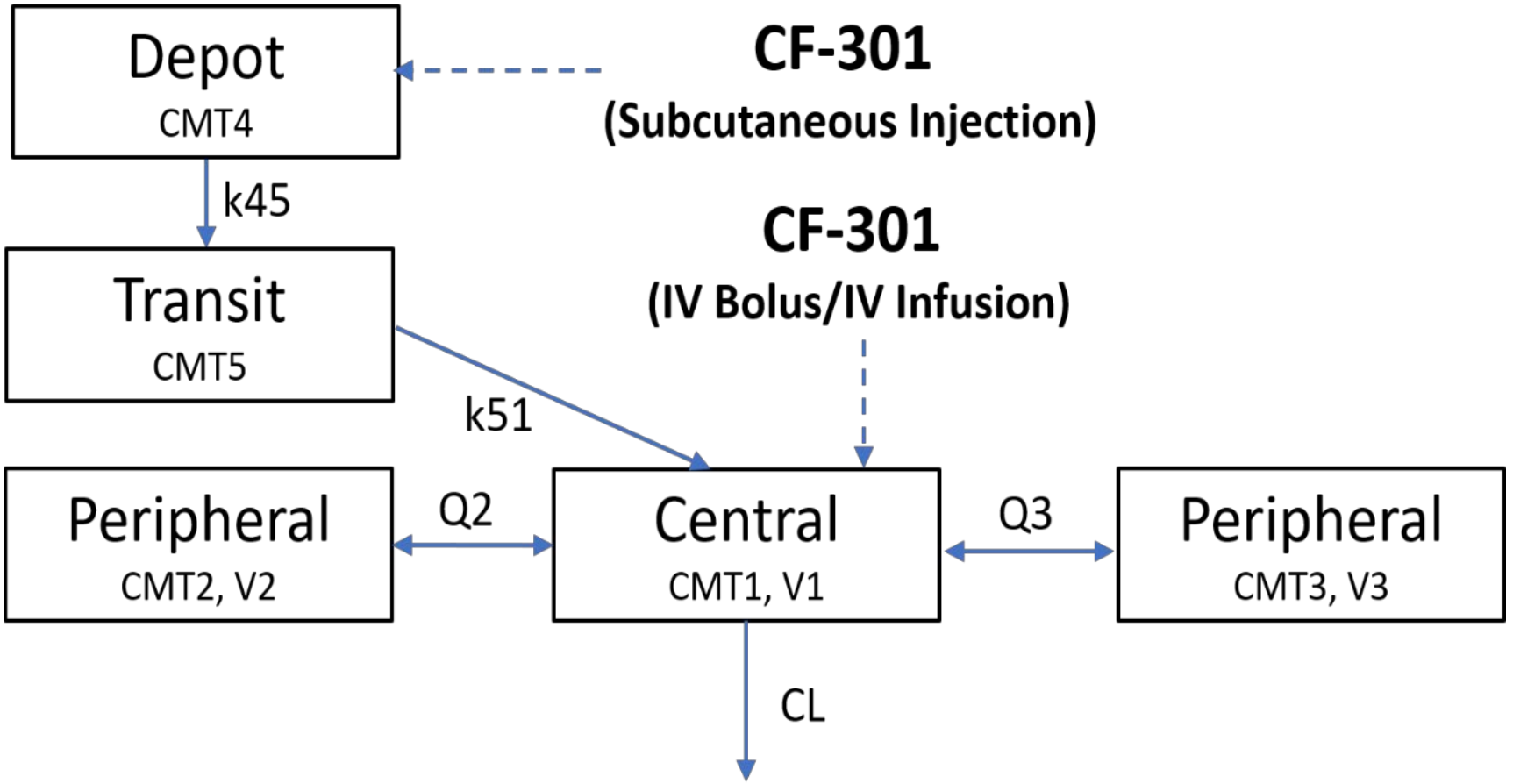
- Pooled from 15 PK studies in 4 animal species (mice, rats, rabbits and dogs)
- Various routes of administration: IV bolus, IV infusion, subcutaneous (SC) injections
- Various dosing regimens 0.125-50 mg/kg, q24h to q8h.
- A total of 2,602 PK observations from 592 animals (42 mice, 316 rats, 156 rabbits and 78 dogs)

For PK-PD analysis:

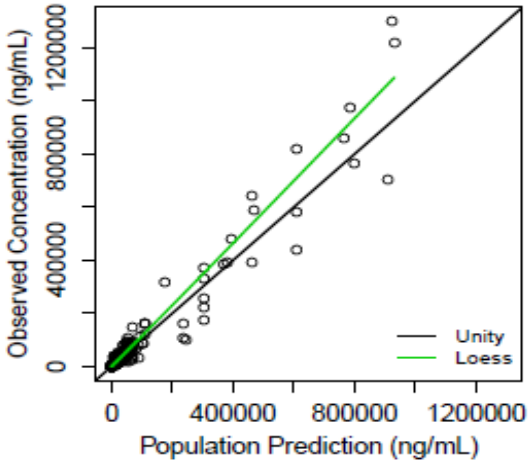
- Data from one study in mouse (NMTI model) with dose range 0.125-90 mg/kg; MICs in mouse serum 16-128 µg/mL
- Two studies in rabbit (IE model) - cardiac vegetation, kidney and spleen with dose range 0.03-1.4 mg/kg; MICs in rabbit serum 0.5-1 µg/mL
- Exebacase was administered at various doses in addition to suboptimal dose of daptomycin

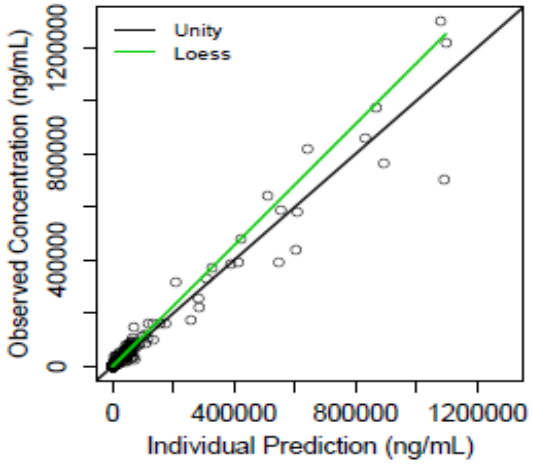
Ref: Indiani C, Sauve K, Raz A, et al., Antimicrobial Agents and Chemotherapy, 2019, 63(4), e02291-18

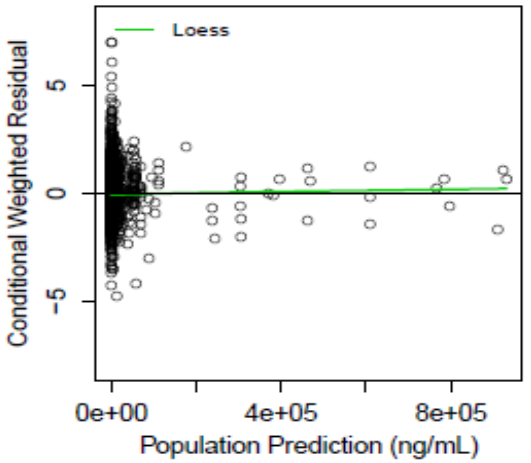
RESULTS - Population PK

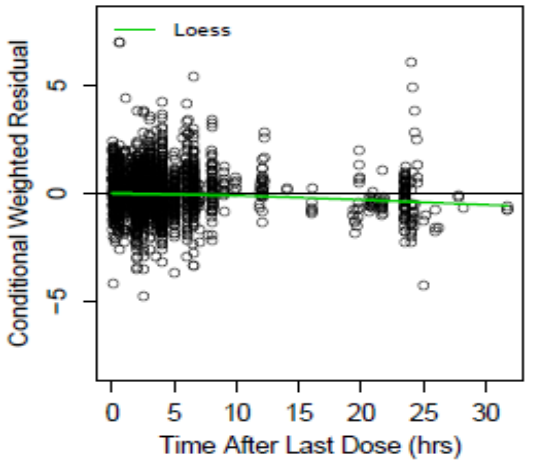


RESULTS - Population PK : GOF Plots

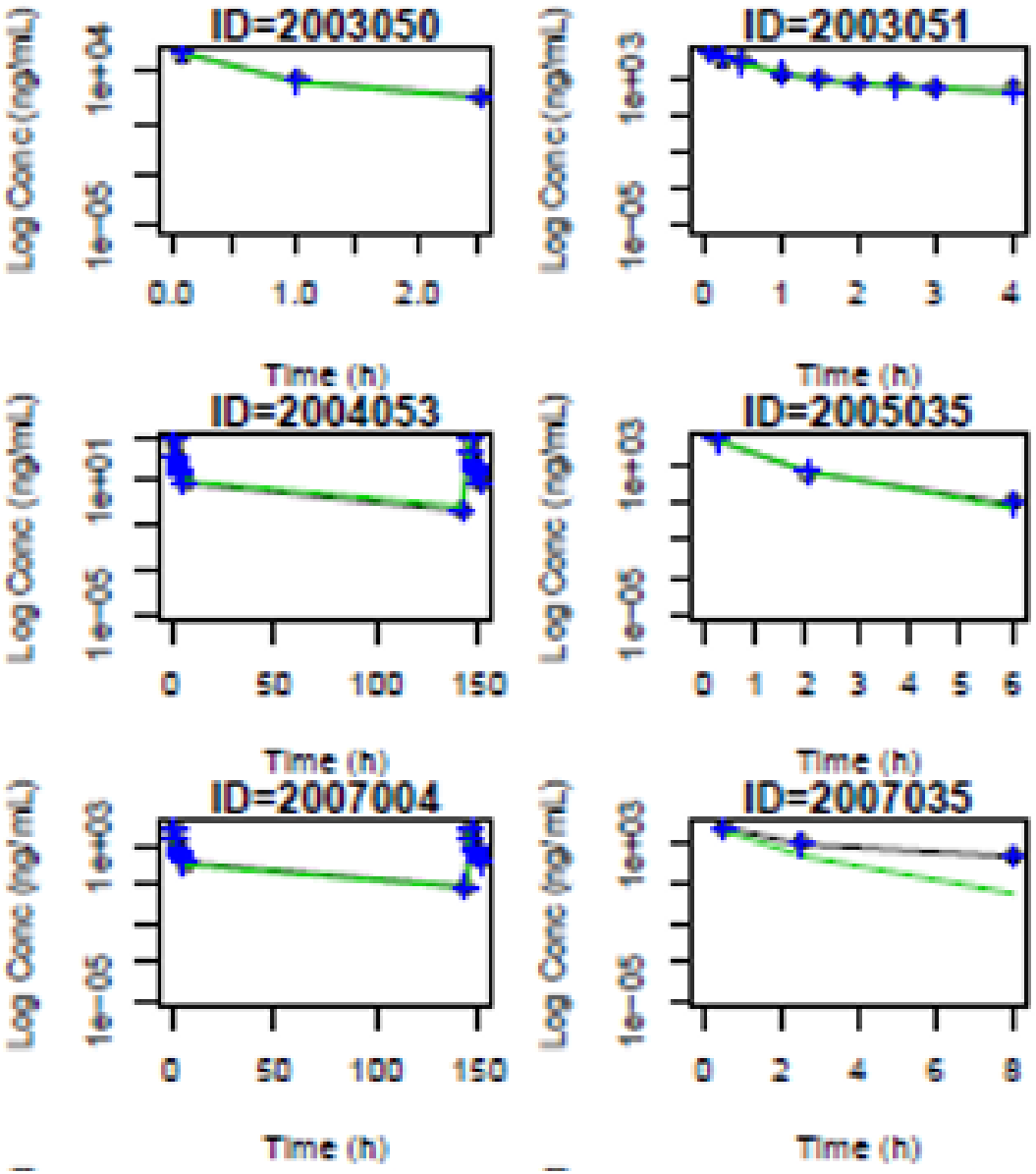






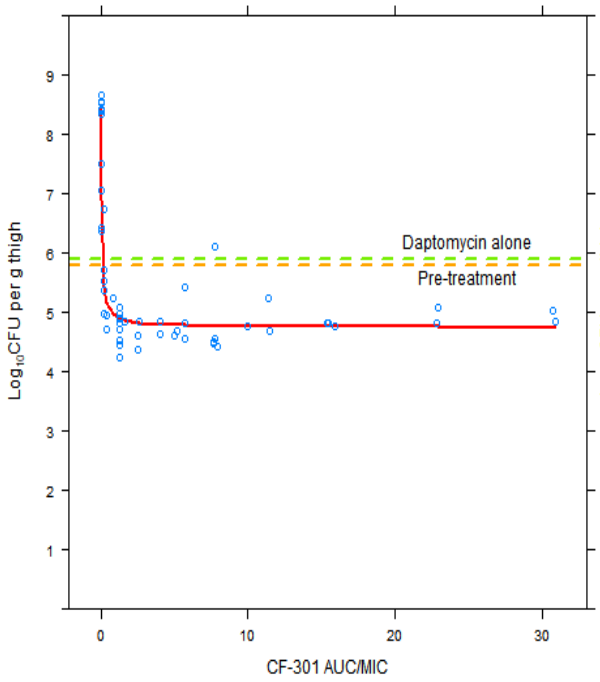


RESULTS - Population PK: individual fit examples

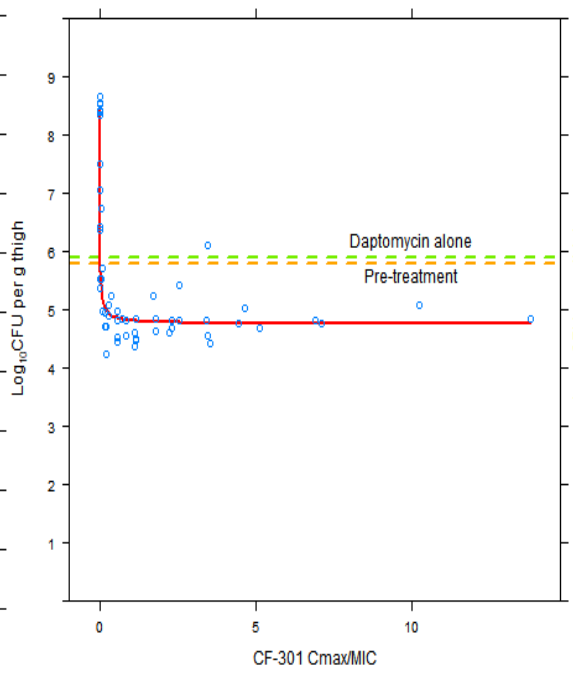


RESULTS – PK-PD NMTI

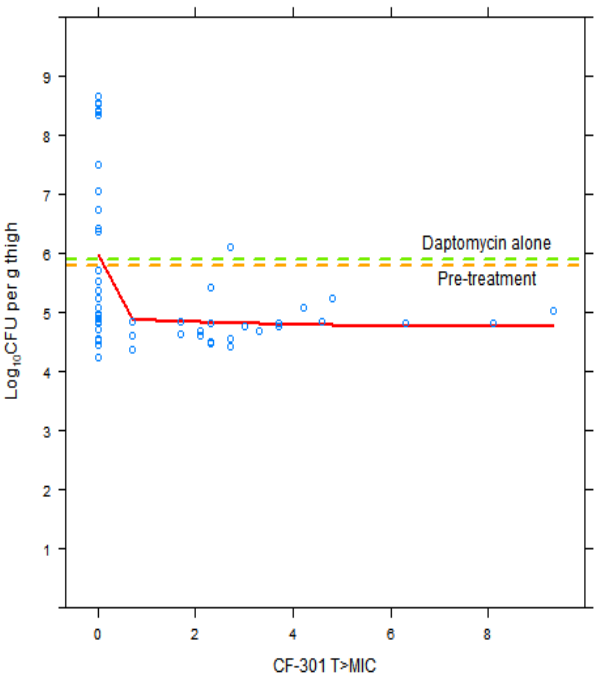
AUC/MIC



C_{max}/MIC



T>MIC

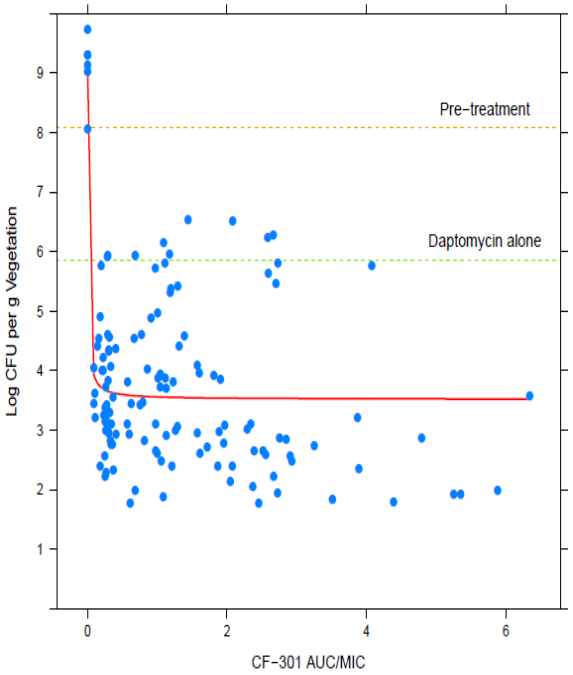


RESULTS – PK-PD Relationship in mouse

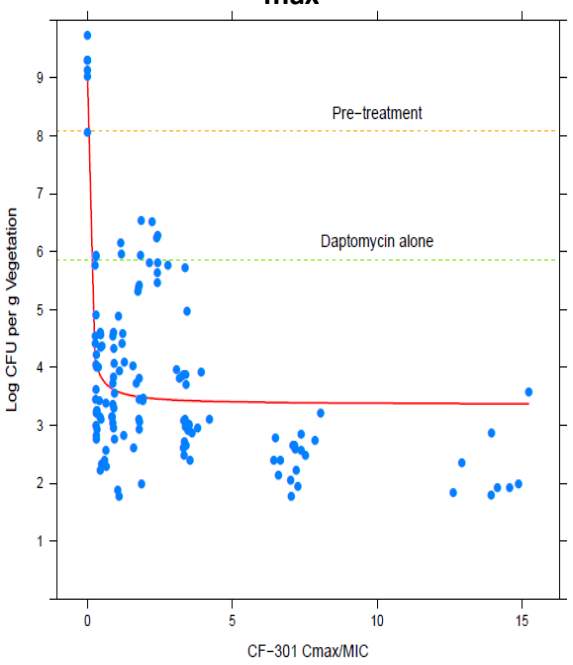
Exposure Index	Parameter	Estimate	SE	p-value	Model RSE
AUC/MIC					0.388
	E_0	8.46	0.16	<0.0001	
	E_{max}	3.72	0.18	<0.0001	
	EC_{50}	0.04	0.01	<0.0001	
	p	0.92	0.18	<0.0001	
C_{max}/MIC					0.390
	E_0	8.46	0.16	<0.0001	
	E_{max}	3.71	0.19	<0.0001	
	EC_{50}	0.01	0.00	0.0003	
	p	0.81	0.17	<0.0001	
T>MIC					1.167
	E_0	5.96	0.21	<0.0001	
	E_{max}	2.00	241.11	0.993	
	EC_{50}	0.16	367.10	1.00	
	p	0.10	15.84	0.995	

RESULTS – PK-PD Rabbit Cardiac Vegetation

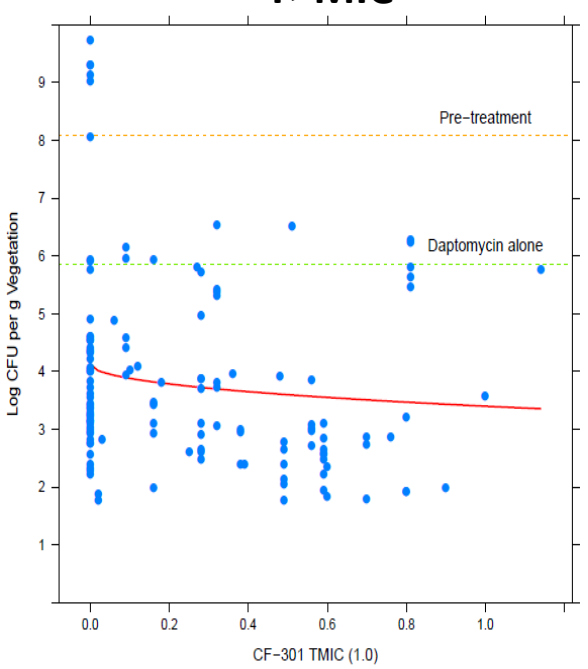
AUC/MIC



C_{max}/MIC

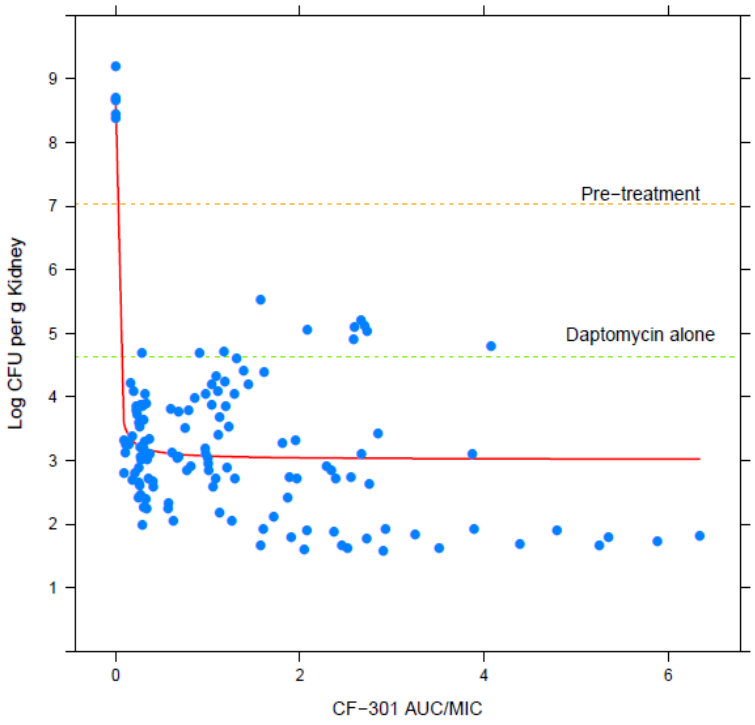


T>MIC

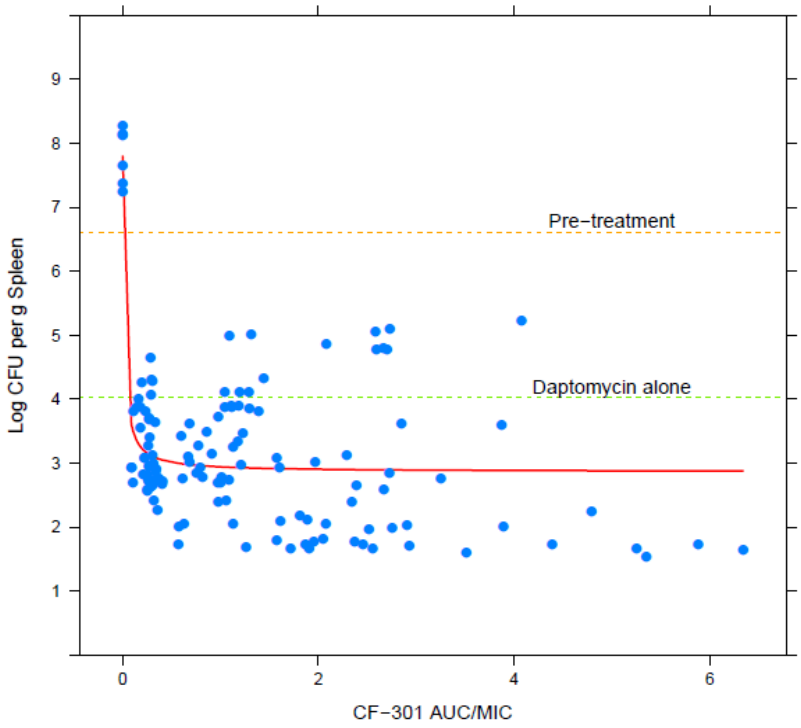


RESULTS – PK-PD Rabbit

Kidney



Spleen



RESULTS – PK-PD Relationship in Rabbit

Exposure Index	Parameter	Estimate	SE	p-value	Model RSE
AUC/MIC					1.212
	E_0	9.10	0.50	<0.0001	
	E_{max}	5.58	0.56	<0.0001	
	EC_{50}	0.01	0.05	0.894	
	p	1.00	2.67	0.708	
C_{max}/MIC					1.193
	E_0	9.09	0.49	<0.0001	
	E_{max}	5.73	0.57	<0.0001	
	EC_{50}	0.04	0.10	0.669	
	p	1.00	1.27	0.432	
T>MIC					1.640
	E_0	4.13	0.23	<0.0001	
	E_{max}	8.00	910.50	0.993	
	EC_{50}	100.00	28160.00	0.997	
	p	0.50	3.61	0.890	

DISCUSSION

- NMTI model :
  - doses 15-30 mg/kg were associated with maximum efficacy, MICs in mouse serum ranged 16-128 µg/mL
- Rabbit IE (cardiac vegetation, kidney or spleen):
  - doses 0.23-0.7 mg/kg were associated with maximum efficacy, MICs in rabbit serum 0.5-1 µg/mL
- Rabbit reached maximum reduction in CFU of 2.3-logs at AUC/MIC ratio =0.10
- Mouse reached maximum reduction in CFU of 1.2-logs at AUC/MIC ratio =0.32
- Efficacious doses in humans should be targeted to achieve a minimum target of AUC/MIC ratio $\geq$ 0.5
- Given the complexity S. aureus BSIs in humans (e.g. metastatic foci in bone, lung, etc.) AUC/MIC ratios well above 0.5 (e.g., 2-10 fold higher) are possible targets to ensure most/all patients achieve efficacious exposures

CONCLUSIONS

- A population PK model developed that can predict PK profiles of individual animals accurately
- Exebacase MICs in serum and absolute exposures required to achieve maximal efficacy are vastly different in mouse and rabbit
- Efficacy was established in mouse (NMTI) and rabbits - cardiac vegetation, kidney and spleen consistently
- AUC/MIC ratio provides an adequate index for target efficacy exposures regardless of species
- An AUC/MIC ratio of about >0.5 (e.g., 2-10 fold higher) is appropriate target for efficacious dose in humans

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RESULTS - Population PK : pcVPC