Estimation of *In Vitro* Susceptibility Breakpoints for Tigecycline Against *Staphylococcus aureus*

Alison K Meagher, PharmD
Cognigen Corporation

45th ICAAC
December 17, 2005

Co-Authors

Julie Passarell, M.A.
Cognigen Corporation

Scott Van Wart, M.S.
Cognigen Corporation

Brenda Cirincione, M.A.
Cognigen Corporation

Paul G. Ambrose, PharmD, FIDSA
Institute for Clinical Pharmacodynamics
Ordway Research Institute

This research was supported by a grant from Wyeth

Introduction

- Susceptibility breakpoints are critical from the patient perspective as well as for society
  - Patient perspective: risk of clinical failure
  - Society perspective : risk of resistance
- Clinical trials collect PK data in target patient populations and provide the opportunity to integrate
  - Patient population PK
  - Exposure-response relationships
  - Distribution of MIC values for clinical isolates

Objective

- Identify MIC susceptibility breakpoints for tigecycline against Staphylococci

Methods

- Tigecycline exposure measures were generated from a population PK model.[1]
- A defined range of PK/PD targets (AUC/MIC) identified in previously presented exposure-response analyses[2] was used.
- MIC susceptibility breakpoints were estimated through integration of these results and the distribution of *S. aureus* from clinical trials.

[1]Van Wart, et al. Population pharmacokinetics of tigecycline in Phase 1 subjects (ICAAC 2004)
[2]Meagher, et al. Exposure-response analysis of the efficacy of tigecycline in patients with complicated skin and skin-structure infections (ECCMID 2005)

Methods
Study Design

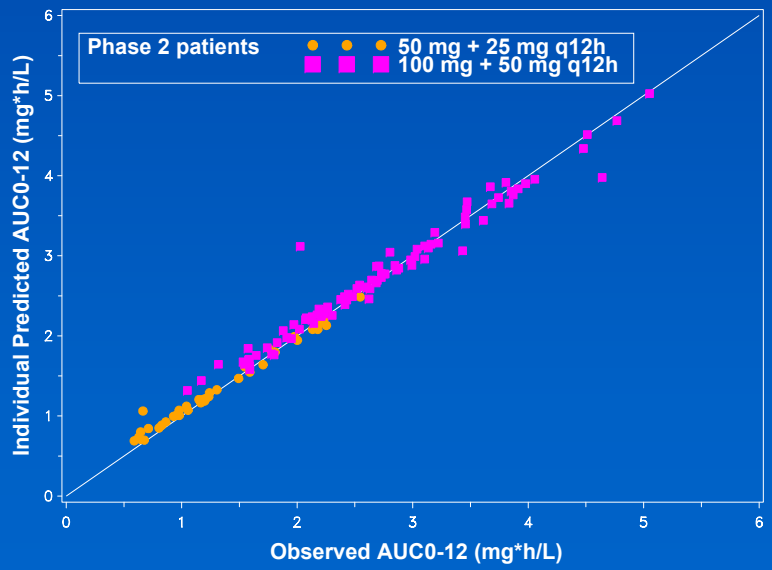
- One Phase 2 and two Phase 3 trials of patients with complicated skin and skin-structure infections (cSSSI)
- 61 patients (91 pathogens) with cSSSI
- Patients received either tigecycline 50-mg loading dose/25 mg q12h or 100-mg loading/50 mg q12h

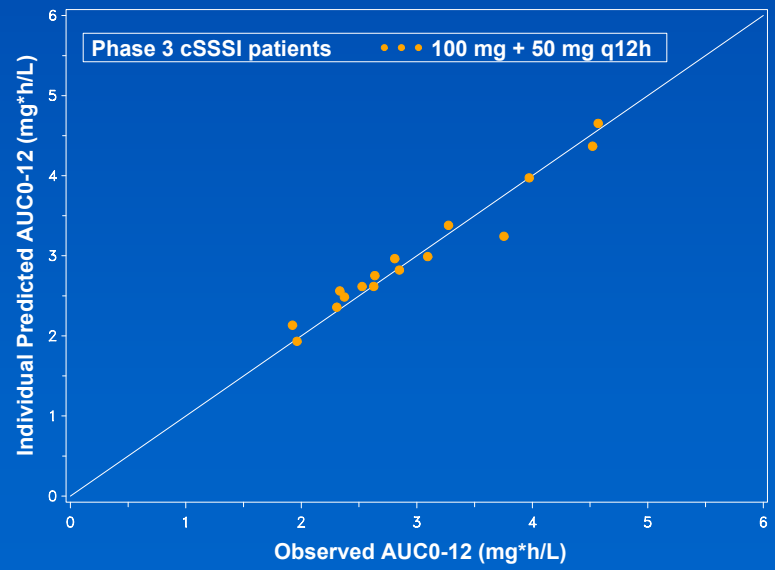
Methods
Outcome Evaluation

- Patients with *S. aureus* and/or streptococci isolated from skin lesions
- Outcome evaluation considered in this analysis was microbiological response
  - Eradication/presumed eradication were considered “successful”
  - Persistence/presumed persistence were considered “failures”

Methods
Pharmacokinetics

- Previously presented population PK model[1]
- Two-compartment model with zero-order input and first-order elimination

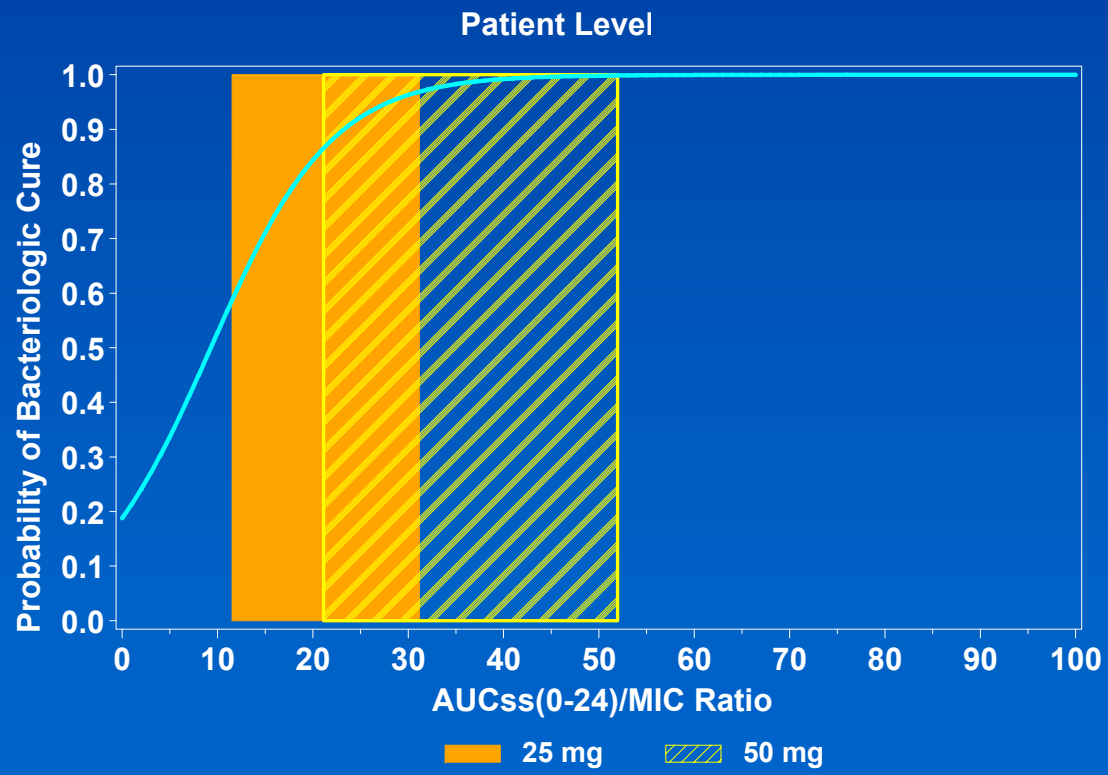




[1]Van Wart, et al. Population pharmacokinetics of tigecycline in Phase 1 subjects. ICAAC 2004.

Methods
PK/PD Analyses

- CART analysis identified AUC/MIC breakpoints at 12.5 (p = 0.0309) and 16.4 (p = 0.0118)



The line represents the model-based predicted probability of the patient level bacteriologic cure.
The bars represent the 25th to 75th percentiles of ratio for each dose group.

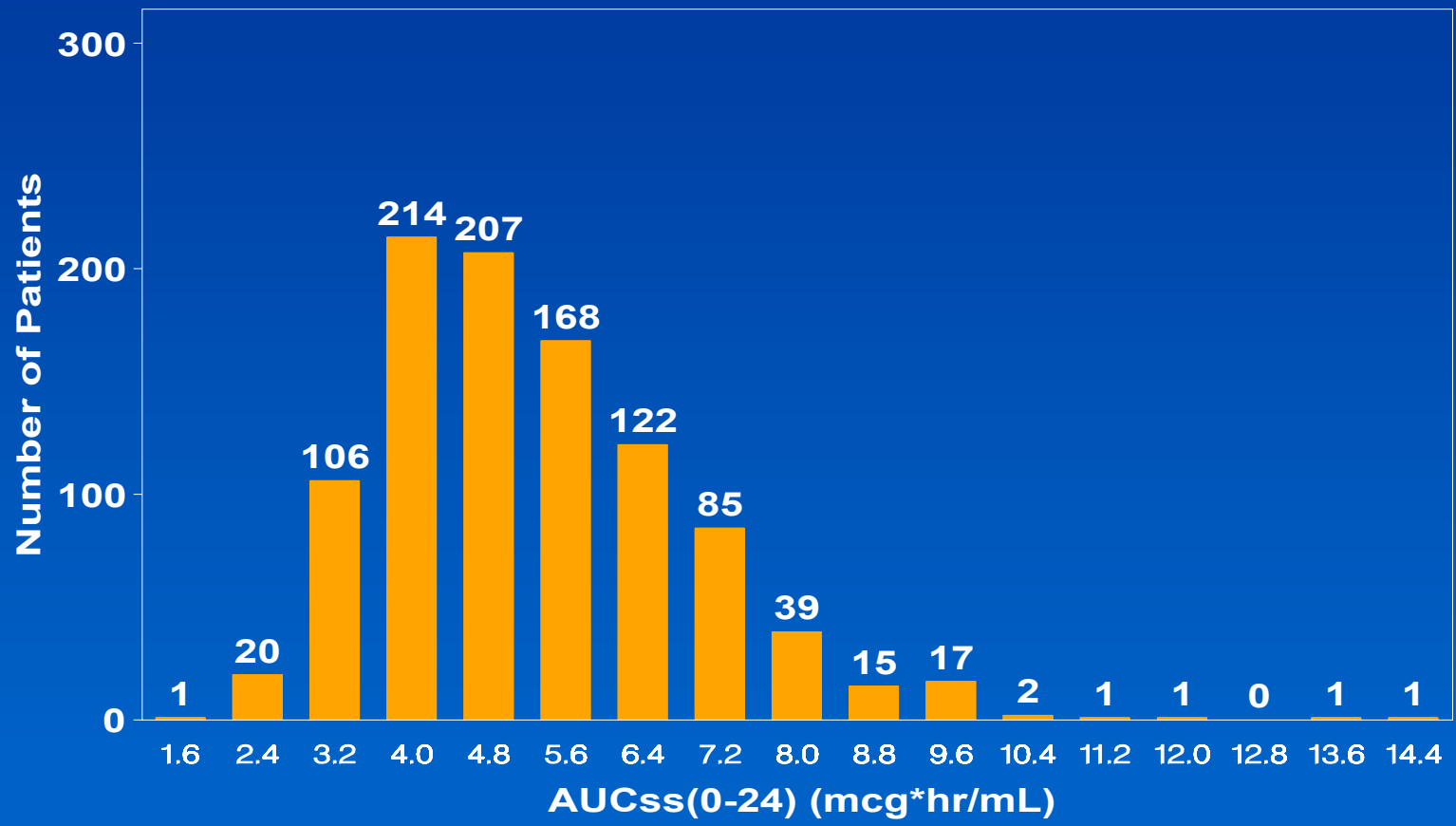
Methods
Bootstrap Confidence Interval

- 1000 randomly simulated datasets with replacement (40 patients each) were generated
- CART analysis was performed to determine breakpoints in the AUC/MIC distribution, based upon microbiological outcomes

Methods
PK/PD Target Attainment

- Within each simulated dataset, AUC values were paired with selected MIC values.
- AUC/MIC ratios were evaluated with the previously identified PK/PD target values of 12.5 and 16.4 and the median bootstrap breakpoint estimate.

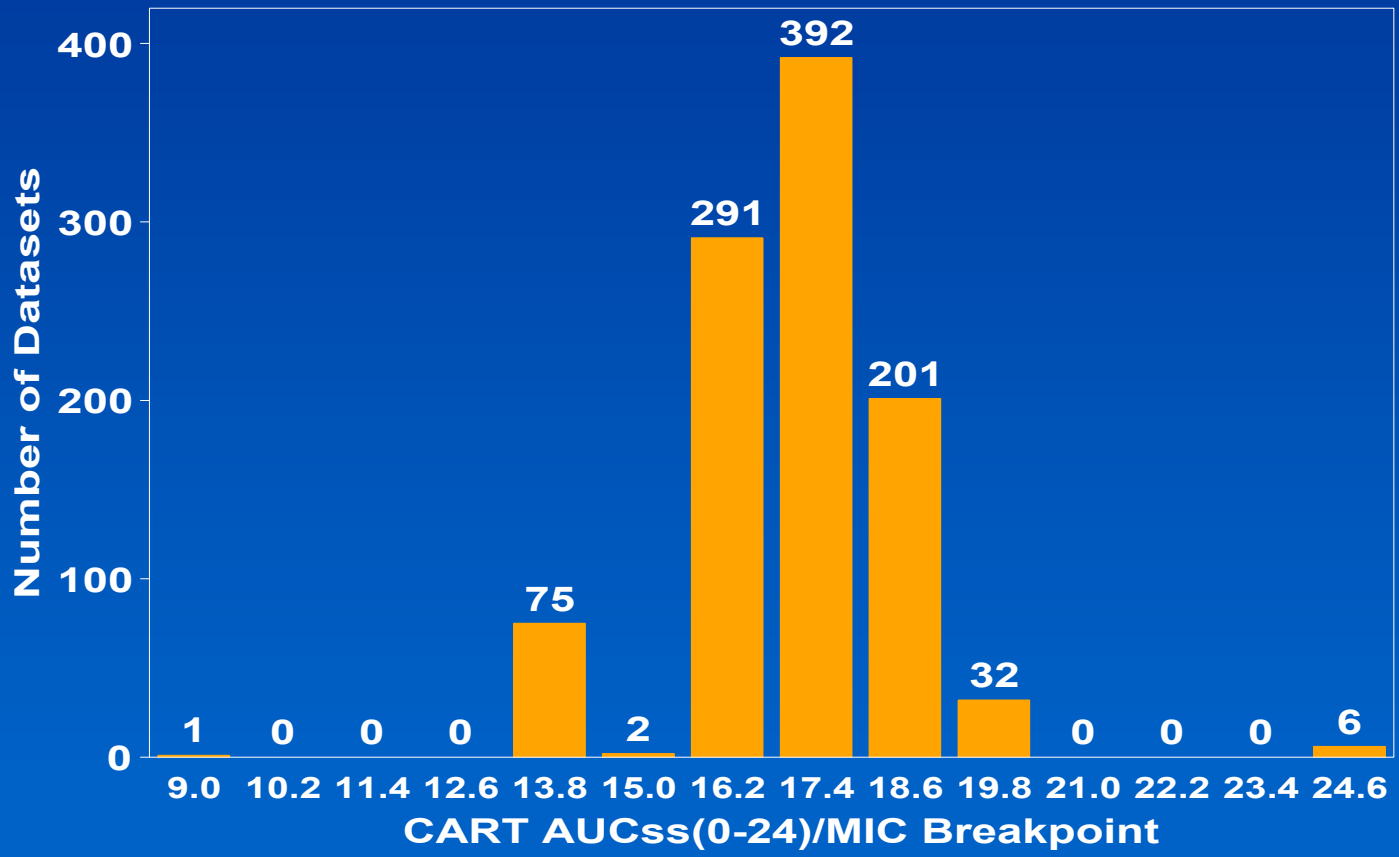
Results
Pharmacokinetics



Mean (SD) observed AUC was 6.02 (2.2) µg•hr/mL (2.6 to 22.58 µg•hr/mL)

Mean (SD) simulated AUC was 6.02 (1.99) µg•hr/mL (1.5 to 26 µg•hr/mL)

Results
Boot Strap Confidence Interval

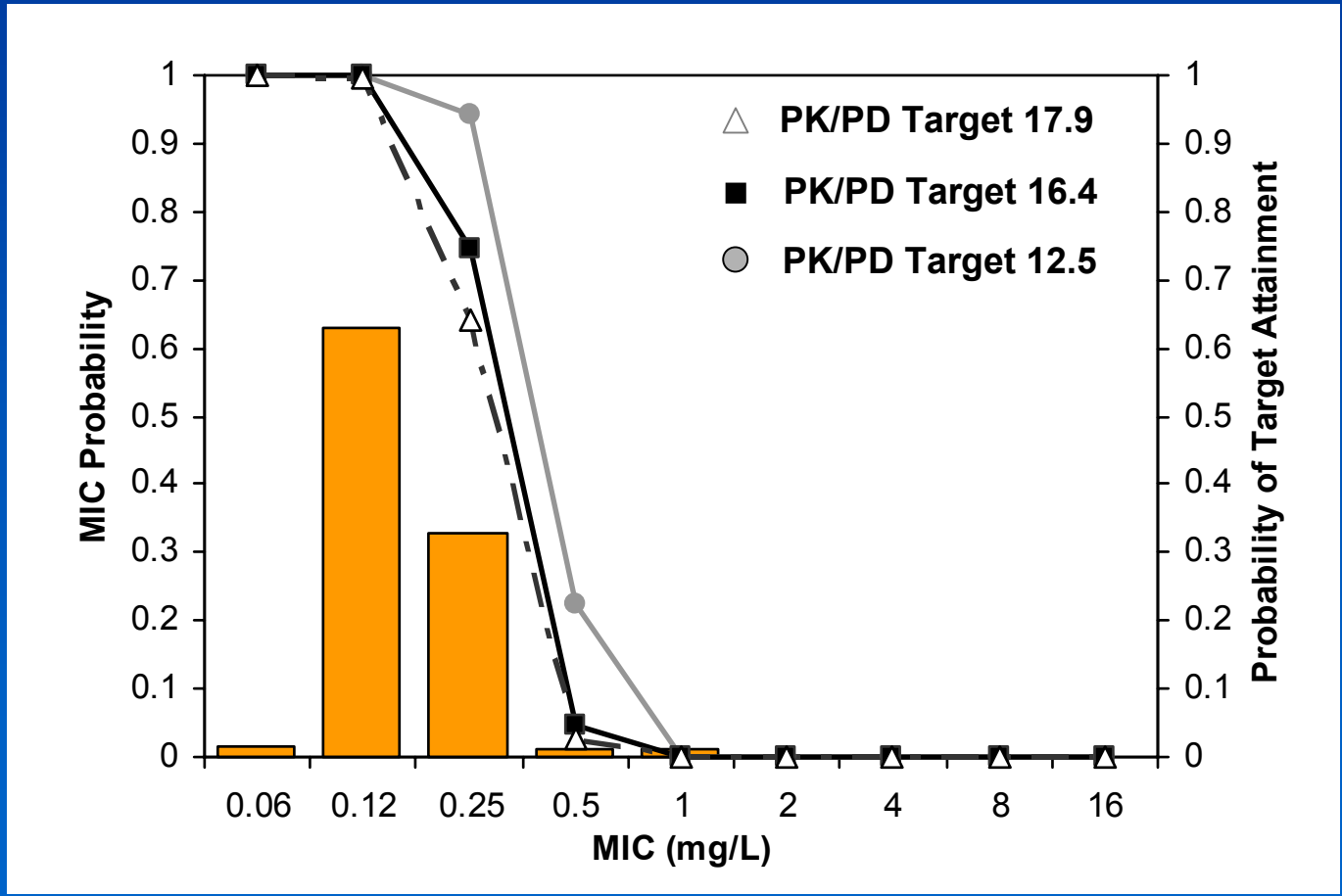


Median of 17.9 served as bootstrap estimate for the 95% CI of 13.9 to 19.5

Results
PK/PD Target Attainment

MIC (µg/mL)	AUC/MIC Breakpoint		
	12.5	16.4	17.9
0.06	100	100	100
0.12	99.99	99.91	99.76
0.25	94.13	74.51	64.25
0.5	22.58	4.82	2.52
1	0.17	0.11	0.10
2	0	0	0

Results
PK/PD Target Attainment



Conclusions

- Integration of population PK, exposure-response analyses, and MIC distributions is a useful approach for evaluating susceptibility breakpoints.
- This analysis provided an estimation of susceptibility breakpoints for tigecycline against Staphylococci.
- In addition to clinical response, these analyses may be a useful component in assessing breakpoints for these organisms.