Anti-infective Drugs Advisory Committee

# Telavancin for the Treatment of Complicated Skin and Skin Structure Infections

Theravance, Inc.

November 19, 2008

# Introduction

**Rebecca Coleman, PharmD**

**Vice President, Regulatory Affairs and Quality**
**Theravance, Inc.**

# Proposed Indication

Telavancin is indicated for the treatment of patients with complicated skin and skin structure infections caused by susceptible Gram-positive microorganisms

# Agenda

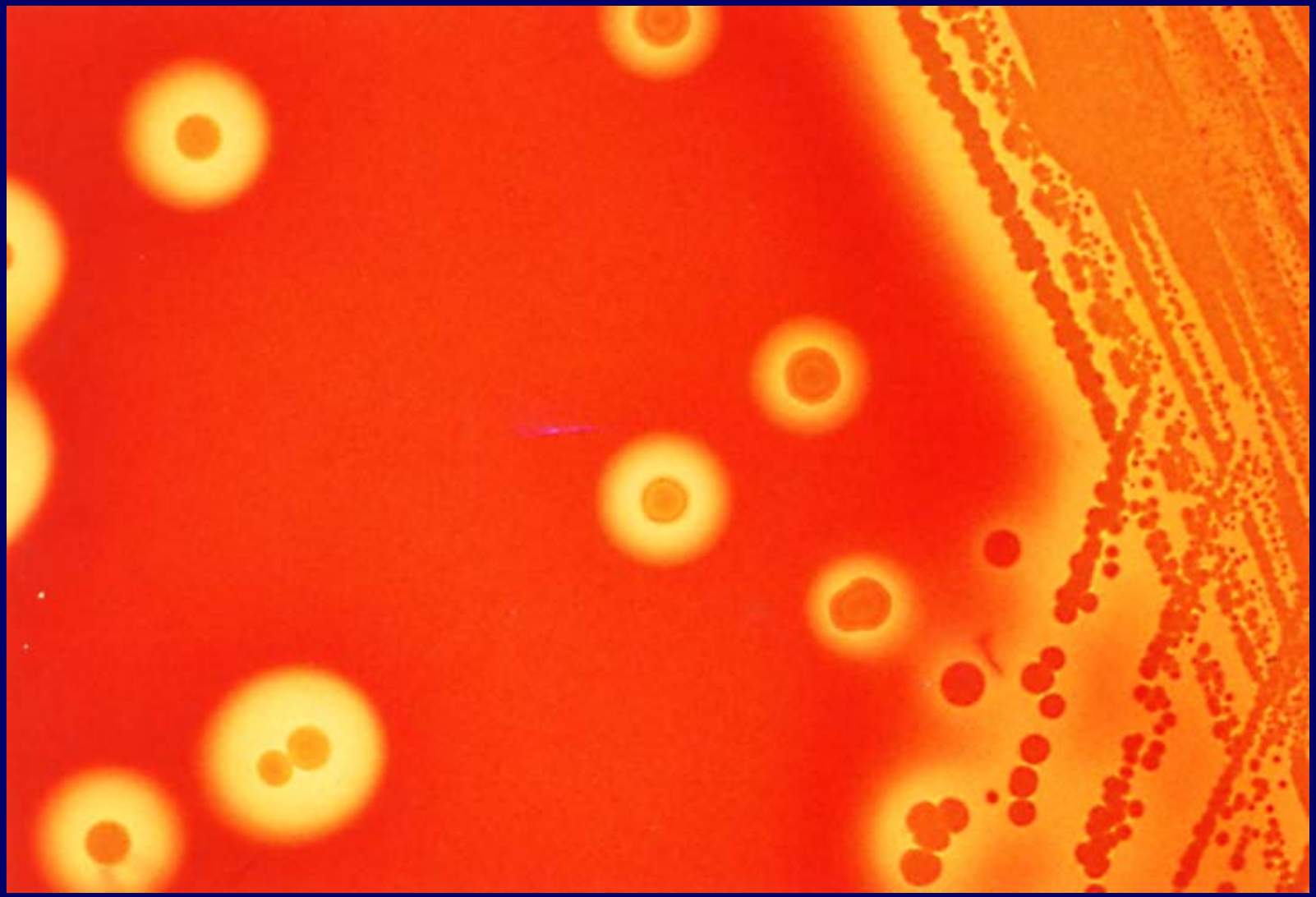
| | |
|---|---|
| **Growing Need** | ***G. Ralph Corey, MD*** |
| **Nonclinical and Clinical Program** | ***Steven Barriere, PharmD*** |
| **Nonclinical Reproductive Studies** | ***Anthony Scialli, MD*** |
| **Risk Management Plan** | ***Rebecca Coleman, PharmD*** |
| **Benefit:Risk** | ***Louis Saravolatz, MD*** |

# The Epidemic of Antibiotic-Resistant Infections

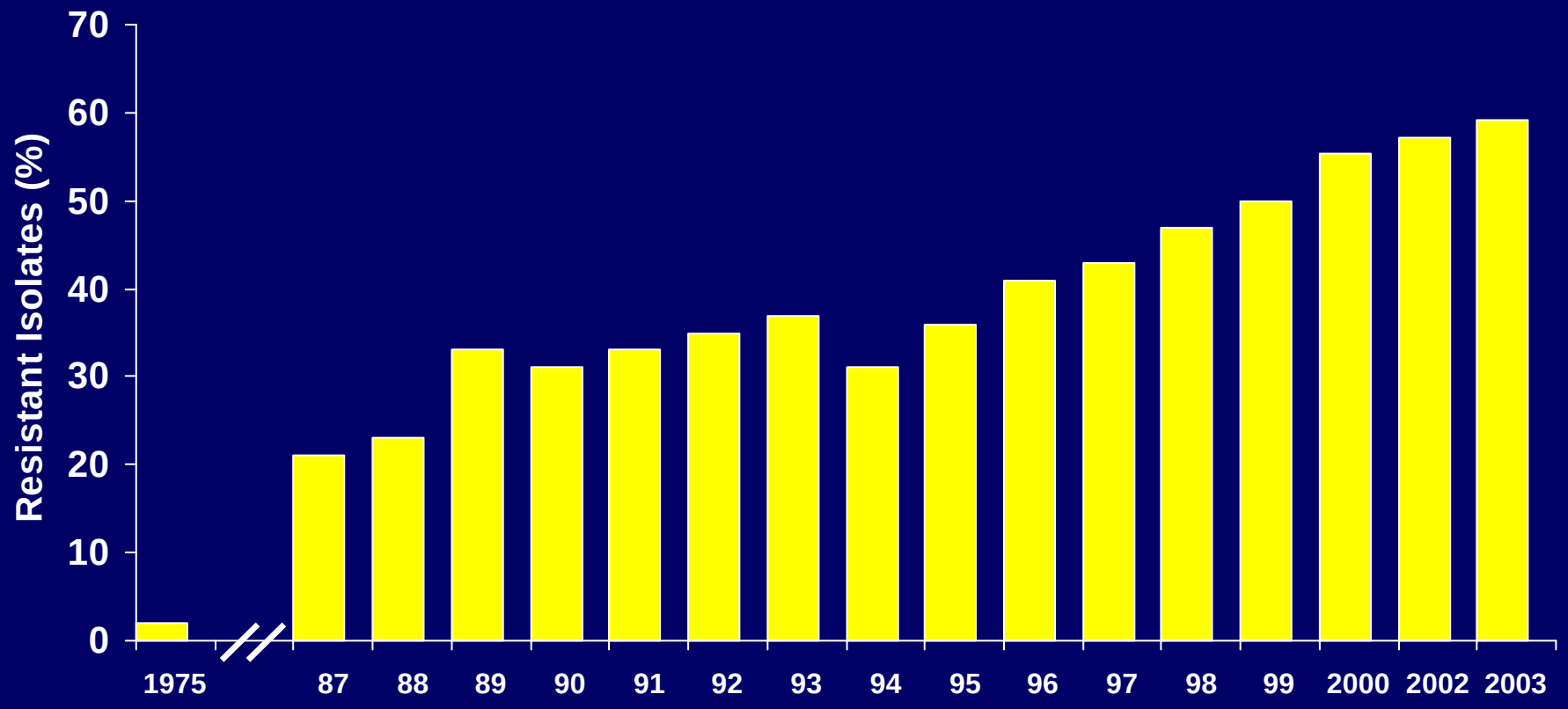
**Ralph Corey, MD**

**Professor of Medicine**
**Duke Clinical Research Institute**

# *Staphylococcus aureus*



# *S. aureus* in Hospitals: Most Isolates Now Methicillin-Resistant






NNIS Antimicrobial Resistance Surveillance Report 2004
http://www.cdc.gov/ncidod/dhqp/pdf/nnis/NNIS_2004.pdf

# In Emergency Rooms: MRSA Now the Most Common Cause of cSSSI

| Site | Patients (N) | MRSA N (%) | MSSA N (%) |
|---|---|---|---|
| Albuquerque, NM | 42 | 25 (60) | 10 (24) |
| Atlanta, GA | 32 | 23 (72) | 4 (12) |
| Charlotte, NC | 25 | 17 (68) | 0 |
| Kansas City, MO | 58 | 43 (74) | 6 (10) |
| Los Angeles, CA | 47 | 24 (51) | 6 (13) |
| Minneapolis, MN | 28 | 11 (39) | 4 (14) |
| New Orleans, LA | 69 | 46 (67) | 11 (16) |
| New York, NY | 20 | 3 (15) | 8 (40) |
| Philadelphia, PA | 58 | 32 (55) | 12 (21) |
| Phoenix, AZ | 30 | 18 (60) | 8 (27) |
| Portland, OR | 13 | 7 (54) | 2 (15) |
| Total | 422 | 249 (59) | 71 (17) |



Moran GJ et al. *NEJM* 2006;355:666

# MRSA in Complicated Skin and Skin Structure Infections

# Annual US Death Rates

| Infectious Disease | Deaths (est) | Year |
|---|---|---|
| **MRSA** | 19,000 | 2005 |
| **AIDS** | 15,798 | 2004 |
| **Tuberculosis** | 662 | 2004 |
| **SARS** | 0 | All |
| **Bird Flu** | 0 | All |

Klevens et al. *JAMA* 2007; 298: 1763-71
Centers for Disease Control and Prevention;
Boucher H. and Corey G. *Clinical Infectious Diseases* 2008

# Approved Therapies for cSSSI When MRSA is Suspected or Confirmed

- **Vancomycin**
- **Daptomycin**
- **Linezolid**
- **Tigecycline**

# Vancomycin is Losing Effectiveness

- **Vancomycin resistance (VISA and VRSA)**
  - **Rare**
- **hVISA: Subpopulations with high MICs**
  - **28% in endocarditis patients (ICE)**
  - **Clinical failures w/sustained hVISA bacteremia**
- **MIC creep**
  - **MICs 1.5-2 µg/mL predicts poor response to vancomycin**
  - **Recent blood stream isolates have high MICs**

Bae. ICAAC 2008
Howden. *CID* 2004;38:21
Soriano et al. *CID* 2008;46: 193-200

# Initial Treatment Failure in cSSSI has Serious Consequences

- **Retrospective review of 47,219 hospitalized cSSSI patients in 2003-04**
- **Evidence of failure of initial antibiotic therapy: 22.8% of cases**
  - **3-fold increase in mortality**
  - **Additional 5 days of inpatient antibiotic Rx**



Edelsberg et al. *Inf Cont and Hosp Epi*. 2008; 29(2):160

# Conclusion: *Staphylococcus aureus* Continues to Evolve

- **Increasing incidence of MRSA**
- **Worsening of MRSA antibiotic resistance**
- **Alternative therapies have limitations**

**We need new effective antibiotics for our patients with cSSSI due to MRSA**

# Telavancin: Nonclinical and Clinical Program in cSSSI

**Steven Barriere, PharmD**

**Vice President, Clinical and Medical Affairs**
**Theravance, Inc.**

# Telavancin: Microbiologic Profile

- **Dual mechanism of action**
  - **Inhibits cell wall synthesis**
  - **Disrupts bacterial membrane function**
- **Broad Gram-positive spectrum**
- **Active against VISA, daptomycin-NS, and linezolid-NS organisms**
- **Potent bactericidal activity**
- **Low potential for emergence of resistance**

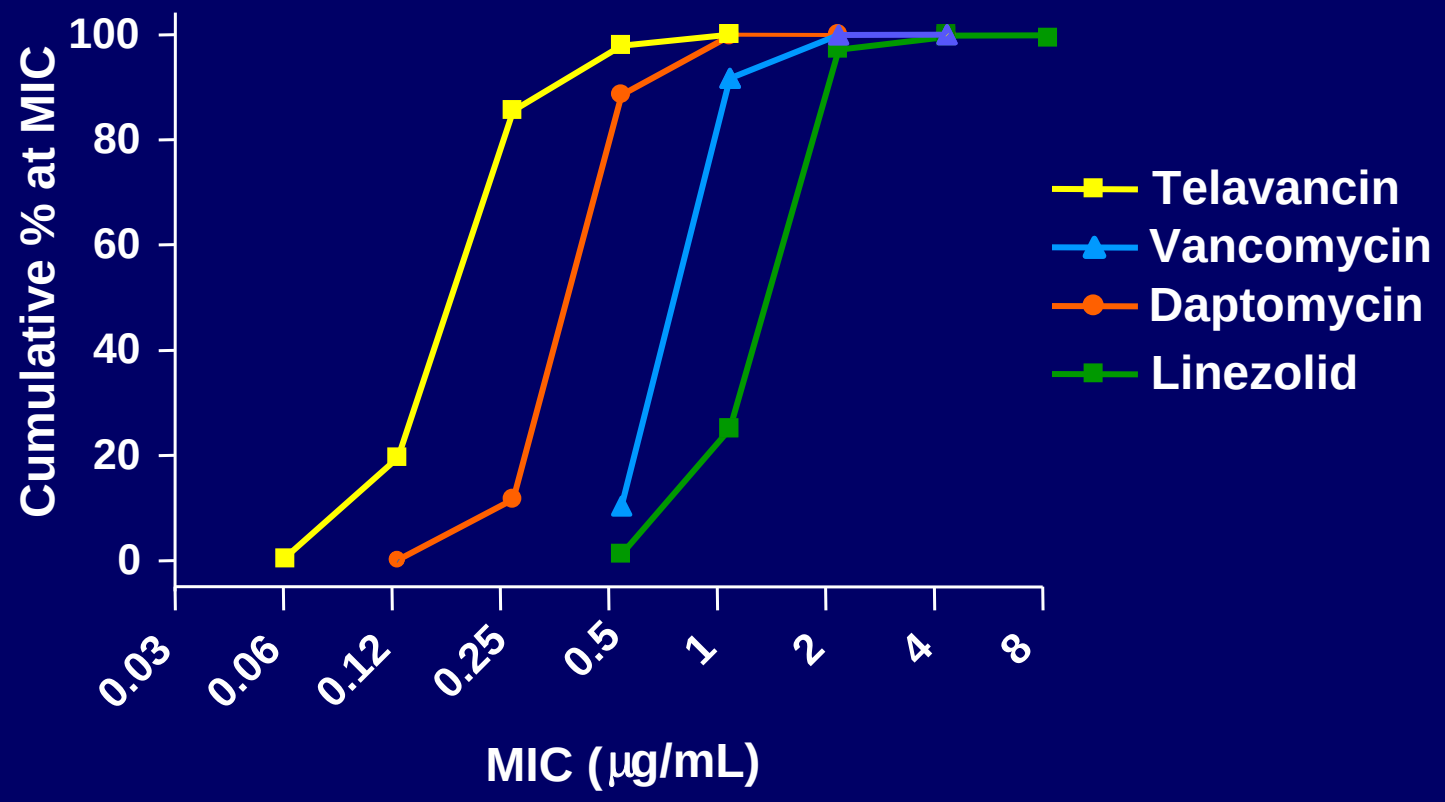
# Spectrum of Gram-positive Activity

| Organism | Telavancin MIC (µg/mL) | | |
|---|---|---|---|
| | No. tested | MIC Range | $MIC_{90}$ |
| *S. aureus* (MSSA) | 3,237 | 0.03 - 0.5 | 0.12 |
| *S. aureus* (MRSA) | 2,658 | 0.03 - 0.5 | 0.25 |
| *S. pyogenes* | 242 | ≤0.015 - 0.25 | 0.06 |
| *S. agalactiae* | 260 | 0.03 - 0.25 | 0.12 |
| *Enterococcus* spp. (VSE) | 1,609 | ≤0.015 - 1 | 0.5 |



Fritsche T. et al ICAAC 2008 #C1-148

# Comparative Activity Against MRSA (N=1629)






Draghi DC et al. *Antimicrob Agents Chemother*. 2008;52:2383-2388
Draghi DC et al. *J Antimicrob Chemother*. 2008;62(1):116-121

# Activity Against cSSSI Pathogens Non-Susceptible to Daptomycin or Linezolid

| Organism | Phenotype | No. Tested | Telavancin MIC Range (µg/mL) |
|---|---|---|---|
| *S. aureus* | DAP-NS | 6 | 0.25 - 0.5 |
| | LIN-NS | 10 | 0.06 - 0.25 |
| *Enterococcus* spp. | DAP-NS | 3 | 0.12 - 0.5 |
| | LIN-NS | 3 | 0.06 - 1 |



Draghi DC et al. *Antimicrob Agents Chemother*. 2008;52:2383-2388
Draghi DC et al. *J Antimicrob Chemother*. 2008;62(1):116-121)

# Activity Against VISA and hVISA

| | MIC (μg/mL) | | | |
|---|---|---|---|---|
| | Range | $MIC_{50}$ | $MIC_{90}$ | Susceptible (%) |
| **Telavancin** | **0.12 - 1** | **0.5** | **1** | **100†** |
| **Vancomycin** | **2 - 8** | **4** | **8** | **13** |
| **Daptomycin** | **0.25 - >1** | **1** | **>1** | **72** |

**N=71**
**Vancomycin S ≤2; NS ≥4**

**Daptomycin S ≤1; NS ≥2**

**†Based upon tentative MIC susceptible breakpoint of ≤1 μg/mL**

Leuthner KD et al. *J Antimicrob Chemother* 2006;58:338-343
Draghi DC et al. *Antimicrob Agents Chemother* 2008;52:2383-2388
Pankuch GA, Appelbaum PC. ICAAC 2008, #C1-191

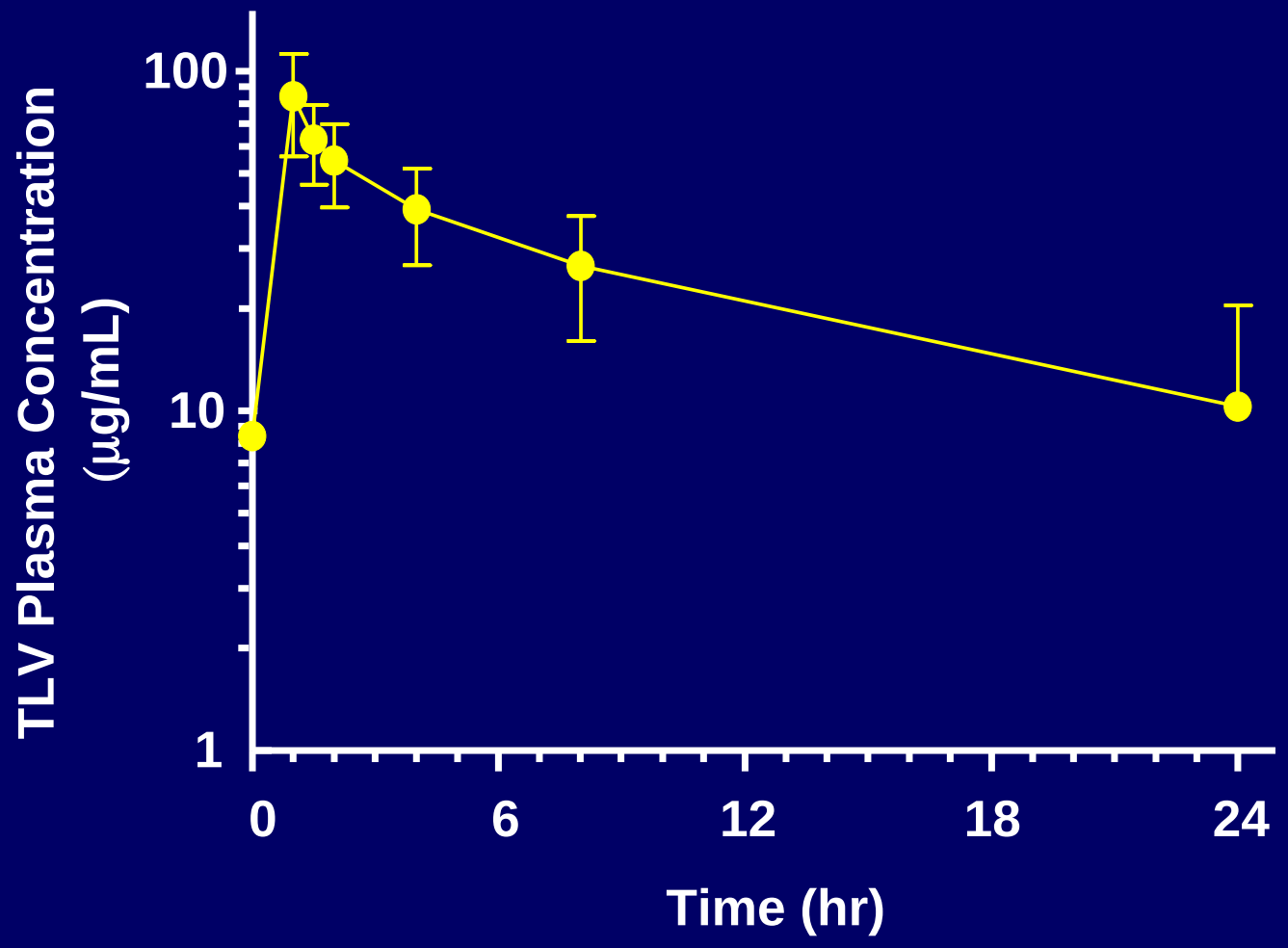
# Animal Models of Infection

| Model | Immuno-compromised | Organisms Studied | Reference |
|---|---|---|---|
| Mouse Thigh | ✓ | MRSA, MSSA, MSSE, MRSE, PSSP, PRSP | AAC Aug 2004 |
| Mouse Subcutaneous Abscess | | MRSA | AAC Aug 2004 |
| Mouse Pneumonia | ✓ | MRSA, MSSA | AAC Oct 2005, JAC Jan 2008 |
| Mouse Bacteremia | ✓ | MRSA, VISA, hVISA | JAC May 2006, ECCMID 2008 ICAAC 2008 |
| Rabbit Endocarditis | | MRSA, VISA | AAC Aug 2005, AAC Jul 2007 |
| Rabbit Meningitis | | MSSA, PRSP | AAC Feb 2006 |
| Rabbit Osteomyelitis | | MRSA | JAC in press |
| Rabbit Indwelling Device | | MRSA | ICAAC 2008 |

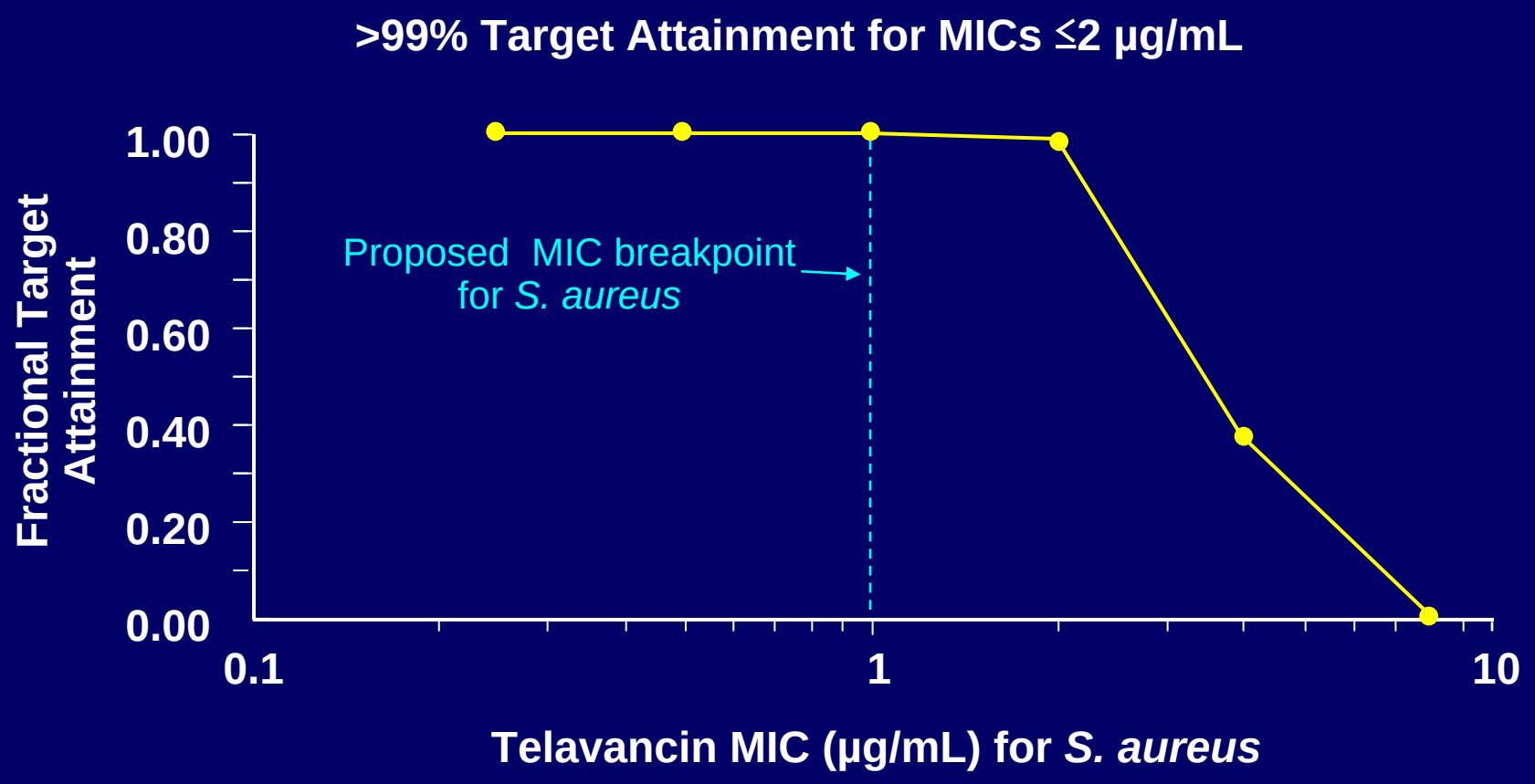
# Resistance Studies

- **Resistance to telavancin has not been identified in target organisms**
  - **In vitro: single-step & serial passage selection studies failed to detect resistance among 16 strains**
  - **Clinical: no resistance during Phase 2 and 3 cSSSI studies or Phase 3 HAP studies**

# Telavancin 10 mg/kg Steady State Concentrations



# Clinical Dose Selection: AUC/MIC Target Attainment Analysis






Hegde SS et al. *Antimicrob Agents Chemother.* 2004;48:3043-3050
Drusano G. et al. Data on file

# Telavancin Clinical Development Program

# cSSSI and HAP Patient Populations

| | TLV | VAN |
|---|---|---|
| **cSSSI Studies 0017 and 0018**<br>**Moderate-Severe Renal Impairment: 12%**<br>**Age ≥65 yr: 19%** | **884** | **910** |
| **HAP Studies 0015 and 0019**<br>**Moderate-Severe Renal Impairment: 34%**<br>**Age ≥65 yr: 54%** | **749** | **754** |
| TOTAL | 1633 | 1664 |

# cSSSI Studies

- Two identical double-blind studies
  - Enrollment 2005–2006
  - 126 sites in 21 countries
- TLV 10 mg/kg IV q 24 h vs VAN 1g q 12 h
- Treatment duration: 7 to 14 days
- Exclusion criteria
  - >24 hr of potentially effective antibiotics
  - Self-limited infections and infections with high surgical incision cure rate
  - Infection with VAN-NS organisms

# Efficacy Analysis Populations

cSSSI Studies 0017 and 0018

| | TLV N (%) | VAN N (%) | Total |
|---|---|---|---|
| **All-treated (AT)** | **884 (100)** | **910 (100)** | 1794 |
| **Clinically Evaluable (CE)** | **714 (81)†** | **720 (79)†** | 1434 |

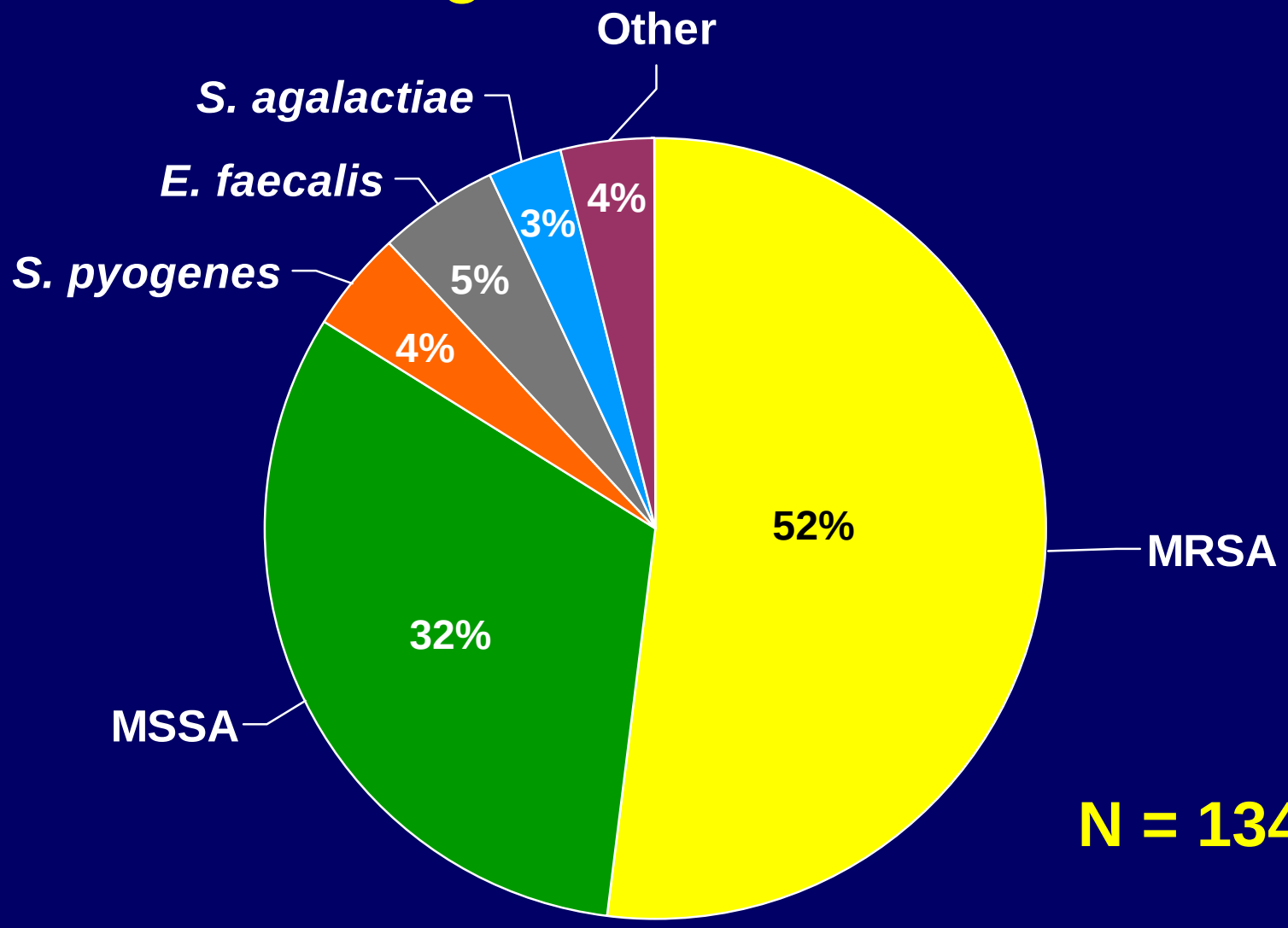
† Percent of AT

# Baseline Characteristics

cSSSI Studies 0017 and 0018

- **Treatment groups well-matched**
  - **Patients with severe renal impairment: TLV = 38; VAN = 28**
  - **Bacteremic: TLV = 31; VAN = 18**
- **Infection involved ~ 20% BSA**
- **Obesity, diabetes, peripheral vascular disease**
- **70% hospitalized at baseline**
- **25% failed prior therapy**

# Baseline Pathogens

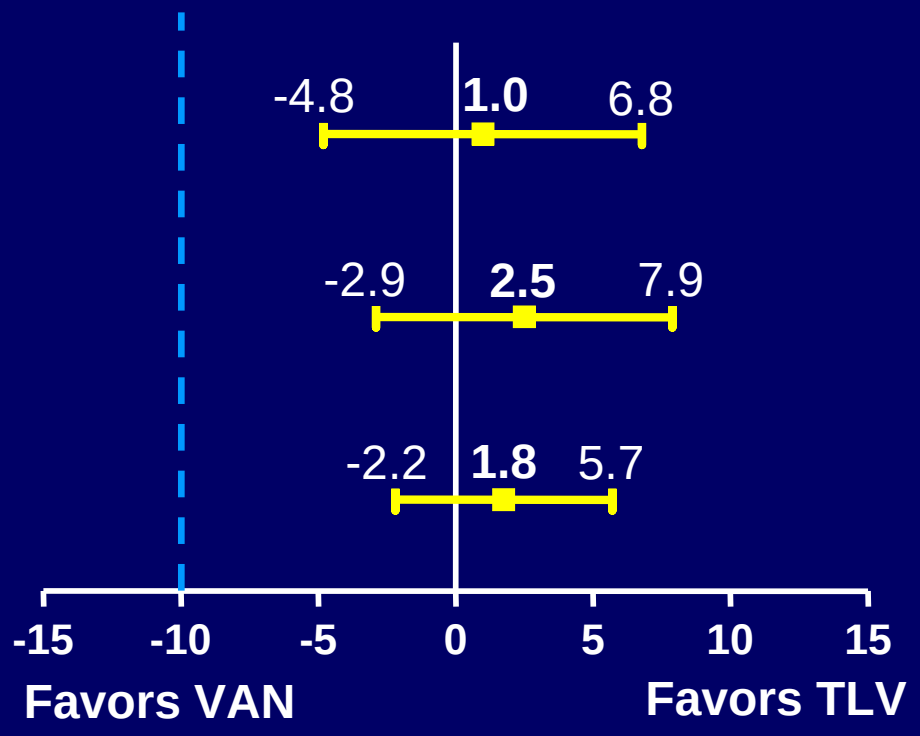



**N = 1340**

**cSSSI Studies 0017 and 0018 – Modified All-Treated (MAT) Population**

# Clinical Response at Test of Cure

## cSSSI AT Population

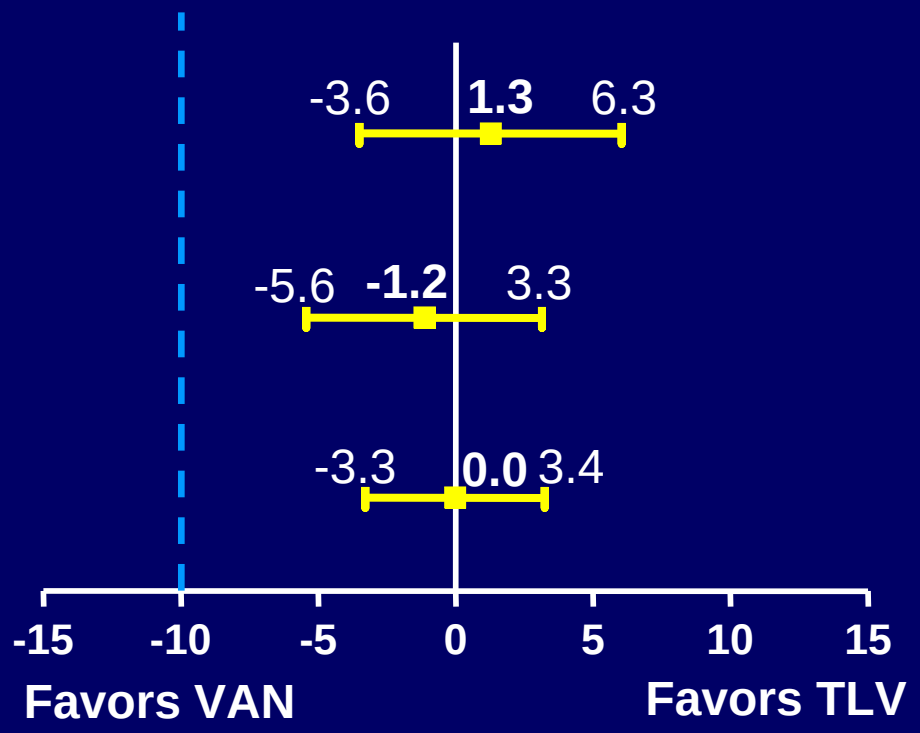



**Difference in Cure Rates**
**(TLV - VAN, %) with 95% Confidence Interval**

| | TLV % Cure (N) | VAN % Cure (N) |
|---|---|---|
| Study 0017 (N = 855) | 75.8 (426) | 74.8 (429) |
| Study 0018 (N = 939) | 78.2 (458) | 75.7 (481) |
| Study 0017 + 0018 (N = 1794) | 77.0 (884) | 75.3 (910) |

# Clinical Response at Test of Cure

## cSSSI CE Population

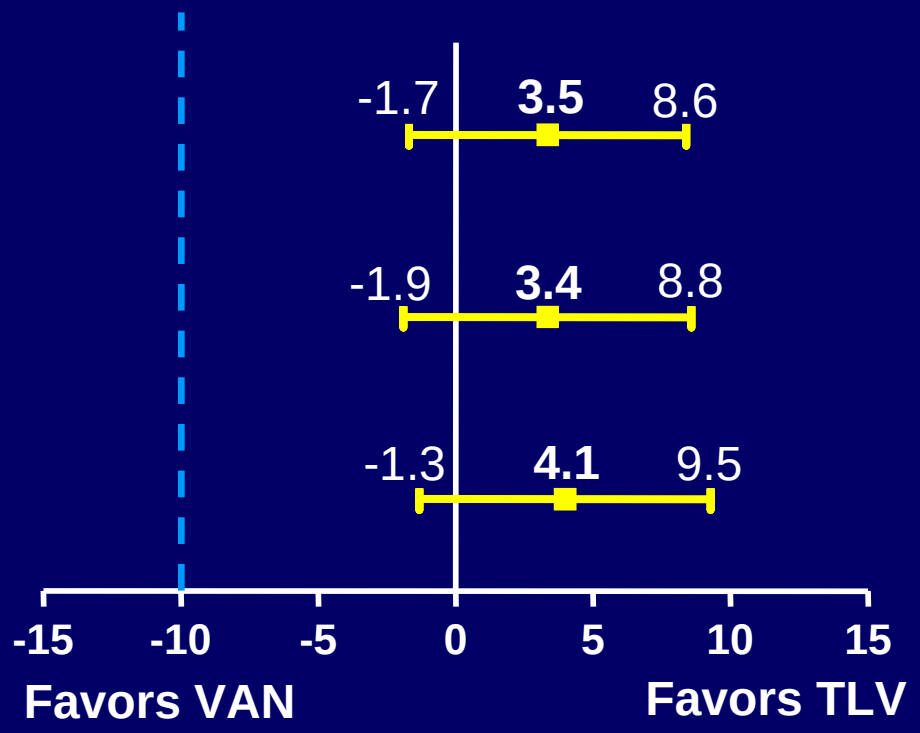



**Difference in Cure Rates**
**(TLV - VAN, %) with 95% Confidence Interval**

| | TLV % Cure (N) | VAN % Cure (N) |
|---|---|---|
| Study 0017 (N = 695) | 87.9 (346) | 86.5 (349) |
| Study 0018 (N = 739) | 88.9 (368) | 90.1 (371) |
| Study 0017 + 0018 (N = 1434) | 88.4 (714) | 88.3 (720) |

# Response in MRSA-infected Patients

## cSSSI Studies 0017 and 0018 – CE Population



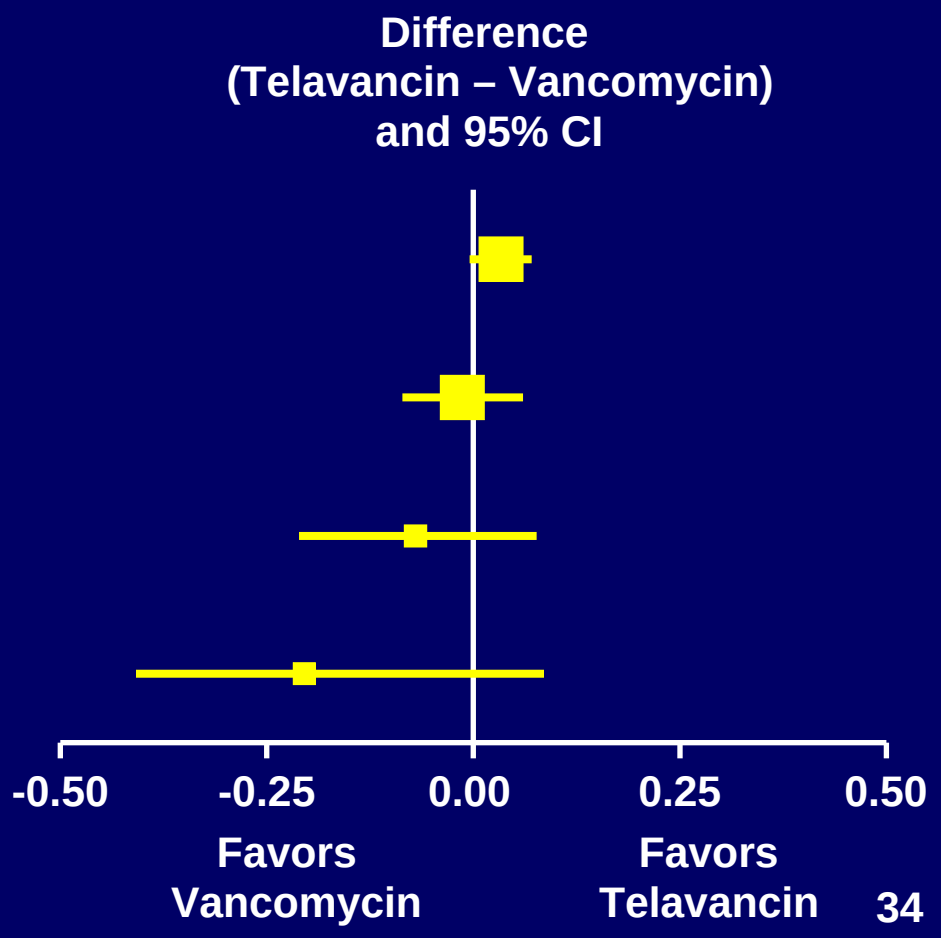

**Difference in Cure Rates**
**(TLV - VAN, %) with 95% Confidence Interval**

| | TLV % Cure (N) | VAN % Cure (N) |
|---|---|---|
| Clinical Cure (N = 563) | 90.7 (269) | 87.1 (294) |
| Microbiological Eradication (N = 563) | 90.0 (269) | 86.4 (294) |
| Overall Response (N = 563) | 90.0 (269) | 85.7 (294) |

# Clinical Response By Baseline Creatinine Clearance

## cSSSI Studies 0017 and 0018 – CE Population

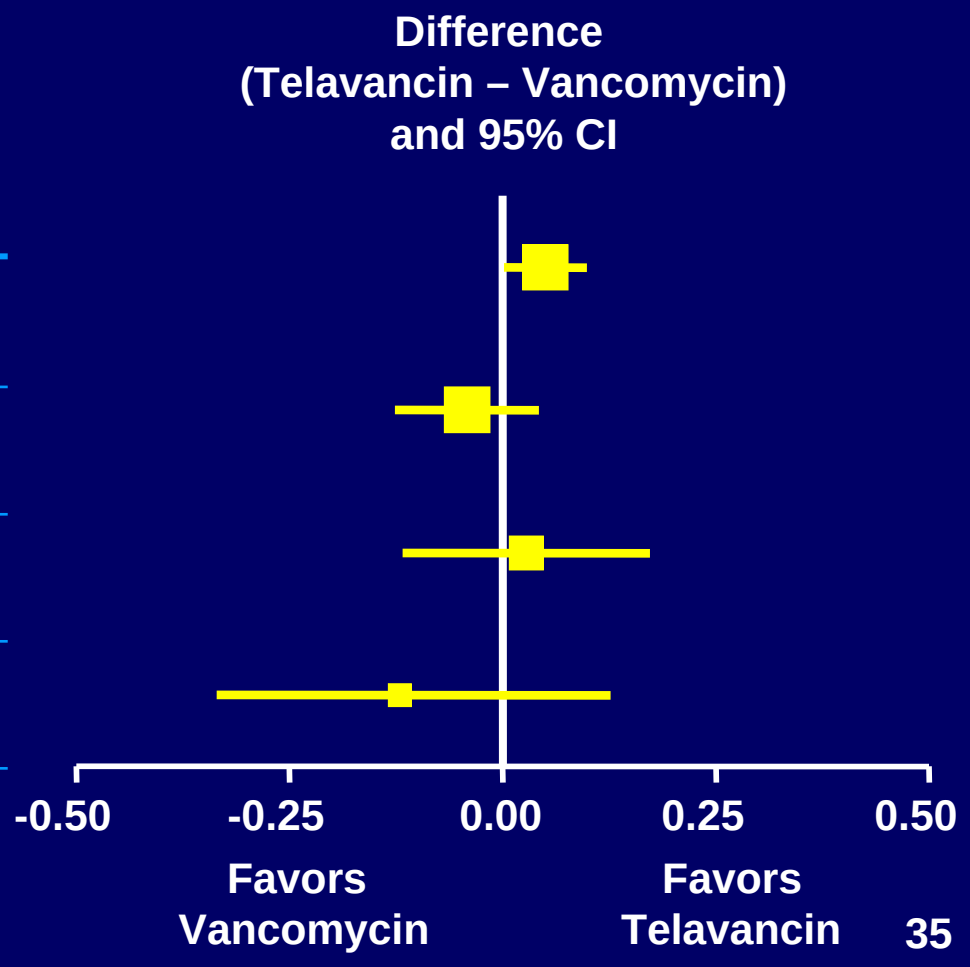
| Baseline Creatinine Clearance (ml/min) | % Cure (Cures/Total) | |
|---|---|---|
| | TLV | VAN |
| >80 | 92.6 (415/448) | 89.2 (406/455) |
| >50-80 | 86.6 (136/157) | 88.0 (146/166) |
| 30-50 | 75.8 (47/62) | 83.3 (55/66) |
| <30 | 69.2 (18/26) | 89.5 (17/19) |



# Clinical Response By Baseline Creatinine Clearance

## cSSSI Studies 0017 and 0018 – AT Population

| Baseline Creatinine Clearance (mL/min) | % Cure (Cures/Total) | |
|---|---|---|
| | TLV | VAN |
| >80 | 80.5 (445/553) | 75.4 (435/577) |
| >50-80 | 73.6 (145/197) | 77.8 (158/203) |
| 30-50 | 74.0 (54/73) | 71.3 (57/80) |
| <30 | 55.3 (21/38) | 67.9 (19/28) |



# Patients with Moderate-Severe Renal Impairment are More Seriously Ill

- **Compared with normal/mild impairment group:**
  - **Older, diabetic, LE infections (cellulitis/ulcers), larger lesion sizes, more comorbidites (e.g. CHF)**
- **Multivariate logistic regression reveals these factors at least as important as treatment by CrCL interaction**
- **More patients on TLV discontinued due to unrelated AE**

# Conclusions: Renal Subgroup Analyses

- **From examination of baseline characteristics and multivariate regression analysis, no firm conclusions could be drawn**
- **Treatment outcome is related to multiple patient and disease characteristics**
- **Include renal subgroup data in product label to inform prescribers**

# Telavancin cSSSI Efficacy Conclusions

- **Efficacy endpoints demonstrated non-inferiority**
  - **Cure rates were lower in patients with severe renal impairment**
- **Telavancin is effective for the treatment of cSSSI due to susceptible Gram-positive bacteria, including MRSA**

# Safety Results

# Safety Populations – cSSSI and HAP

| | TLV | VAN |
|---|---|---|
| **cSSSI Studies 0017, 0018, and 202b**<br>**Moderate-Severe Renal Impairment: 11%**<br>**Age ≥65 yr: 18%** | **1029** | **1033** |
| **HAP Studies 0015 and 0019**<br>**Moderate-Severe Renal Impairment: 34%**<br>**Age ≥65 yr: 54%** | **751** | **752** |
| TOTAL | 1780 | 1785 |

# Overview of Safety

## cSSSI Studies 0017, 0018, and 202b

| | TLV 10mg/kg N = 1029 % | VAN N = 1033 % |
|---|---|---|
| AEs | 77 | 71 |
| DC due to AEs | 8 | 5 |
| SAEs | 7 | 4 |
| DC due to SAEs | 2 | 1 |
| Deaths† | < 1 (n=9) | < 1 (n=9) |

† In-window deaths; includes one patient treated with 7.5 mg/kg telavancin

Seven additional deaths reported spontaneously after final study visit

# Common Adverse Events (≥10%)

cSSSI Studies 0017, 0018, and 202b

| | TLV 10mg/kg N = 1029 % | VAN N = 1033 % |
|---|---|---|
| Altered taste | 32 | 6 |
| Nausea | 26 | 14 |
| Headache | 13 | 12 |
| Vomiting | 13 | 7 |
| Foamy urine | 12 | 3 |
| Insomnia | 10 | 9 |
| Constipation | 10 | 7 |
| Pruritus | 6 | 12 |
| Infusion-related events | 11 | 20 |

# Effect on ECG:
# QT Prolongation

# Mean and Maximum Day 3 QTcF Change from Baseline

Study 104 – Thorough QT Study

| Drug / Dose | Mean ΔΔQTcF (Upper 90% CI) msec | Max ΔΔQTcF (Upper 90% CI) msec |
|---|---|---|
| TLV 7.5 mg/kg | 4.1 (7) | 11.6 (16) |
| TLV 15 mg/kg | 4.6 (8) | 15.1 (20) |
| Moxifloxacin 400 mg | 9.5 (13) | 21.6 (26) |

Fridericia corrected
Upper CI from a two-sided 90% CI on difference from placebo (msec)

# QTcF Data

## cSSSI Studies 0017, 0018, and 202b

| | TLV 10mg/kg N = 1004 | VAN N = 992 |
|---|---|---|
| Mean Average Change (msec) | 9.6 | 2.7 |
| Mean Max Change (msec) | 16.2 | 8.4 |
| Max Change from Baseline >60 msec (N) | 14 | 5 |
| Max >500 msec (N) | 1 | 2 |
| Both >60 msec Change & Max >500 msec (N) | 0 | 1 |

# Cardiac Event Summary

cSSSI Studies 0017, 0018, and 202b

| | TLV 10 mg/kg N = 1029 | VAN N = 1033 |
|---|---|---|
| Any Cardiac AE | 50 | 37 |
| Cardiac SAE | 11 | 11 |
| Non-fatal Cardiac SAE Leading to DC | 0 | 2 |
| Cardiac SAE with Death | 4 | 6 |

# Cardiac Safety Conclusions

- Phase 1 QT Study
  - QTcF changes with TLV were numerically less than moxifloxacin
- cSSSI Studies
  - QTcF outliers similar in TLV and VAN
  - Incidences of cardiac SAEs were similar for TLV and VAN
  - No difference in cardiac death or total mortality between treatment groups
- Low arrhythmic risk

# Renal Impairment

# Renal Events

cSSSI Studies 0017, 0018, and 202b

| | TLV N = 1029 N (%) | VAN N = 1033 N (%) |
|---|---|---|
| **Renal AEs** | **35 (3.4)** | **12 (1.2)** |
| **Renal SAEs** | **12 (1.2)** | **4 (0.4)** |
| **DC due to renal AEs** | **14 (1.4)** | **3 (0.3)** |
| **Deaths associated with renal event†** | **1 (<0.1)** | **1 (<0.1)** |

† In-window death

Renal AEs = acute renal failure, chronic renal failure, renal impairment, renal insufficiency, and increased blood creatinine.

# Renal AEs and Comorbidities

| cSSSI Studies | TLV n/N (%) | VAN n/N (%) |
|---|---|---|
| Renal AEs | 35/1029 (3.4) | 12/1033 (1.2) |
| No baseline comorbidities | 2/518 (0.4) | 3/532 (0.6) |
| Baseline comorbidities | 33/511 (6.5) | 9/501 (1.8) |

| HAP Studies | | |
|---|---|---|
| Renal AEs | 74/751 (10) | 57/752 (8) |
| No baseline comorbidities | 2/141 (1) | 5/142 (4) |
| Baseline comorbidities | 72/610 (12) | 52/610 (9) |

Comorbidities include but not limited to heart failure, hypotension, sepsis diabetes, hypertension.

# Follow-Up of FDA-Identified Unresolved Serious Renal Adverse Events

| Pt ID | Serum Creatinine (mg/dL) | | | Follow-up Obtained Post-study | Final Investigator Assessment |
|---|---|---|---|---|---|
| | Baseline | Peak | Last | | |
| 2099 | 0.9 | 6.0 | 2.0 → 1.5 | Day 26 | Complete Recovery |
| 2498 | 0.7 | 2.7 | 1.5 → 1.2 | Day 30 | Complete Recovery |
| 2007 | 0.7 | 3.4 | 1.9 | None | Improving |

# Changes in Creatinine

cSSSI Studies 0017 and 0018

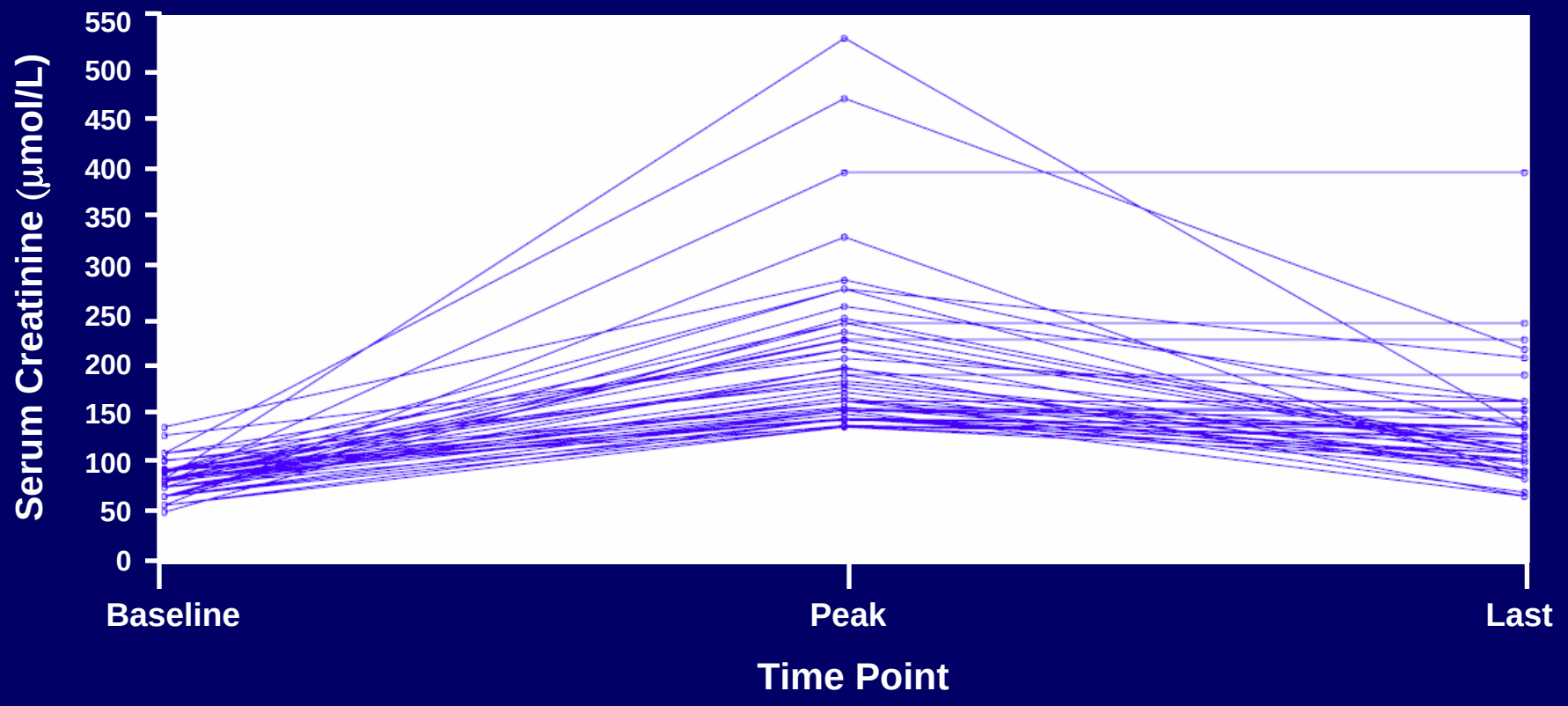
| | TLV | VAN |
|---|---|---|
| | n/N (%) | |
| Cr ≥1.5 mg/dL & ≥ 50% above baseline | 48/822 (6) | 17/856 (2) |

| Highest Serum Creatinine (mg/dL) | TLV | VAN |
|---|---|---|
| | N=48 | N=17 |
| | n (%) | |
| 1.5 to <2.0 | 24 (50) | 13 (76) |
| 2.0 to <3.0 | 17 (35) | 2 (12) |
| ≥3.0 | 7 (15) | 2 (12) |

Patients with normal baseline value

# Baseline to Peak to Last Serum Creatinine Results in Telavancin Patients with PCS Increase in Serum Creatinine from Normal Baseline

cSSSI Studies 0017 and 0018



# Renal Safety Conclusions

- **Renal adverse events**
  - **More in telavancin group (3.4% vs 1.2%)**
  - **Occur in patients with risk factors**
  - **Improving or recovered in the majority of patients in both treatment groups**
- **Monitoring of serum creatinine is recommended in all patients**
- **Dosage should be adjusted on the basis of estimated creatinine clearance**

# Nonclinical Developmental Studies

**Anthony R. Scialli, MD**

**Clinical Professor, OB-GYN**

**George Washington University**

**Adjunct Professor, OB-GYN & Biochemistry**
**Georgetown University**

**Principal Scientist**
**Tetra Tech Sciences**

# Developmental Toxicology Studies

- **Dosing from implantation through palate closure**
- **Examination near term**
- **Conducted in 2 species**
- **Maternal toxicity at the high dose**

# Nonclinical Developmental Toxicology Expert Panel

- **2 developmental toxicology experts**
  - **Jeanne Manson, PhD**
  - **Anthony Scialli, MD**
- **Independent review**
  - **Interpretation of the results with respect to possible human risk**

# Conclusion of Independent Expert Panel Assessment of Nonclinical Studies

- **Telavancin causes a decrease in fetal weight at 100 and 150 mg/kg/day in rats**
- **There is no teratogenic signal for telavancin**
  - **Limb findings were mechanistically dissimilar, not reproducible in rats, and not attributable to telavancin**

# Rat Developmental Study

| Dose (mg/kg/day) | Litter findings |
|---|---|
| 0 | 1 fetus with anophthalmia, micrognathia, macroglossia, malformed nose<br>1 fetus with anophthalmia and microstomia* |
| 50 | No abnormalities |
| 100 | ↓ fetal weight, 1 fetus with anophthalmia, syndactyly, and "limb shortening" on external exam, normal skeletal exam† |
| 150 | ↓ fetal weight, 1 fetus with "limb shortening" on external exam, no skeletal exam‡ |

* Total of 319 fetuses, 25 litters
† Total of 332 fetuses, 24 litters
‡ Total of 322 fetuses, 25 litters
Exposure at 100 mg/kg/day approximately 1.6 x Clinical Exposure

# Pre- and Post-Natal Developmental Study in Rats

- Doses of 50, 100 or 150 mg/kg/day on gestation days 6 through lactation day (LD) 21
- No limb defects in F1 generation pups
- "…pup with transient (LD 6 and 7) limited use of a forelimb…"

| Dose (mg/kg/day) | LD4 (post cull) | LD6 | LD7 | LD14 | LD21 |
|---|---|---|---|---|---|
| 0 (D5W) | 0/176 | 0/176 | 0/176 | 0/176 | 0/175 |
| 0 (placebo) | 0/167 | 0/166 | 0/166 | 0/166 | 0/166 |
| 50 | 0/192 | 0/192 | 0/192 | 0/184 | 0/184 |
| 100 | 0/192 | 0/192 | 0/192 | 0/192 | 0/192 |
| 150 | 0/177 | 1/176 | 1/176 | 0/176 | 0/175 |

# Vancomycin Developmental Toxicity

- **Studied in rats at 0, 40, 120, 200 mg/kg/day**
  - **2 fetuses with small/absent eyes at 120 mg/kg/day**
  - **1 fetus with cleft lip, microphthalmia, misshapen heart, small lungs, and small kidney at 200 mg/kg/day**
- **Studies in rabbits at 0, 40, 80, 120 mg/kg/day**
  - **1 fetus with filamentous tail, skeletal anomalies, and fused kidneys at 80 mg/kg/day**
  - **Decreased fetal weight at 120 mg/kg/day**
- **Exposures at high doses equivalent to human exposure at clinical dose**
- **Vancomycin is not considered teratogenic**



Fundamental and Applied Toxicology 23, 590-597 (1994).

# Other Antimicrobials with Developmental Effects in Experimental Animals[1]

| Antimicrobial Agent | Abnormalities |
|---|---|
| → Zyvox® (linezolid) | Embryo & pup death |
| → Avelox® (moxifloxacin) | Rib, vertebral |
| Septra® (trimethoprim, sulfamethoxazole) | Cleft palate |
| Cipro® (ciprofloxacin) | Abortion |
| → Levaquin® (levofloxacin) | Fetal mortality, ↓weight |
| Pediazole® (erythromycin, sulfisoxazole) | Cleft palate |
| Prevpac® (lansoprazole, amoxicillin, clarithromycin) | Cleft palate, cardiovascular |
| Coly-Mycin® (colistimethate) | Talipes |
| Biaxin® (clarithromycin) | Cleft palate, cardiovascular |
| Factive® (gemifloxacin) | Brain, ocular |
| Priftin® (rifapentine) | Multiple malformations |
| Rifater® (rifampin, isoniazid, pyrazinamide) | Spina bifida, cleft palate |
| → Floxin® I.V. (ofloxacin) | Fetal mortality, ↓weight |
| Noroxin® (norfloxacin) | Embryo loss |
| → Primaxin® (imipenem, cilastatin) | Embryo loss |



[1] Based on Product Package Insert; All are Pregnancy Category C

# Complicated Skin and Skin Structure Infections in Pregnant Women

- **Infected diabetic skin ulcers**
- **Immunocompromised women**
- **Bartholin abscess with cellulitis**
- **Enterocutaneous fistulas**

Untreated or inadequately treated infection can pose risk to the pregnant woman and to the fetus

# Overall Conclusions

- **The developmental toxicology profile of telavancin is similar to that of commonly used drugs like vancomycin**
- **The decision to use telavancin therapy is appropriately left to the patient and her clinician**
- **Use in pregnancy will be addressed in a Risk Management Plan**

# Risk Management Plan

**Rebecca Coleman, PharmD**

**Vice President, Regulatory Affairs and Quality**
**Theravance, Inc.**

# Goals

- **Minimize risk of nephrotoxicity**
- **Minimize risk related to QT prolongation**
- **Minimize exposure of pregnant women to the potential risk of adverse effects on fetal development**

# Tools

- **Label**
- **Education plan**
- **Initiation in a controlled healthcare setting**
- **Enhanced pharmacovigilance**

# Proposed Precautions: Renal

- Monitor serum creatinine in all patients
- Adjust dose based on estimated CrCL

| CrCL (mL/min) | Recommended Dosage |
|---|---|
| > 50 | 10 mg/kg every 24 hours |
| 30 to 50 | 7.5 mg/kg every 24 hours |
| < 30 | 10 mg/kg every 48 hours |

- Label to include efficacy data by renal subgroup

# Proposed Precautions: QT Prolongation

- **Caution warranted in patients taking drugs known to prolong the QT interval**
- **The following conditions were excluded in clinical studies; use of telavancin should be avoided in patients with these conditions**
  - **Congenital long QT syndrome**
  - **Known prolonged QT interval**
  - **Uncompensated heart failure**
  - **Severe left ventricular hypertrophy**

# Proposed Warnings: Pregnancy

- **Pregnancy Category C**
- **Avoid use during pregnancy unless the benefit to the patient outweighs the potential risks to the fetus**
- **Nonclinical study data in proposed label**
  - **Adverse effects on fetal weight**
  - **Developmental toxicology findings**

# Education Plan

**Educational materials will be distributed to:**

- **Healthcare professionals who**
  - **Prescribe**
  - **Dispense**
  - **Administer**
- **Hospital formulary and pharmacy & therapeutics committees**

# Controlled Distribution

- **Treatment initiation in a controlled healthcare setting**
- **Distribution via wholesalers and distributors to:**
  - **Hospitals**
  - **Inpatient hospital pharmacies**
  - **Home healthcare pharmacies**

# Enhanced Pharmacovigilance

- **Targeted data collection**
  - **Renal events**
  - **Cardiac events associated with QT prolongation**
- **Report every 3 months for the first 2 years**
- **Monitoring of distribution data**
- **Monitoring and registration of pregnancies**

# Assessments

- Study of physician compliance
- Healthcare professional surveys
  - Knowledge
  - Attitudes
  - Behavior

# Telavancin
# Benefit vs Risk

**Louis Saravolatz, MD**

**Professor and Chairman, Department of Medicine**
**St. John Hospital and Medical Center**
**Wayne State University School of Medicine**
**Detroit, MI**

# Increasing Burden of cSSSI due to MRSA

- ~ 70% of *S. aureus* infections are MRSA
- CA-MRSA most common cause of cSSSI
- Treatment of cSSSI is increasingly difficult
  - Significant clinical impact
  - Treatment failure
  - Re-infection
  - MRSA is continually evolving
- Available agents limited by emerging resistance, toxicity

**We need new effective antibiotics for our patients with cSSSI due to MRSA**

# Individualization of Care

- Assess each patient
- Determine severity of infection
  - Surgical vs nonsurgical
  - IV antibiotics vs oral
- Cover likely pathogens
  - Patient history
  - Local epidemiology
- Choose appropriate therapy and dose
- Monitor for efficacy and safety

# Telavancin – Beneficial Features

- **Dual mechanism of action**
- **Bactericidal**
- **Activity against resistant strains**
- **Low potential for development of resistance**
- **Penetration into sites of infection**
- **Once daily dosing**

# Telavancin – Demonstrated Benefits

- **Telavancin is effective in the treatment of cSSSI**
  - **Statistically non-inferior to VAN**
  - **Efficacy in largest MRSA cohort**
- **No emergence of resistance seen to date in clinical trials**
- **Fewer infusion reactions than VAN**

# Telavancin – Potential Benefits

- **Effective in treatment of cSSSI caused by strains with reduced susceptibility or resistance**
  - **VISA, hVISA strains susceptible to TLV**
  - **DAP-, LZD-NS strains susceptible to TLV**
- **Reduced rate of treatment failure**
- **Reduced days of hospitalization and IV antibiotics**

# Telavancin – Demonstrated Risks

- **Renal events**
  - **More than VAN**
    - **Similar rates in patients without comorbidities**
  - **Detectable, manageable, reversible**
- **QT prolongation**
  - **Less than moxifloxacin**
  - **Incidence of cardiac serious adverse events and deaths similar for TLV and VAN**

# Telavancin – Potential Risks

- **Effects on animal fetus**
  - **Reduced litter weight in animals**
- **No human pregnancy data**
- **Avoid use during pregnancy unless the benefit to the patient outweighs the potential risks to the fetus**

# Conclusion

- **Burden of MRSA cSSSI is increasing**
- **Clinicians need alternative therapies for cSSSI**
- **Telavancin has positive Benefit:Risk profile**
  - **Effective against resistant strains**
  - **Safety well-characterized and manageable**

# Consultants

| | |
|---|---|
| **G. Ralph Corey, MD** | ***Duke University*** |
| **Anthony Scialli, MD** | ***Georgetown U. & Tetra Tech Sciences*** |
| **Louis Saravolatz, MD** | ***St. John Hospital, Detroit*** |

---

| | |
|---|---|
| **Craig Pratt, MD** | ***Cardiology, Texas Methodist Hospital*** |
| **Julia Lewis, MD** | ***Nephrology, Vanderbilt University*** |
| **Gary Koch, PhD** | ***Biostatistics, University of N. Carolina*** |
| **Richard Sweet, MD** | ***OB-Gyn, University of California Davis*** |