Anti-Infective Drugs Advisory Committee Meeting

November 29, 2012

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Deputy Division Director, DAIP

Meeting Objectives

- Discuss NDA 22-407: Telavancin for injection (VIBATIV®)
  - Applicant: Theravance, Inc.
  - Formulation: 250 or 750 mg vials for reconstitution
  - Dose: 10 mg/kg by intravenous infusion once every 24 hours
  - Proposed Indication: Treatment of patients with nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP), caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates) or *Streptococcus pneumoniae* (penicillin susceptible strains).

Telavancin for NP NDA Package: Two Phase 3 Trials- 0015 and 0019

- Randomized, double-blind, active-controlled, parallel-group, multicenter, multinational trials of identical design
- Objective to establish the noninferiority (NI) of telavancin to vancomycin for a clinical response endpoint at the test-of-cure (TOC) visit
- Prespecified NI margin of 20% for clinical response
  - Mortality collected as a safety outcome
- Together, 0015 and 0019 enrolled 1503 adult subjects with NP

Regulatory History: Telavancin (TLV) for NP Juxtaposed with Evolution of Drug Development for NP

- Telavancin approved for treatment of adult patients with complicated skin and skin structure infections on September 11, 2009
- Also under development for nosocomial pneumonia caused by Gram-positive bacteria
- 1998 Guidance for Industry "Nosocomial Pneumonia-Developing Antimicrobial Drugs for Treatment"
  - Recommended a clinical response endpoint (investigator-assessed)
- Pivotal trials for TLV for NP (0015 and 0019) used a noninferiority (NI) design, a clinical response endpoint, and were conducted from 2005-2007

Regulatory History: Telavancin (TLV) for NP Juxtaposed with Evolution of Drug Development for NP

- July 2008-AIDAC meeting for doripenem for NP
  - Historical evidence insufficient to justify clinical response endpoint
  - Data available to justify an all-cause mortality endpoint
- NDA 22-407 submitted January 2009
- FDA co-sponsored a workshop with IDSA, ATS, ACCP in April 2009 to discuss all aspects of clinical trial design for the NP indication
  - Variety of endpoints discussed: clinical response, change in CPIS or other scores, all-cause mortality, PaO_2/FiO_2, among others
  - Difficulty justifying an NI margin for endpoints other than mortality remained

Regulatory History: Telavancin (TLV) for NP Juxtaposed with Evolution of Drug Development for NP

- Complete response issued November 2009 for the following deficiencies:
  - Incomplete mortality data (29-35% of subjects)
  - Concern that subjects did not have disease of interest; need to determine if study subjects met criteria for NP based on ATS/IDSA guidelines of chest x-ray plus two clinical features[1]
- Resubmission June 2010
  - Substantial recovery by applicant of missing mortality data (now $\leq$ 6%)
  - 86% of enrolled study population met ATS/IDSA criteria for diagnosis of NP

[1]Am J Respir Crit Care Med; 2005; 171: 388-416

Regulatory History: Telavancin (TLV) for NP Juxtaposed with Evolution of Drug Development for NP

- November 2010, FDA issues Draft Guidance "Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment":

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf
  - Recommended 28 day all-cause mortality endpoint
  - Two randomized, controlled studies
  - NI margin of 10% for all-cause mortality in microbiological intent-to-treat population (mITT), if using NI trial design
- Complete response issued December 21, 2010 for deficiencies:
  - Study 0015 did not meet 10% NI margin for mortality based on microbiological population with Gram + pathogens (any);
  - Study 0019 did but it was not sufficient to stand on its own as evidence of treatment effect

Regulatory History: Telavancin (TLV) for NP Juxtaposed with Evolution of Drug Development for NP

- Theravance submits Formal Dispute Resolution Request (FDRR) on August 24, 2011 to Dr. Edward Cox, Director, Office of Antimicrobial Products, which was denied
- Appeal of FDRR submitted to Dr. John Jenkins, Director, Office of New Drugs, in October 2011, which was denied
  - Recommended resubmission, AIDAC meeting, careful consideration of all available data
- Quote from Dr. John Jenkins February 2012 response to Theravance's Formal Dispute Resolution Appeal, "The evolution in the Agency's approach to NI trials has been driven by a more complete understanding of the scientific issues that underlie the design, analysis, and interpretation of these trials."

Regulatory History: Telavancin (TLV) for NP Juxtaposed with Evolution of Drug Development for NP

- AIDAC meeting on November 4, 2011 to discuss clinical trial design for HABP/VABP
  - Convened to address comments to docket regarding draft guidance which included concerns about feasibility, low rates of mortality making mortality endpoint not practical, trial population too large
  - AC recommended:
    - 28 day all-cause mortality endpoint for NI trial using a margin of 1.7 for odds ratio metric or a 10% margin for risk difference metric (if active control mortality rate is 20% or more);
    - single HABP or VABP trial using mITT as the primary analysis population with adequate supportive evidence may be acceptable.
- Ongoing dialogue about willingness to accept more uncertainty in estimate of treatment effect (e.g. a larger NI margin) to increase trial feasibility and therefore availability of new drugs (CDER's Antibacterial Task Force, Brookings, Duke's CTTI)
- Theravance resubmits NDA 22-407 on July 12, 2012

Today's Agenda

- Theravance's Presentations
- FDA's Presentations
  - Dr. Benjamin Lorenz: Review of Regulatory History and Safety
  - Dr. Scott Komo: Efficacy Findings from Trials 0015 and 0019
- Open Public Hearing
- Questions for the Committee

Questions for the Committee

1. Considering the totality of data presented, including the analyses of clinical cure and 28-day all-cause mortality:

   Do the results provide substantial evidence of the safety and efficacy of telavancin for the treatment of nosocomial pneumonia? VOTE

   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed.

Questions for the Committee

2. Considering the totality of data presented, including the analyses of clinical cure and 28-day all-cause mortality:

   Do the results provide substantial evidence of the safety and efficacy of telavancin for the treatment of nosocomial pneumonia when other alternatives are not suitable? VOTE

   - If yes, please provide any recommendations concerning labeling.
   - If no, what additional studies/analyses are needed.

Questions for the Committee

3. The nephrotoxicity of telavancin has been established based on experience with the treatment of complicated skin and skin structure infections. For the treatment of nosocomial pneumonia, are there any additional comments or further recommendations, particularly concerning the use in patients with baseline renal dysfunction?

   If so, what are these recommendations?

Presentation of Regulatory History and Safety: Telavancin for Nosocomial Pneumonia

Meeting of the Anti-Infective Drugs Advisory Committee

Benjamin Lorenz, M.D.
Medical Reviewer
Division of Anti-Infective Products
OAP/OND/CDER/FDA

Outline

- Regulatory History
- Microbiology
- Non-clinical Toxicology
- Trial Design
- Clinical Safety
- Nephrotoxicity

Regulatory History

- Telavancin initially approved in 2009 for cSSSI caused by Gram+ organisms
- Decreased efficacy with moderate/severe baseline renal impairment (CrCL <50mL/min)
- PMC: effect of renal function on the biological activity of telavancin?

Nosocomial Pneumonia: First Cycle

- November 2007: final SAP submitted for two Phase 3 clinical ATTAIN trials for NP (Studies 0015 and 0019), with clinical response efficacy endpoint (20% NIM) submitted to the FDA
- July 2008: FDA presented a justification for a NIM using 28-day all-cause mortality, but there was insufficient evidence to justify a margin for clinical cure
- January 2009: NDA 22-407 submitted to FDA

Complete Response

1) Obtain all mortality data
2) Provide a rationale for pooling across two clinical trials, given difference certain baseline prognostic factors for mortality
3) Determine if patients enrolled in the trials met ATS/IDSA criteria for NP (CXR+2F)

Second Cycle

- June 2010: incorporated missing mortality data
  - Primary analysis: As-Treated (AT)
  - Supportive: CXR+2F
  - Micro: Modified (MAT), any Gram+, only Gram+
- December 2010 CR: Study 0015 failed to demonstrate noninferiority (10% NIM) with 28-day all-cause mortality

Formal Dispute Resolution

- Applicant: Studies 0015 and 0019 met the statutory standard for approval based on the prespecified endpoint, clinical cure
- After meeting with OND, OAP, and the Division, the Applicant agreed to proceed with a resubmission, public discussion with AIDAC
- July 2012: amendment to NDA submitted with new analyses for AC discussion

Microbiology

- NP trials: 647 isolates of *S. aureus* collected, 315 described as MRSA
- *S. aureus* isolates: MIC_{90} = 0.5 mcg/mL
- Highest MIC noted: 1.0 mcg/mL
- Microbiological eradication (baseline pathogen absent in the last post-baseline culture) in the single Gram+ only population: TLV 136/164 (82.9%), VAN 125/165 (75.8%)

Non-clinical Renal Toxicity

- Studies conducted:
  - Rats: up to 6 months, maximum dose 100 mg/kg/day
  - Dogs: up to 3 months, maximum dose 100 mg/kg/day
- All studies included a hydroxy-beta-cyclodextran (HBCD) only group.
- All studies, including single-dose, had renal findings.
- Renal findings with the HBCD tended to be more frequent/severe with the highest dose tested of telavancin.

Observations

- BUN/creatinine was increased in both HBCD and HD animals.
- Urine volume, incidence of granulomatous casts, occult blood were increased in treated animals.
- Kidney weights were increased in rats at the HD.
- Renal epithelial cell vacuolization, dilatation, and interstitial inflammatory cell infiltrates were seen in HBCD, telavancin rats.
- Renal tubular degeneration was observed at HD.

ATTAIN Trials: Study Design

- Studies 0015 & 0019: active-controlled, randomized, double-blind, NI trials
- Primary efficacy endpoint: clinical response, determined by the investigator, at the test of cure (TOC) evaluation
- Prospectively intended to be combined to assess the superiority in patients with MRSA infections
- Post-hoc plan for analysis of all-cause mortality in various patient populations (particularly AT, MAT any Gram+, and MAT only Gram+).

ATTAIN Trials: Study Design

- Randomization: 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours.
- Treatment duration: 7 to 21 days
- Empiric Gram-neg coverage: aztreonam and/or metronidazole, but piperacillin/tazobactam was permitted if aztreonam resistance suspected

ATTAIN Trials: Study Design

Major inclusion criteria:

- ✓ 2 clinical symptoms, 2 clinical signs
- ✓ CXR c/w pneumonia
- ✓ Appropriate respiratory specimens

Major exclusion criteria:

- ✓ More than 24hrs of potentially effective systemic antibacterial therapy
- ✓ Respiratory specimens with only Gram-neg
- ✓ Refractory shock, ✓ Severe neutropenia
- ✓ Baseline QTc > 500 msec, congenital long QT syndrome, uncompensated heart failure

Prospectively Defined Analysis Populations

- **All-treated (AT):** All subjects who received any amount of study medication.
- **Modified All-treated (MAT):** Subjects in the AT population who also had a baseline pathogen identified from baseline respiratory cultures known to cause pneumonia.
- **Clinically Evaluable (CE):** Subjects in the AT population who adhered to the protocol
- **Microbiologically Evaluable (ME):** Subjects in the CE Population who also had a Gram-positive baseline respiratory pathogen.

Post-Hoc Analysis Sets

- Patients in the AT population who met ATS/IDSA criteria for pneumonia
- Patients in the MAT population who had *at least one* Gram+ baseline respiratory pathogen (may include mixed infections)
- Patients with *only* Gram+ baseline respiratory pathogens
- Patients who had MRSA identified as *at least one* baseline respiratory pathogen (may include mixed)
- Patients with *only* MRSA identified

ATTAIN Trials: Study Design

- Pre-specified analyses were to test both noninferiority and superiority of telavancin to vancomycin with respect to clinical response at TOC
- AT and CE analysis populations were considered co-primary
- Applying ATS/IDSA criteria results in a population that accounts for 85.8% of enrolled patients (AT)

Baseline Characteristics

- Study 0015 enrolled 761 patients (381 TLV, 380 VAN)
- Study 0019 enrolled 771 patients (386 TLV, 385 VAN)
- Study 0015 was conducted in 22 countries with 31% of patients from the US
- Study 0019 was conducted in 29 countries with 14% of patients from the US

Analysis Populations

	Study 0015		Study 0019	
Population	**TLV** n (%)	**VAN** n (%)	**TLV** n (%)	**VAN** n (%)
AT	372 (100)	374 (100)	377 (100)	380 (100)
AT–ATS/IDSA	309 (83)	316 (84)	325 (86)	339 (89)
CE	141 (38)	172 (46)	171 (45)	170 (45)
MAT w/ ≥1 Gram+	187 (50)	180 (48)	224 (59)	206 (54)
MAT Gram+ only	137 (50)	135 (50%)	130 (51)	125 (49)
≥1 MRSA	115 (31)	114 (30)	118 (31)	117 (31)
Only MRSA	79 (47)	91 (54)	59 (47)	66 (53)

Source: NDA 22-407, 2.7.3, Summary of Clinical Efficacy, v3.0, Table 44
MAT based on both respiratory and blood specimens but predominately respiratory
Sponsor-defined "PP": Patients in the MAT analysis set who had **at least one** Gram-positive baseline respiratory pathogen
Sponsor-defined "MPP": Patients in the MAT analysis set who had **only** Gram-positive baseline pathogens

Baseline Characteristics

	Study 0015 (N=746)		Study 0019 (N=757)		
	n	%	n	%	p-value
History of diabetes	232	31.1%	162	21.4%	<0.0001
Chronic renal failure	67	9.0%	28	3.7%	<0.0001
Baseline CrCL < 50 mL/min	267	35.8%	203	26.8%	0.0002
Diabetic at baseline	200	26.8%	134	17.7%	<0.0001
On hemodialysis at baseline	20	2.7%	8	1.1%	0.0325

Source: FDA Reviewer

Days of Study Medication

- Most patients received 7-10 days of treatment.

	Study 0015		Study 0019	
	TLV	**VAN**	**TLV**	**VAN**
<3 days	23 (6%)	15 (4%)	17 (5%)	17 (4%)
3-6 days	77 (21%)	62 (17%)	52 (14%)	53 (14%)
7-10 days	152 (41%)	172 (46%)	163 (43%)	160 (42%)
11-14 days	79 (21%)	85 (23%)	95 (25%)	97 (26%)
15-21 days	39 (10%)	38 (10%)	48 (13%)	47 (12%)
>21 days	2 (<1%)	2 (<1%)	2 (<1%)	6 (2%)

Source: NDA 22-407, ISE, v1.0, Table 5-20

Clinical Safety

- Compared to patients in cSSSI trials, patients tended to be older, with more comorbid conditions
- Patients at baseline with APACHE II scores ≥20 points: TLV: 22%, VAN: 25%.
- More than half of all patients were in the ICU at baseline

Current USPI (cSSSI)

- Renal toxicity and potential for QTc prolongation were the most significant safety issues identified.
- The mean maximum baseline-corrected, placebo-corrected QTc prolongation at the end of infusion was estimated to be 12-15 msec for TLV 10mg/kg.
- Warnings and Precautions: “Use with caution in patients taking drugs known to prolong the QT interval”.
- Increases in serum Cr to 1.5× baseline occurred more frequently among TLV-treated patients with normal baseline serum Cr (15%) compared with VAN-treated patients (7%).

- *In NP trials: increases in serum Cr to 1.5× baseline also occurred more frequently among TLV-treated patients (16%) compared with VAN-treated patients (10%).

Premature Study Drug Discontinuations

Study 0015:

- TLV: 175/381(45.9%)
- VAN: 150/380 (39.5%)

  Δ = 6.5%*

  95% CI: (-0.5%, 13.5%)

  p-value = 0.07

*This difference was not seen in Study 0019

"Death", "unsatisfactory therapeutic response" and "Gram+ coverage no longer indicated" were the most frequent reasons listed for premature discontinuation.

Premature Study Drug Discontinuations Due to AEs*

Study 0015:

- TLV: 6%
- VAN: 3%

  odds ratio = 2.0

  exact 95% CI: (0.9, 4.8)

  Fisher's exact p-value = 0.07

- This difference was not seen in Study 0019

*Determined to be related by Investigator

TEAE and Discontinuation of Study Medication

	Study 0015		Study 0019	
	TLV	VAN	TLV	VAN
	N =372	N=374	N=379	N=378
n (%)	33 (8.9%)	17 (4.5%)	27 (7.1%)	23 (6.1%)
95% CI (TLV-VAN)	(0.75, 7.90)*		(-2.50, 4.58)	
SOC: Renal and Urinary Disorders				
	8	3	3	3

*Statistically significant, Source: FDA Reviewer

All Renal-related TEAEs

- Acute renal failure was the most frequently reported renal-related TEAE in Study 0015 and Study 0019.

AE Preferred term	Study 0015		Study 0019	
	TLV N=372	VAN N=374	TLV N=379	VAN N=378
Blood creat increased	11 (2.96%)	6 (1.60%)	7 (1.85%)	6 (1.59%)
Renal failure acute	18 (4.84%)	10 (2.67%)	16 (4.22%)	18 (4.76%)

Source: FDA Reviewer

Serious Renal TEAE's

AE Preferred Term	Study 0015		Study 0019	
	TLV N=372	VAN N=374	TLV N=379	VAN N=378
	n (%)	n (%)	n (%)	n (%)
Blood creatinine incr	3 (0.8%)	0 (0%)	0 (0%)	0 (0%)
Renal failure acute	11 (3.0%)	3 (0.8%)	7 (1.8%)	8 (2.1%)
Renal failure chronic	0 (0%)	0 (0%)	1 (0.3%)	0 (0%)
Renal impairment	0 (0%)	0 (0%)	0 (0%)	1 (0.3%)
Renal insufficiency	3 (0.8%)	4 (1.1%)	1 (0.3%)	0 (0%)
Renal tubular acidosis	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total #of subjects with Serious Renal-TEAEs	17 (4.6%)	7 (1.9%)	9 (2.4%)	9 (2.4%)
95% CI for % Difference	2.70 (0.17, 5.23)*		-0.01 (-2.17, 2.16)	

*Statistically significant, Source: FDA Reviewer

Renal TEAE Stratified by Baseline Serum Creatinine

Baseline Creatinine	Study 0015		Study 0019	
	TLV N=372	VAN N=374	TLV N=379	VAN N=378
≤1.2 mg/dL	19 (5.1)	19 (5.1)	21(5.5)	20 (5.3)
>1.2 mg/dL	17 (4.6)	9 (2.4)	16 (4.2)	9 (2.4)
Missing	2 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
Total # of pts w/ renal TEAE	38 (10.2)	30 (8.0)	37 (9.8)	29 (7.7)

Source: FDA Reviewer

Laboratory: Measures of Central Tendency

Parameter (units)	Study 0015		Study 0019	
	TLV n Mean Δ (SD)	**VAN** n Mean Δ (SD)	**TLV** n Mean Δ (SD)	**VAN** n Mean Δ (SD)
Creatinine (μmol/L)	346 **13.2** (74.9)	356 **-6.4** (91.5)	354 **8.4** (52.8)	358 **-0.5** (67.9)
Creatinine clearance (ml/min)	337 **-1.7** (32.5)	346 **4.02** (36.9)	347 **-4.6** (38.4)	352 **6.3** (43.0)

Source: FDA Reviewer

Acknowledgements

- Alfred Sorbello, DO, MPH
- Janice Pohlman, MD, MPH
- Eileen Navarro Almario, MD

Back-up Slides

Proposed Dose Adjustments by Renal Function

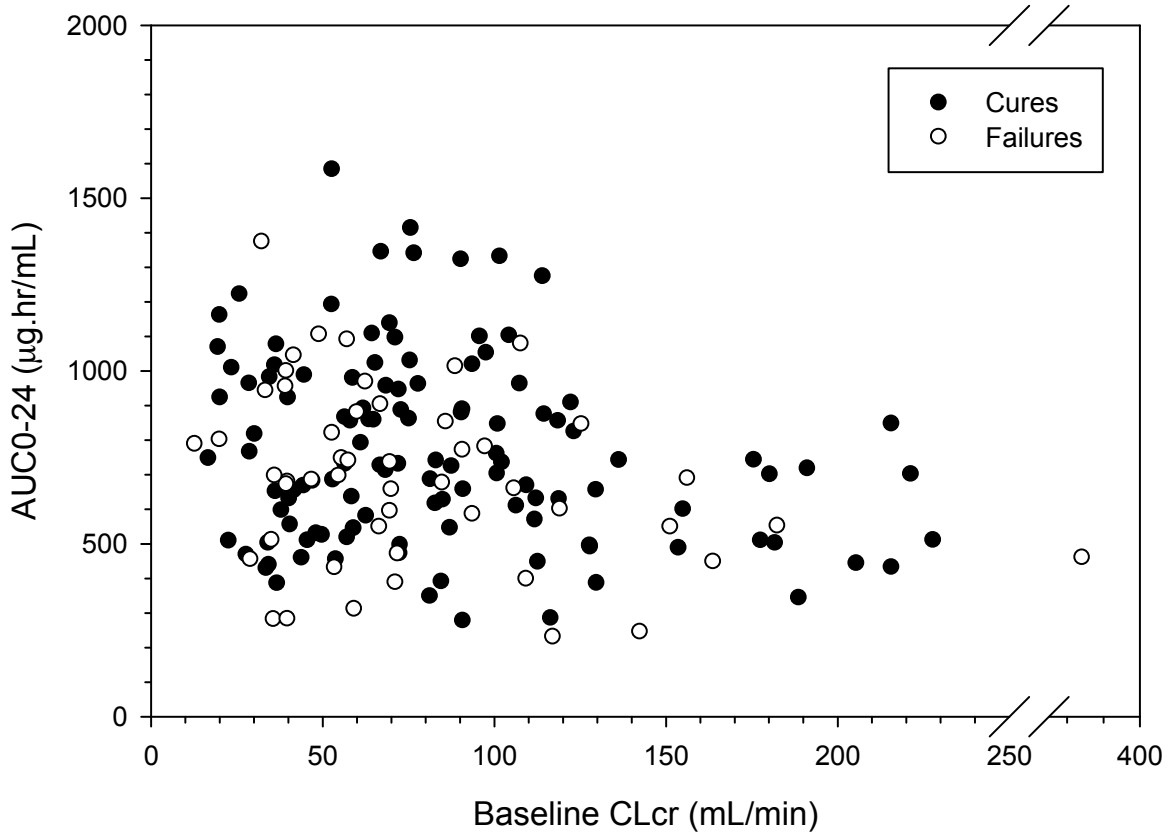
- The recommended dose for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to 21 days. A dosage adjustment is required for patients with creatinine clearance less than or equal to 50 mL/min according to the following table:

Creatinine Clearance (mL/min)	Telavancin Dosage Regimen
> 50	10 mg/kg every 24 hours
> 30-50	7.5 mg/kg every 24 hours
10-30	10 mg/kg every 48 hours

Performance of the Telavancin Dose Adjustment for Renal Function for Studies 015 and 019

Creatinine Clearance Category	Observed $AUC_{ss(0\text{-}48h)}$ (µg·hr/mL) (Median [Range])	Predicted $AUC_{ss(0\text{-}48h)}$ (µg·hr/mL) (Median [Range])
> 80 mL/min	1264 [553-3237]	1271 [529-3261]
> 50-80 mL/min	1497 [619-2795]	1452 [616-2778]
>30-50 mL/min	1235 [568-1903]	1089 [570-1875]
≤ 30 mL/min	1166 [371-2272]	1006 [393-3035]

Relationship Between Baseline Renal Function and Telavancin Exposure Stratified by Clinical Outcome



Presentation of Efficacy: Telavancin for Nosocomial Pneumonia

Anti-Infective Drugs Advisory Committee Meeting
November 29, 2012

Scott Komo, Dr.P.H.
Statistical Reviewer
Division of Biostatistics IV
OB/OTS/CDER/FDA

Outline

- Clinical response
  - Concerns
    - Lack of historical data to justify NI margin
    - Some deaths in close temporal proximity to the time of clinical cure assessment with inability to rule out pneumonia as being related to death
  - Clinical response results
- All-cause mortality
  - NI margin determination
  - 28-day all-cause mortality results
  - Subgroup analyses by baseline creatinine clearance
  - Additional subgroup analyses by factors that affect renal function

Issues with the Clinical Response Endpoint: Lack of Historical Data to Justify an NI Margin

- Critical in the interpretation of a noninferiority trial
- Unable to differentiate between an effective and ineffective drug without historical data demonstrating a treatment effect for the active control
- Lack of historical data has been discussed at both
  - 2009 workshop cosponsored by FDA, Infectious Diseases Society of America (IDSA), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and Society of Critical Care Medicine (SCCM)
  - November 2011 meeting of the AIDAC

Deaths Occurred Close to Time of Clinical Cure Assessment

- Occurred in 33 patients
- For many of these patients, not able to rule out NP as related to the death
- Could be related to
  - Lack of clear definition of clinical response resulting in an endpoint that is not well defined and reliable

  OR

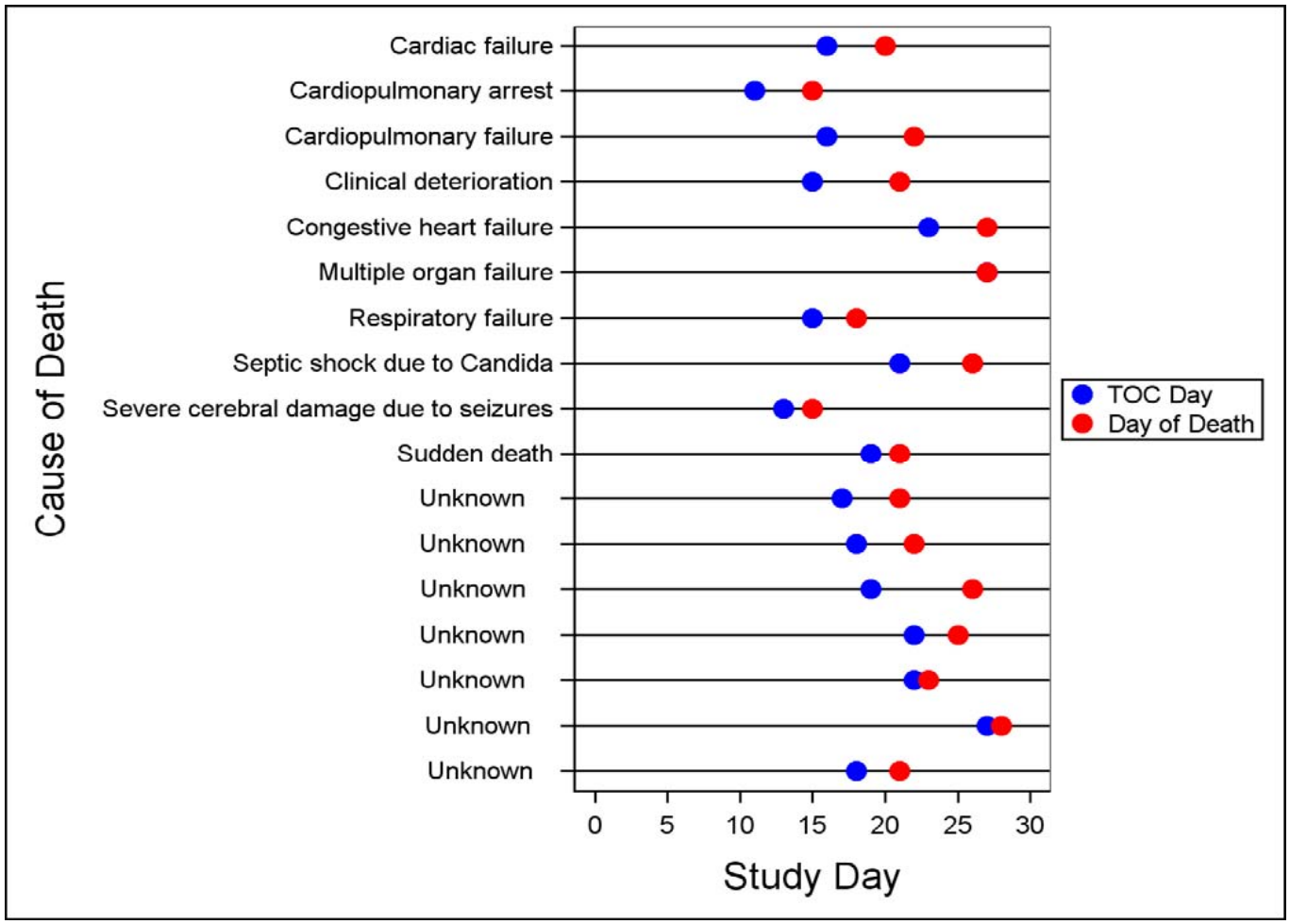
  - Issue with determining the window that maximizes the number of deaths related to NP and minimizes the number of non-infection related deaths

Clinical Response Definition at TOC (7-14 days after last day of therapy)

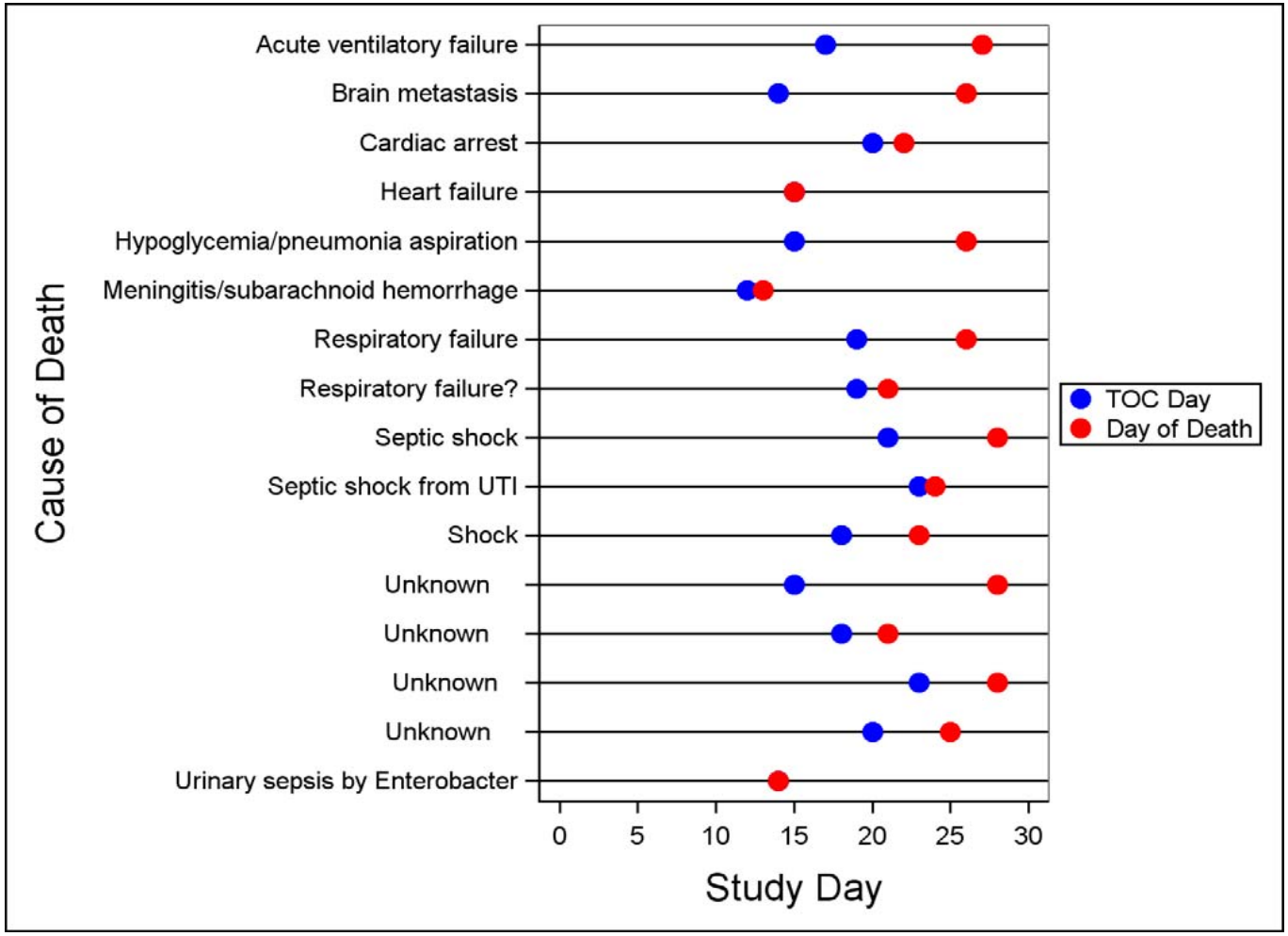
- Cure:
  - Signs and symptoms of pneumonia resolved, and
  - Baseline radiographic findings improved or did not progress
- Failure: at least one of the following:
  - Relapsed pneumonia with the same Gram-positive organism after termination of study medication
  - Death on or after Study Day 3 and before TOC evaluation—or if no TOC evaluation was done, within 28 days after last study medication—where the death is attributable to the HAP episode under study
- Indeterminate: Inability to determine outcome

Note: failures at EOT were carried forward to TOC

TOC Clinical Cure and Died by Day 28 (Telavancin AT Population)



TOC Clinical Cure and Died by Day 28 (Vancomycin AT Population)

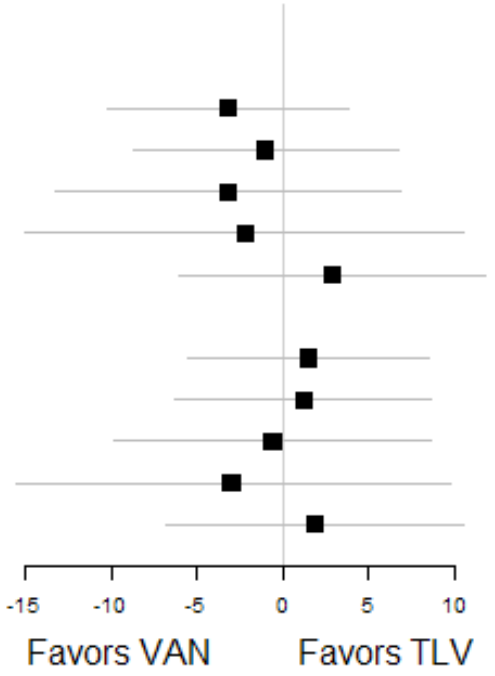


Analysis Populations

- All-treated population: includes all patients who received study drug [N=1503]
- AT – ATS/IDSA population: includes all treated patients who met the ATS/IDSA criteria at baseline
  [N=1289 (86%)]
- Patients who had at least 1 Gram+ pathogen isolated at baseline (includes both mixed and gram+ only infections) [N=797 (53%)]
- Patients who had at least 1 MRSA pathogen isolated at baseline (includes both mixed and gram+ only infections) [N=464 (31%)]
- Patients who were considered clinically evaluable (CE)
  [N=654 (44%)]

Clinical Response — Cure (Death by Day 28 Considered Failure)

Study	Population	Telavancin n/N	Telavancin Rate	Vancomycin n/N	Vancomycin Rate	Difference (95% CI)
0015	All-Treated (AT)	203/372	(54.6)	216/374	(57.8)	-3.2 (-10.3, 3.9)
	AT - ATS/IDSA	173/309	(56)	180/316	(57)	-1 (-8.7, 6.8)
	≥ 1 gram+	101/187	(54)	103/180	(57.2)	-3.2 (-13.3, 6.9)
	MRSA	62/115	(53.9)	64/114	(56.1)	-2.2 (-15, 10.6)
	CE	114/141	(80.8)	134/172	(77.9)	2.9 (-6.1, 11.8)
0019	All-Treated (AT)	221/377	(58.6)	217/380	(57.1)	1.5 (-5.5, 8.5)
	AT - ATS/IDSA	189/325	(58.2)	193/339	(56.9)	1.2 (-6.3, 8.7)
	≥ 1 gram+	128/224	(57.1)	119/206	(57.8)	-0.6 (-9.9, 8.7)
	MRSA	56/118	(47.5)	59/117	(50.4)	-3 (-15.6, 9.8)
	CE	136/171	(79.5)	132/170	(77.6)	1.9 (-6.8, 10.6)



28-Day All-Cause Mortality

- Evidence of treatment effect based on an Agency literature review and discussions at both the 2009 NP workshop and the 2011 AIDAC meeting
- Not a clear consensus on the appropriate timing of assessment for evaluating all-cause mortality
- Discussion at the workshop focused on the timepoint of 28 days after randomization / initiation of therapy
- There was some concern on the sensitivity of the all-cause mortality endpoint because of the possible effect of non-infection related deaths
- A 10% noninferiority margin is felt to be justifiable based on historical data for all-cause mortality

NI Margin: Historical Evidence of Treatment Effect for Active Comparator

- Identified 36 original journal articles (1970-2008)
- No placebo-controlled clinical trials
- No placebo data for assessing clinical response identified
- Placebo effect for all-cause mortality could be estimated indirectly:
  - 12 studies of patients administered inappropriate, delayed, or inadequate initial treatment that reported all-cause mortality
    - Non-randomized, observational cohort studies
- Active control effect:
  - 9 randomized, active-controlled clinical trials
    - Primary endpoint: Clinical response
    - Secondary endpoint: all-cause mortality

NI margin: Selection of Studies

- Comparability of groups

  Selected a subset of studies due to concerns on the comparability of patients based on

  – Age

  – Severity of Illness
- Placebo

  Selected 2 out of 12 studies
- Active control

  Selected 5 out of 9 studies

NI Margin: Estimation of the Active Control Treatment Effect

- Fixed margin approach
- Estimated the placebo and active control mortality rates separately using DerSimonian and Laird random effects meta-analyses
  - Weighted Placebo mortality rate: 62%;
    95%CI: (52%, 71%)
  - Weighted Active control mortality rate: 20%;
    95% CI: (18%, 23%)
- Active control treatment effect estimate: 29%
  = [52% - 23%]

NI Margin: Limitations

- No placebo-controlled studies
- Observed treatment effect of HABP/VABP derived from only 7 studies: 2 “placebo” and 5 active control
- Some studies were open-label comparisons or observational studies — potential for bias
- Variability in baseline patient demographics and disease severity across studies
- Studies assessed mortality at different time points or did not state when mortality was assessed
- Uncertainties due to cross-study comparisons
- Technological advances over time in ICU patient management lead to potential concerns on the constancy of treatment effect

NI Margin Determination

- A 10% NI margin was felt to be justifiable given the large active control treatment effect

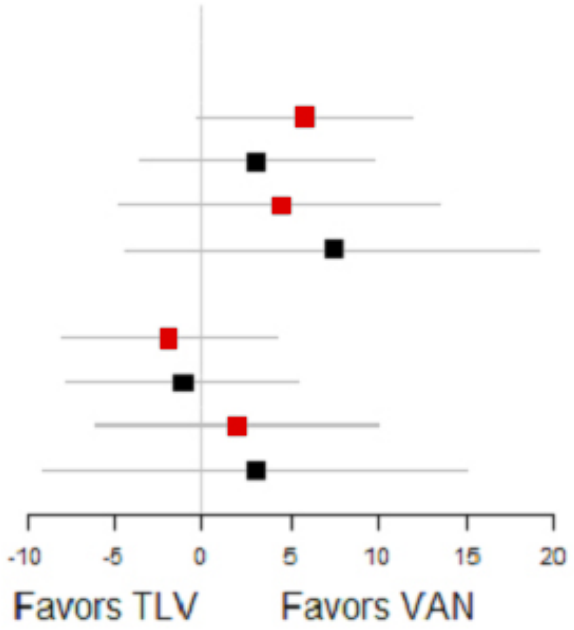
- There are concerns using an NI margin of greater than 10% for a mortality endpoint

Telavancin Trials: Missing Mortality Data

- Incomplete survival data for the 28-day period in the original NDA
  - Study 0015: 34.9% and Study 0019: 28.5%
- Occurred primarily because protocol required follow-up through 7-14 days after EOT and duration of treatment was 7-21 days (with most patients receiving 7-10 days of treatment). Thus, a large number of patients were not followed up to Day 28
- Applicant retrospectively determined survival status and the percentage of patients with incomplete survival for the 28-day period has substantially decreased (Study 0015: 6%; Study 0019: 5%)
- In the analyses, patients with incomplete survival data were considered to be censored on the last day they were known to be alive. Mortality difference was estimated using the difference in Kaplan-Meier estimates at Day 28

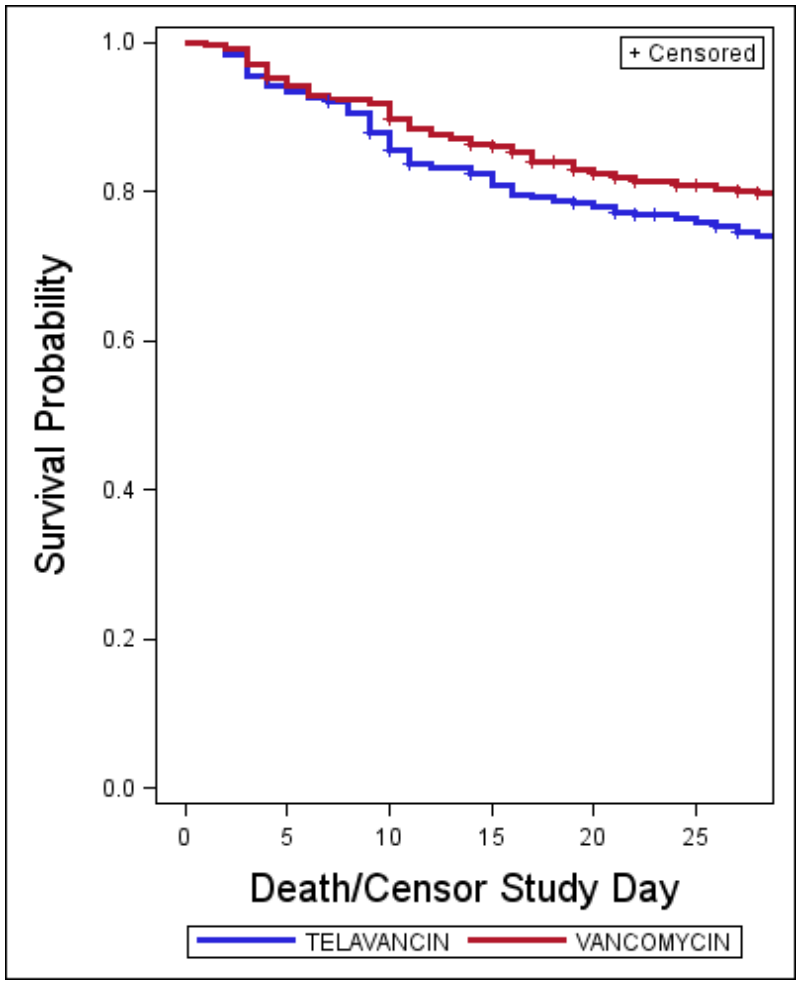
28-Day All-Cause Mortality: Kaplan-Meier Estimates

Study	Population	Telavancin N	Telavancin Rate	Vancomycin N	Vancomycin Rate	Difference (95% CI)
0015	All-Treated (AT)	372	(25.9)	374	(20.1)	5.8 (-0.3, 11.9)
	AT - ATS/IDSA	309	(24.6)	316	(21.6)	3.0 (-3,6, 9.7)
	≥ 1 gram+	187	(28.7)	180	(24.3)	4.4 (-4.7, 13.5)
	MRSA	115	(31.7)	114	(24.3)	7.4 (-4.3, 19.1)
0019	All-Treated (AT)	377	(22.3)	380	(24.2)	-1.9 (-8.0, 4.2)
	AT - ATS/IDSA	325	(23.0)	339	(24.1)	-1.1 (-7.7, 5.4)
	≥ 1 gram+	224	(24.3)	206	(22.3)	2.0 (-6.1, 10.0)
	MRSA	118	(33.3)	117	(30.3)	3.0 (-9.0, 15.0)

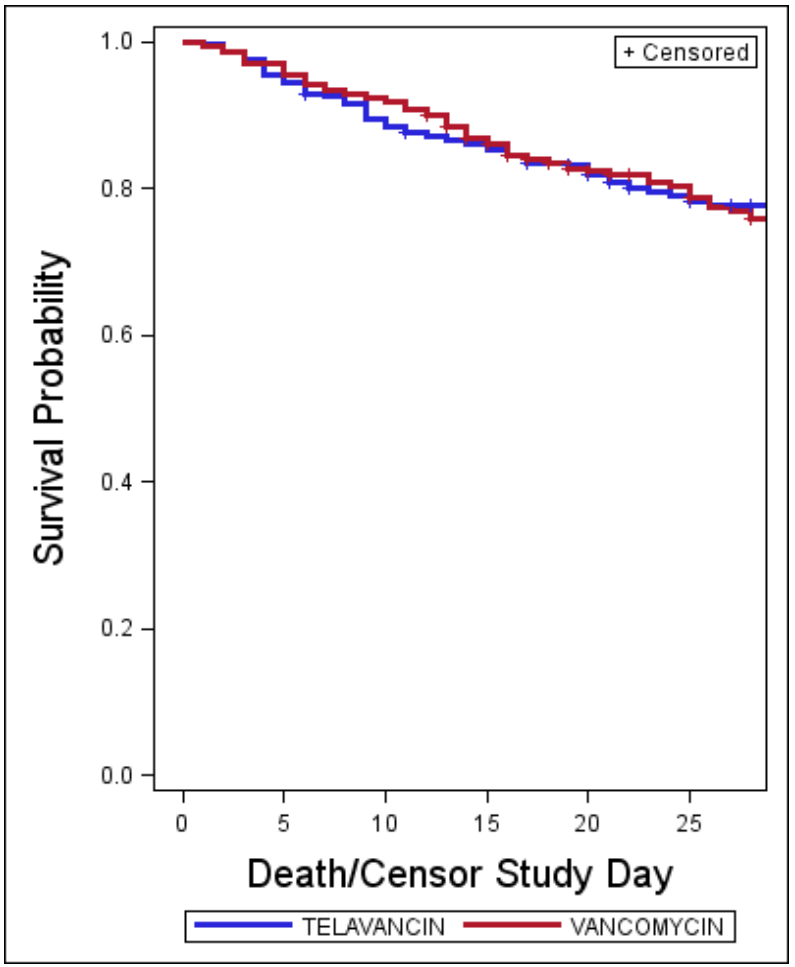


Kaplan-Meier Survival Curves (AT)

Study 0015

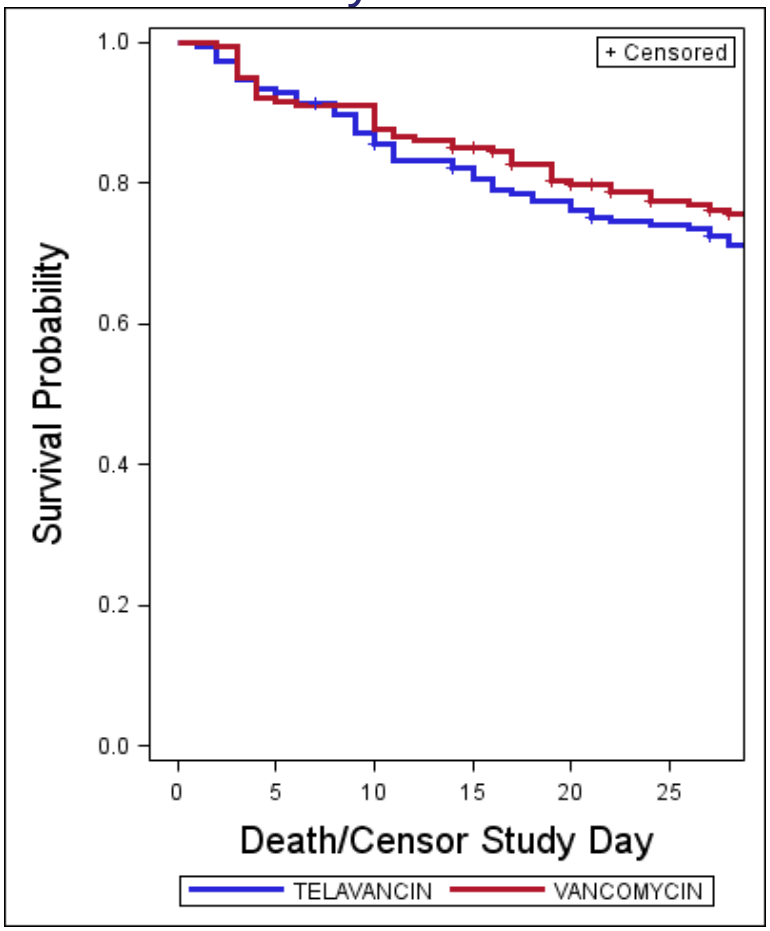


Study 0019

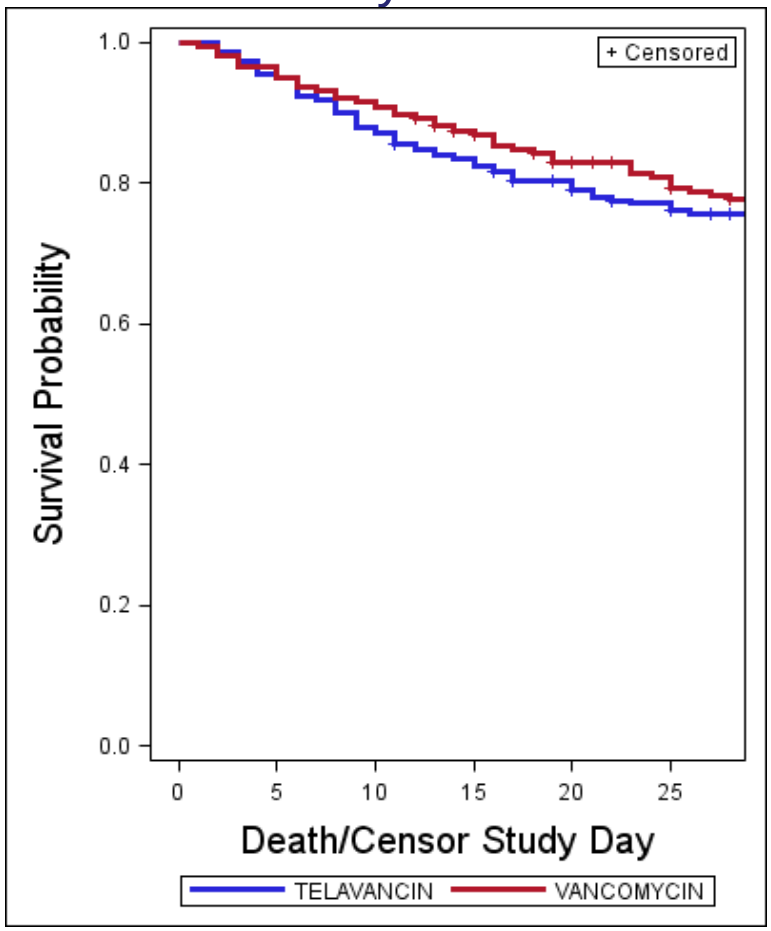


Kaplan-Meier Survival Curves
(At least 1 baseline Gram+ pathogen)

Study 0015



Study 0019



Subgroup Analyses

- Goal is to assess the consistency of treatment effect
- Need to interpret the results cautiously
- Serious multiplicity issue because of the exploratory nature of the analyses (i.e., looked at multiple factors) resulting in an increase in the chance of a false positive finding
- Interaction test often has low statistical power thus may not detect a subgroup effect even when one exists

Because of the major concern with the over-interpretation of subgroups effects, we used prior biological evidence and primarily focused on factors that either measure baseline renal function or are baseline risk factors for renal injury.

Prior Evidence: Clinical Response in cSSSI

	Telavancin	Vancomycin
AT Population		
CrCl >50 mL/min	75.3% (565/750)	73.7% (575/780)
CrCl ≤50 mL/min	63.1% (70/111)	69.4% (75/108)
CE Population		
CrCl >50 mL/min	87.0% (520/598)	85.9% (524/610)
CrCl ≤50 mL/min	67.4% (58/86)	82.7% (67/81)

Source: Current telavancin label

Additional Prior Evidence — Renal Effect

- Nephrotoxicity seen in the cSSSI trials
- Renal effects seen in the preclinical studies

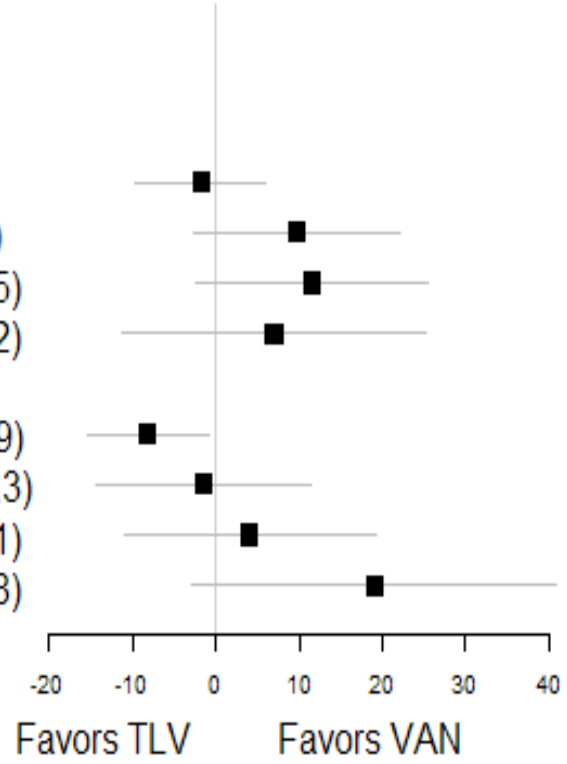
28-day All-Cause Mortality: Potential Effect Modifiers

	Study 0015			Study 0019		
	Chi-square	df	p-value	Chi-square	df	p-value
Baseline creatinine clearance	4.16	3	0.25	6.67	3	0.08
History of diabetes	0.13	1	0.72	0.09	1	0.76
Age (<65, ≥65)	0.04	1	0.84	0.31	1	0.58
Congestive heart failure	3.05	1	0.08	0.05	1	0.82
Baseline nephrotoxic medications	3.50	1	0.06	3.07	1	0.08

28-Day All-Cause Mortality: Stratified by Baseline Creatinine Clearance*

*AT population

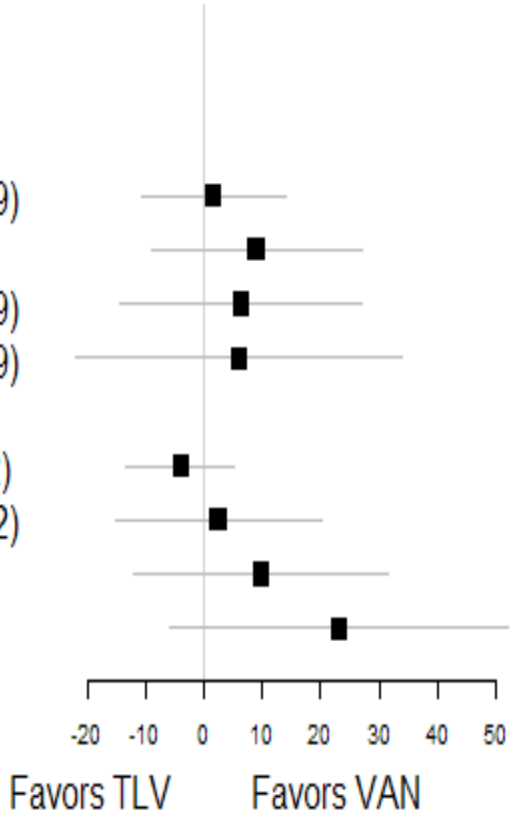
Study	Creatinine Clearance (mL/min)	Telavancin N	Telavancin Rate	Vancomycin N	Vancomycin Rate	Difference (95% CI)
0015	>80	143	(12.2)	152	(14.1)	-1.8 (-9.6, 6.0)
	>50-80	88	(27.4)	88	(17.7)	9.7 (-2.7, 22.1)
	30-50	80	(34.7)	83	(23.1)	11.5 (-2.5, 25.5)
	<30	61	(44.3)	51	(37.3)	7.0 (-11.2, 25.2)
0019	>80	181	(10.5)	181	(18.7)	-8.2 (-15.5, -0.9)
	>50-80	96	(25.6)	90	(27.1)	-1.5 (-14.4, 11.3)
	30-50	62	(27.7)	68	(23.7)	4.0 (-11.1, 19.1)
	<30	38	(61.1)	41	(42.1)	19.0 (-2.9, 40.8)



28-Day All-Cause Mortality: by Baseline Creatinine Clearance*

*Patients who had at least 1 baseline Gram+ pathogen

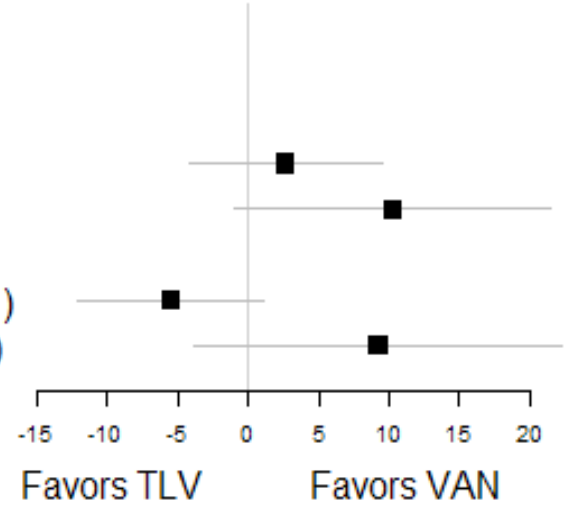
Study	Creatinine Clearance (mL/min)	Telavancin N	Telavancin Rate	Vancomycin N	Vancomycin Rate	Difference (95% CI)
0015	>80	77	(18.5)	74	(16.9)	1.6 (-10.8, 13.9)
	>50-80	47	(27.8)	38	(18.9)	8.9 (-9.1, 27)
	30-50	39	(36.7)	43	(30.4)	6.3 (-14.3, 26.9)
	<30	24	(50)	25	(44)	6.0 (-21.9, 33.9)
0019	>80	111	(11.7)	104	(15.8)	-4.1 (-13.4, 5.2)
	>50-80	60	(30.2)	44	(27.8)	2.4 (-15.3, 20.2)
	30-50	33	(33.6)	34	(23.8)	9.8 (-12, 31.5)
	<30	20	(60.6)	24	(37.5)	23.1 (-6, 52.2)



28-Day All-Cause Mortality: Stratified by Baseline Creatinine Clearance*

*AT population

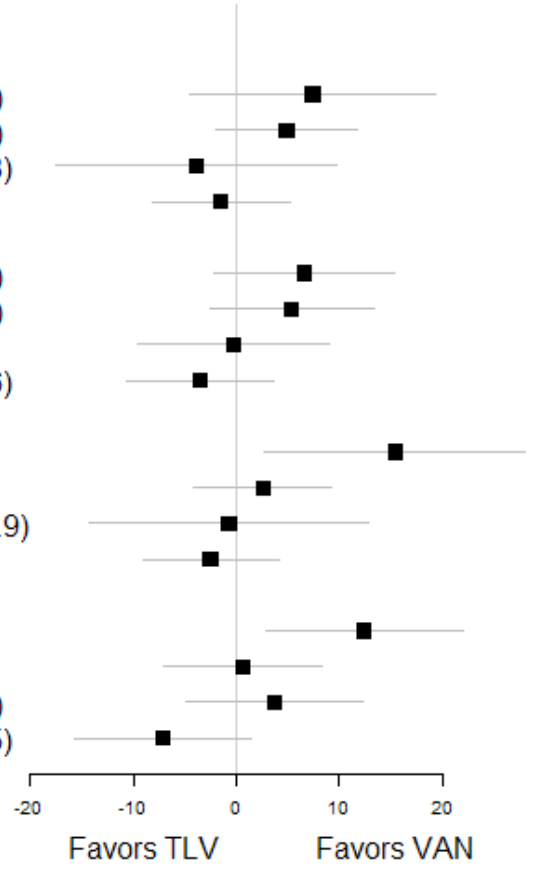
Study	Creatinine Clearance (mL/min)	Telavancin N	Telavancin Rate	Vancomycin N	Vancomycin Rate	Difference (95% CI)
0015	≥ 50	231	(18.0)	240	(15.4)	2.6 (-4.2, 9.5)
	<50	141	(38.8)	134	(28.6)	10.2 (-1, 21.4)
0019	≥ 50	278	(16.0)	271	(21.5)	-5.5 (-12.1, 1.1)
	<50	99	(39.8)	109	(30.6)	9.2 (-3.8, 22.3)



28-Day All-Cause Mortality: Other Risk Factors for Renal Injury*

*AT population

	Study		Telavancin N	Telavancin Rate	Vancomycin N	Vancomycin Rate	Difference (95% CI)
History of diabetes	0015	Yes	118	34.3	114	26.8	7.4 (-4.5, 19.4)
		No	254	22	260	17.2	4.9 (-2.0, 11.8)
	0019	Yes	85	23.9	77	27.7	-3.8 (-17.5, 9.8)
		No	292	21.8	303	23.2	-1.5 (-8.2, 5.3)
Age	0015	≥ 65 years	202	31.9	212	25.3	6.6 (-2.1, 15.3)
		< 65 years	170	18.7	162	13.3	5.4 (-2.6, 13.4)
	0019	≥ 65 years	195	31.8	196	32	-0.2 (-9.5, 9.1)
		< 65 years	182	12.1	184	15.7	-3.5 (-10.7, 3.6)
Congestive heart failure	0015	Yes	100	41.3	115	26	15.4 (2.7, 28)
		No	272	20.1	259	17.6	2.6 (-4.1, 9.3)
	0019	Yes	95	32.1	90	32.7	-0.7 (-14.3, 12.9)
		No	282	19	290	21.5	-2.5 (-9.1, 4.2)
Baseline nephrotoxic medication	0015	Yes	165	33.9	174	21.5	12.4 (2.9, 22)
		No	207	19.5	200	18.8	0.7 (-7, 8.4)
	0019	Yes	182	23.2	182	19.5	3.7 (-4.8, 12.2)
		No	195	21.3	198	28.4	-7.1 (-15.7, 1.5)



Summary

Predefined primary endpoint of clinical response:

- Similar response rates for both treatment groups seen in both trials however the interpretation of the results is not clear
- Difficult to interpret the results because of lack of historical data to justify the NI margin
- Inability to rule out pneumonia as being related to the death for some patients who died in close temporal proximity to the day of the clinical cure assessment. Could be related to
  - Lack of clear definition of clinical response resulting in an endpoint that is not well defined and reliable

  OR
  - Issue with determining the window that maximizes the number of deaths related to NP and minimizes the number of non-infection related deaths

Summary (continued)

28-day all-cause mortality endpoint:

- Endpoint with evidence of a treatment effect
- Telavancin met the 10% NI margin in Study 0019 for the Agency's primary analysis population of patients who had at least 1 baseline Gram-positive pathogen
- Noninferiority was not demonstrated in Study 0015
- Trend of increased mortality for telavancin in Study 0015 in the All-Treated population
- Subgroup analyses identified possible effect modifiers related to baseline
  - Creatinine clearance
  - Congestive heart failure
  - Receipt of nephrotoxic medications

Acknowledgements

- Thamban Valappil, Ph.D.
- Daniel Rubin, Ph.D.

Thank you

Backup Slides

Days of Study Medication (AT)

	Study 0015		Study 0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
<3 Days	23 (6%)	15 (4%)	17 (5%)	17 (4%)
3-6 Days	77 (21%)	62 (17%)	52 (14%)	53 (14%)
7-10 Days	152 (41%)	172 (46%)	163 (43%)	160 (42%)
11-14 Days	79 (21%)	85 (23%)	95 (25%)	97 (26%)
15-21 Days	39 (10%)	38 (10%)	48 (13%)	47 (12%)
>21 Days	2 (<1%)	2 (<1%)	2 (<1%)	6 (2%)
- Total -	372 (100%)	374 (100%)	377 (100%)	380 (100%)

Adjunctive Agents for Gram-Negative Coverage

	Study 0015		Study 0019	
Antimicrobial	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=378)	Vancomycin (N=380)
Aztreonam	160	167	160	169
Piperacillin/tazobactam*	42	36	23	33
Imipenem	4	0	5	2

* 1 telavancin patient received piperacillin alone

Last Day Subjects Known to be Alive for Patients with Missing Survival Status

	0015		0019	
	Telavancin n (%)	Vancomycin n (%)	Telavancin n (%)	Vancomycin n (%)
Day 1-6	0 (0)	1 (3.6)	1 (5.9)	0 (0)
Day 7-13	5 (26.3)	1 (3.6)	1 (5.9)	3 (15.0)
Day 14-20	4 (21.1)	14 (50.0)	6 (35.3)	11 (55.0)
Day 21-28	10 (25.6)	12 (42.9)	9 (52.9)	6 (30.0)
- Total -	19	28	17	20

28-Day All-Cause Mortality: Patients with at least 1 baseline Gram-positive pathogen who did not receive concomitant medications with Gram-positive activity

Study	Treatment	N	Estimated K-M Mortality at 28 Days (%)	Difference (%) (TLV - VAN) 95% CI
0015	TLV	164	29.0	4.6
	VAN	163	24.4	(-5.0, **14.3**)
0019	TLV	130	23.6	2.6
	VAN	125	21.0	(-5.8, **11.0**)

28-Day All-Cause Mortality: Patients with MRSA who did not receive adjunctive agents with MRSA coverage

Study	Treatment	N	Estimated K-M Mortality at 28 Days (%)	Difference (%) (TLV - VAN) 95% CI
0015	TLV	115	31.7	7.4
	VAN	114	24.2	(-4.3, **19.1**)
0019	TLV	118	33.3	3.6
	VAN	116	29.7	(-8.4, **15.6**)

Imbalance in Risk Factors

- Because patients are randomized, we expect treatments groups to be balanced with respect to both measured and unmeasured risk factors
- Any differences are due to chance: the type I error takes this into account
- Likely to find apparent imbalances in risk factors that go in both directions