CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22-407
Drug Name:	Vibativ (telavancin for injection)
Indication(s):	Treatment of nosocomial pneumonia
Applicant:	Theravance Inc.
Date(s):	7/12/12 (received)
Review Priority:	Class 2 Resubmission
Biometrics Division:	DBIV
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewer:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective Products (DAIP)
Clinical Team:	Benjamin Lorenz, MD
Project Manager:	J. Christopher Davi, M.S.

Keywords: active control/non-inferiority, treat.-by-baseline interaction, subgroup analyses
Link to keywords:
http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

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1 EXECUTIVE SUMMARY

The Applicant provided evidence that telavancin is effective for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia (HAP/VAP). However, there is a serious concern of increased mortality for patients with baseline renal impairment, especially for those with a baseline estimated creatinine clearance (CrCl) ≤50 mL/min. This is consistent with the renal findings that were seen in the complicated skin and skin structure infection (cSSSI) application (NDA 22-110), where there was a finding of decreased efficacy among patients with moderate/severe pre-existing renal impairment (baseline CrCl ≤50 mL/min) included in the Warnings and Precautions section of the current telavancin label. In addition, concerns for nephrotoxicity based on new onset or worsening renal impairment occurred in both the cSSSI (NDA 22-110) application as well as the current HAP/VAP application. Renal toxicity was also seen in the preclinical studies. Given the concerns of increased mortality for patients with a baseline estimated CrCl≤50 mL/min and the relatively few number of treatment options for nosocomial pneumonia caused by *S. aureus* along with the incidence of increasing resistance to these antibacterials, I recommend that the label include a statement on the finding of increased mortality for telavancin treated patients with baseline CrCl ≤ 50 ml/min with use limited to situations where other treatment options are not available.

The Applicant conducted two Phase 3 trials (0015 and 0019), with identical protocols, in patients with HAP/VAP. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours for 7 to 21 days. Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively. Study 0015 was conducted in 22 countries with 31% of the randomized and treated patients coming from the United States, while Study 0019 was conducted in 29 countries with a much lower percentage (14%) of the patients enrolled in the United States.

Because the trials were not originally designed to collect 28-day all-cause mortality, there were a substantial number of patients whose survival status was not known through Day 28 (Study 0015: 35%; Study 0019: 28%), in their original submission. However, the Applicant retrospectively collected this data for most of the patients and the number of patients with missing 28-day all-cause mortality data decreased to 6% for Study 0015 and 5% for Study 0019. Most of patients whose survival status is not known through Day 28 had their test-of-cure (TOC) visit prior to Day 28 and were not followed beyond this point as per the protocol. The Applicant considered these patients to be censored at the last day they were known to be alive and the difference in 28-day Kaplan-Meier estimates of all-cause mortality was used to assess treatment efficacy.

Because both treatment groups have only gram-positive activity, the Division decided that the primary efficacy analyses should be performed in patients who had at least one gram-positive pathogen isolated at baseline. In this population using a 10% NI margin, noninferiority of telavancin to vancomycin for 28-day all-cause mortality was demonstrated for Study 0019 [difference = 2.0% (telavancin: 24.3%; vancomycin: 22.3%); 95% CI = (-6.1%, 10.0%)] but not

for Study 0015 [difference = 4.4% (telavancin: 28.7%; vancomycin: 24.3%); 95% CI = (-4.7%, 13.5%)]. It is important to note that noninferiority was demonstrated only in Study 0019 based on an NI margin of 10%, although it was a borderline finding. However, at the November 2011 AIDAC meeting, there was a recommendation that only a single successful HAP/VAP trial was needed if there are other supportive evidence available, which in this case would be the two successful cSSSI trials that led to approval of the cSSSI indication.

A major concern with this application is that for Study 0015 there was a nearly statistically significant increase in 28-day all-cause mortality for telavancin patients relative to vancomycin patients in the All-treated population [treatment difference: 5.8%; 95% CI: (-0.3%, 11.9%)].. Even though this finding was not replicated, this raises serious safety concerns. A possible explanation for this finding is that there were more patients in Study 0015 who had baseline renal impairment or risk factors for renal injury, which may be effect modifiers.

In both trials, telavancin patients with normal baseline renal function tended to have lower all-cause mortality than vancomycin patients. However, in both trials, telavancin patients with baseline renal impairment tended to fare worse than vancomycin patients. In both trials, telavancin patients with a baseline estimated creatinine clearance (CrCl) ≤50 mL/min had higher mortality than vancomycin patients. It is less clear for patients with baseline CrCl in the 50-80 ml/min range because the trends were not consistent between the two trials.

Although the test of a homogeneous treatment effect between the US and non-US in the Division's primary analysis population (≥1 baseline gram+ pathogen) was not a statistically significant for either trial, it is concerning that almost the entire mortality imbalance in Study 0015 is driven by the US sites (Table 23). This result was not replicated in Study 0019 but it should be noted that US patients constituted a much smaller proportion of the population in Study 0019 (14%) than for Study 0015 (31%). Additional stratified analyses were then performed by both US/non-US and the baseline creatinine clearance (AT: Table 24; ≥1 baseline gram-positive pathogen: Table 25). In Study 0015, the mortality is markedly higher for telavancin relative to vancomycin patients for US patients with a baseline creatinine clearance ≤50 ml/min. This was not seen for the non-US patients in Study 0015. The analyses for Study 0019 must be interpreted carefully because of the small number of US patients, which results in very small cell sizes. In Study 0019, mortality appears to be increased for US patients with baseline creatinine clearance <80 ml/min although the same sizes are very small. This was not seen for non-US patients where the only telavancin patients with increased mortality were those with baseline creatinine clearance <30 ml/min.

It is also important to note that there are only two drugs approved to treat HAP/VAP or lower respiratory tract infections due to MRSA as opposed to infections due to MSSA where there are additional treatment options, i.e. beta-lactams.

The AIDAC did not find that there was substantial evidence of effectiveness and safety for telavancin in the treatment of NP (Yes: 6; No: 9). However, the AIDAC voted overwhelmingly (Yes: 13; No; 2) that there was substantial evidence of effectiveness and safety for televancin in the treatment of NP when other alternatives are not suitable, Many of the members recommended limiting use for MRSA only while some also recommended use in MSSA if other

treatment options were not suitable, e.g. in patients with a severe beta-lactam allergy. Additionally, many of the members also voiced serious concerns on the observed mortality imbalance for patients with baseline renal impairment and felt use should be limited in this population.

In conclusion, there is evidence that telavancin is effective for the treatment of HAP/VAP in specific patient groups. However, there are serious concerns for increased mortality in patients with baseline renal impairment, especially for those with a baseline CrCl ≤50 mL/min. Given the concerns of increased mortality for patients with a baseline estimated CrCl ≤50 mL/min and the relatively few number of treatment options for nosocomial pneumonia caused by *S. aureus* along with the incidence of increasing resistance to these antibacterials, I recommend that the label include a statement on the finding of increased mortality for telavancin treated patients with baseline CrCl ≤ 50 ml/min with use limited to situations where other treatment options are not available.

2 INTRODUCTION

2.1 Overview

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin with rapid, concentration-dependent bactericidal activity against clinically relevant Gram-positive bacterial pathogens, including *S. aureus* (methicillin-susceptible and resistant isolates), *S. pneumoniae*, and vancomycin-resistant *E. faecalis*. It contains hydroxypropyl-ß-cyclodextrin as a solubilizing agent. The proposed indication is the treatment of nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant strains) and *Streptococcus pneumoniae* (penicillin susceptible strains).

The proposed dosing regimen for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days.

Telavancin is eliminated primarily by the kidney. The dosage is adjusted for patients with renal impairment. For patients with moderate (creatinine clearance [CrCl] 30-50 mL/min) impairment, the dosage is decreased to 7.5 mg/kg every 24 hours. In contrast, for those with severe (CrCl 10-30 mL/min) renal impairment, the dosage is decreased to 10 mg/kg every 48 hours. Finally, there are no dosage recommendations for patients with end-stage renal disease (CrCl <10 mL/min), including patients receiving hemodialysis.

Telavancin was studied previously for the treatment of complicated skin and skin structure infections (cSSSI). Three clinical trials (202b, 0017, and 0018) were conducted in patients with cSSSI at the same dosage (10 mg/kg) as the current submission. The dosage was increased from 7.5 mg/kg to 10 mg/kg during the Phase 3 trials based on the results of the results of Study 202b. Another study, 202a, was conducted at the lower the 7.5 mg/kg dosage. Telavancin was approved to treat patients with cSSSI at the 10 mg dose on 11 September 2009.

This NDA was initially submitted on 1/26/09 and a complete response letter was issued by the Agency on 11/23/09. The 11/23/09 complete response letter cited the following deficiencies:

> The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia (NP). Both trials were designed and powered for a clinical response endpoint. However, as discussed at the FDA Anti-Infective Drugs Advisory Committee meeting for NDA 22-171 on July 16, 2008, the published scientific literature (identified to date) does not permit interpretation of non-inferiority studies of antibacterial drugs for NP and Ventilator-Associated Pneumonia (VAP) using clinical response as the primary endpoint due to the lack of scientific data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. Published historical evidence will only permit interpretation of non-inferiority trials for NP and VAP using all-cause mortality as the primary endpoint.
>
> In this application, all-cause mortality was a secondary endpoint. The two submitted trials were of insufficient size and statistical power to identify a difference in all-cause

mortality between telavancin and comparator-treated patient groups if such a difference existed. The submitted mortality data were incomplete and at this time, it is unclear whether an analysis of the all-cause mortality data derived by pooling the results of Studies 0015 and 0019 will be sufficient to determine the efficacy and safety of telavancin. Differences in the distribution of baseline prognostic factors for mortality across the two trials may preclude pooling; if, upon further review, pooling of the mortality data is determined to be acceptable, the collective all-cause mortality data may only be of sufficient size and statistical power to be considered analogous to one adequately sized trial with a mortality endpoint and additional evidence supporting safety and effectiveness would still be required.

In order to resolve these deficiencies:

1. Submit all available all-cause mortality data and account fully for any censored information. In addition, provide a listing of the patients by trial in which mortality status is not known up to the end of the mortality reporting window. The listing should include study number, subject ID, randomized treatment group, actual treatment group, and last Study Day that mortality status is known. A tabulation of the subjects whose mortality status is unknown should also be provided by trial and treatment group, as well as a summary that presents the distribution of the Study Day where censoring occurs by trial and treatment group.
2. Provide a scientific rationale for pooling all-cause mortality data across the two clinical trials. The rationale should address the consistency of the treatment difference for telavancin relative to vancomycin across the trials given the difference in the distribution of baseline prognostic factors for mortality between the two trials and the proportion of subjects whose mortality status is censored.
3. In design of the new clinical trials for the NP indication, consider the following:
    a. The study population should contain patients with a high likelihood of having the disease of interest. Therefore, the inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever > 38°C, leukocytosis or leukopenia, and purulent lower respiratory tract secretions.
    b. Chest radiograph interpretation should be performed by a blinded healthcare provider, preferably a radiologist or pulmonologist, not directly involved in assessment of the patient for enrollment or during subsequent care.
    c. Uniform criteria should be applied to identify the quality of sputum and endotracheal aspirate specimens for culture and subsequent pathogen identification.
    d. The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

The Applicant subsequently submitted a response on 12/22/09. However, the response was deemed to be incomplete on 1/25/10. The following deficiency from the initial action letter still needed be addressed:

While we acknowledge that additional mortality data and analyses have been provided to support pooling the two phase 3 clinical trials (Studies 0015 and 0019), even if this is

acceptable, the two pooled studies would equate to only one adequate and well-controlled trial and would not constitute substantial evidence of efficacy. The adequacy and similarity of populations across studies for purposes of pooling has not yet been determined, and is a review issue.

In addition, the design elements for the recommended new trial(s) outlined in the initial complete response letter were also reiterated.

The Applicant then submitted a response on 6/30/10. The response was again deemed to be incomplete on 12/21/10. The following deficiencies:

1. The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia. While a substantial amount of missing mortality data has been recovered and provided for analysis, the analysis in the population of interest (i.e. patients with nosocomial pneumonia caused by Gram positive bacteria) in Study 0015 does not demonstrate noninferiority of telavancin relative to vancomycin. When the same analysis population was assessed in Study 0019, the observed treatment difference in 28-day all-cause mortality rates is 2.0% (telavancin: 24.3%; vancomycin: 22.3%) and the upper bound of the 95% CI is 10.0%, (-6.1%, 10.0%), and does not provide sufficient evidence for the noninferiority of telavancin to vancomycin.
2. In addition, the method of selection of patients did not provide adequate assurance that they had the disease being studied due to uncertainties with respect to interpretations of chest radiographs and adequacy of respiratory tract specimens.
3. Your analysis method that compares the telavancin-treated patients from your Phase 3 trials to the historical studies of patients receiving inadequate, inappropriate, and delayed therapy is problematic. Specifically, the baseline characteristics of the patients in the telavancin trials patients are not comparable to those in the historical control groups.
4. The pooling of patients across the two Phase 3 trials is not appropriate because subjects in study 0015 had more potential risk factors for mortality (e.g., diabetes mellitus and renal impairment/failure) than the subjects in study 0019.
5. The inclusion of post-hoc selected prognostic risk factors for mortality in the analyses is not acceptable because they may bias the results.
6. The diagnosis of renal failure was left to the discretion of the investigator, and in some cases it was unclear whether some of the patients may have had acute as well as chronic renal failure. For patients with potential risk factors, renal status should have been more specifically defined by standardized measures at entry and followed more closely for at least 28 days

As before, the design elements for the recommended new trial(s) outlined in the initial complete response letter were again reiterated.

The Applicant then submitted a Formal Dispute Resolution on 4/28/11. The appeal was denied on 5/10/11 because a post-action meeting was not been held between the Applicant and the Division of Anti-Infective Products (DAIP) following the December 21, 2011 complete response

action. Thus, the Agency felt it would be inappropriate to consider this matter under formal dispute resolution at this time.

The Applicant then submitted a Formal Dispute Resolution to the Director of the Office of Antimicrobial Products on 8/25/11. The appeal was denied on 10/14/11. Dr. Ed Cox denied the appeal because he felt that the application should be discussed at a meeting of the Anti-Infective Drugs Advisory Committee to address the following issues:

- The trials were originally designed with different primary endpoints and numerous subgroup analyses are being analyzed to evaluate a mortality endpoint.
- Collection and evaluation of respiratory tract samples and radiographic evaluation for patients enrolled in the trials
- The role and effect of prior and/or concomitant antibacterial drug therapy, empiric therapy, and de-escalation of adjunctive antibacterial drug therapy in the interpretation of trial results
- The appropriate analysis population, given that the spectrum of activity of telavancin is against Gram-positive organisms and that patients may have received prior or concomitant antibacterial drug therapy
- The role of supporting data from other indications and the role that such information may play in whether one trial vs. two trials can provide sufficient information to support the indication you seek
- The analysis of mortality data in patients with baseline renal failure and the definition of renal failure as applied in the clinical trials

The Applicant then submitted a Formal Dispute Resolution to the Director of the Office of New Drugs on 12/7/11. The appeal was denied on 2/17/12. Dr. John Jenkins denied the appeal because he felt, similar to Dr. Cox, that the Applicant should resubmit the application for further review by the Agency with a presentation at the Anti-Infective Drugs Advisory Committee.

Finally, the Applicant submitted the current application on 7/12/12.

Table 1: List of all studies included in the analyses

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
0015	3	7-21 days	Study day 28	381 telavancin 380 vancomycin	Gram-positive HAP
0019	3	7-21 days	Study day 28	386 telavancin 385 vancomycin	Gram-positive HAP

2.2 Data Sources

Information of demographics, disposition, clinical response, concomitant medication use, and adverse events were contained in the original application:

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Additional information on deaths through study day 28 and potential effective antibacterial use administered prior and during the trial are contained in the current application:

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

A sponsor inspection was performed from 10 September 2009 – 25 September 2009 to review the conduct of clinical studies performed in support of this application. The purpose of the inspection was to evaluate the Applicant's completion of regulatory obligations for Studies 0015 and 0019. In addition, the inspection was conducted to evaluate a complaint received by the Agency that asserted that the Applicant had improperly manipulated study data to achieve desired outcomes for Studies 0015 and 0019.

The sponsor inspection did not reveal any regulatory violations and there was no evidence of improper study data manipulation. However, during the inspection, it was ascertained that data was added/revised after treatment unblinding. In addition, some parts of the medical review process occurred after treatment unblinding. These determinations included decisions that would affect evaluability as well as whether patients received adequate gram-negative coverage. The adequacy of gram-negative coverage is an important issue because it is one of the factors that the Applicant is using to explain the observed increase in mortality seen for the telavancin arm relative to the vancomycin arm. A summary of the inspection and findings is provided below.

The Applicant's documentation of dates of data transfer/data files transferred from (b) (4) ((b) (4) the CRO responsible for data management of the two Phase 3 trials, are consistent with data transfer dates/data files/file content that were documented by (b) (4) and reviewed during the Agency inspection of the CRO and in a subsequent comparison of datasets.

Although the inspection did not reveal any regulatory violations, it did shed light on some blinding issues that will be summarized below.

1st data unlock
The following issues were identified by the Applicant and data were added/changed during this unlocking of the database:

- MIC sensitivity data
  MIC sensitivity data for ninety-two patients (198 records) from thirty-eight sites were inadvertently left out of the for Study 0015 database. The explanation given was that (b) (4) was receiving incremental updates from (b) (4) (CRO responsible for laboratory analyses) and failed to include this data in the treatment unblinded data transfer. Prior to treatment unblinding, the Applicant had previously received treatment blinded data from (b) (4) that included this MIC sensitivity data. However, when the unblinded data was transferred, Applicant staff noticed that the MIC sensitivity data for the subset of ninety-two patients was missing. The Applicant then asked (b) (4) to include the missing data in a new data transfer.
- SAE and deaths

Applicant staff noticed after treatment unblinding that there were inconsistencies in the data that indicated that death occurred, where death was flagged in one section but SAE and/or death report forms were not reported or included. Death could be marked in the AE, death report, Drug Discontinuation, Clinical Response at EOT, Study Completion/Follow-up/Test of Cure, and Clinical Response for Test of Cure sections.

The Applicant asked that the CRF as well as the SDTM data be updated so that deaths would be consistently captured. All of the inconsistencies found were for fourteen deaths that occurred during the safety reporting period for patients who did not have a test-of-cure (TOC) visit. The reporting period in this case was twenty-eight days after the last dose of study drug was received.

- ECG
  Applicant staff discovered that ECG data for patients who were screening failures (i.e., non-randomized patients) were mistakenly included in the ECG dataset and notified (b) (4) also found some errors in protocol, site, and subject# for some patients. These errors included five patients (two in 0015 and three in 0019) who had incorrect site numbers, four patients who had an incorrect protocol# (i.e. in the Study 0019 dataset and but who were Study 0015 patients), and one patient had the wrong subject number listed. The Applicant was notified by (b) (4) of these discrepancies and the Applicant then told (b) (4) to notify the ECG vendor ((b) (4) to make these corrections and delete the screening failure data. Corrections were made by the ECG vendor who sent the corrected database to (b) (4) Corrected data were included in the updated SDTM datasets from (b) (4) during the 1st data unlock.

It was stated that the main reasons to unlock the database were to add SAE and death data and also MIC sensitivity data.

2nd database unlock

The corrections/updates made during the second database unlocking involved 33 patients. The following issues were identified by Applicant who notified (b) (4) who updated the data:

- Updates to renal AE status
  This data was obtained from the Applicant's renal follow-up effort undertaken in May 2008. The objective was to follow up on patients who had a renal AE whose sequela was either continuing or resolving and to provide a status update sixty days after the patients completed the study. Queries were communicated to (b) (4) who then queried the sites.
- Dosing and weight correction
  The dosing database was not locked until approximately six months after SDTM database was treatment unblinded. The Applicant was still issuing queries through (b) (4) to the sites while the dosing database was open. As a result of these queries, datapoints common to the dosing database and the SDTM database needed to be updated. During this process, data entry errors were also indentified in the SDTM database.

The primary reason stated to unlock was to include the data from the renal follow-up effort.

3rd database unlock
The Applicant undertook a remonitoring effort which involved an audit of a sample of sites. It was stated that this audit was performed in response to their experience with their complicated skin and skin structure infection application (NDA 22-110). This audit was performed by (b) (4) who audited patient records primarily looking at eligibility and clinical outcome assessment data. In addition, if AEs were found that were not previously noted, these would also be identified. Three deaths and two SAEs were indentified at the sites during the remonitoring effort and Theravance was informed. Theravance notified (b) (4) to update the database to reflect the new information. (b) (4) updated the database and transferred it to Theravance.
In addition to the data changes that occurred after treatment unblinding, the inspection also revealed that some parts of the Applicant's medical review occurred after the database was treatment unblinded. A summary is provided below.

Medical Review Process
A medical review process was performed by the Applicant to make determinations on issues such as clinical evaluability, whether a patient received potentially effective antibiotics, whether a patient received adequate gram-negative coverage, etc. It was ascertained that the review by the medical monitor occurred in some instances after the SDTM database was treatment unblinded. This is relevant because the medical monitor made determinations that affected patient populations as well other issues that were reflected in the Analysis files. The Analysis files would be affected by either changes in the SDTM datasets or medical review process determinations on a particular issue, e.g. potentially effective antibiotics use.

The Medical Review process consisted of a spreadsheet created from the SDTM files that contained the relevant datapoints necessary to make a determination on a particular issue.

The following is a list of the explanations given by the Applicant for the major medical review determinations made after treatment unblinding occurred

- PEA (Potentially effective antibiotics)
  The medical monitor found forty-two patients had inadvertently been omitted from the original spreadsheet that was used to make a PEA determination. This PEA determination also affects clinical evaluability. Note it was stated that the treatment code was not included in the spreadsheet used to make the determination.
- GNECGOVM and GNEGVN (adequacy of gram-negative coverage)
  These spreadsheets were used to look at the adequacy of gram-negative coverage for the purpose of exploring some of the findings in the study and performing sensitivity analyses. It should be noted that both of these spreadsheets were created approximately six months after treatment unblinding.

3.2 Evaluation of Efficacy

The Applicant conducted two Phase 3 trials (0015 and 0019), with identical protocols, in patients with NP. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours. Treatment duration was to be from 7 to 21 days. Because both the test and comparator drugs do not have activity against gram-negative

pathogens, a substantial number of patients received empiric gram-negative coverage. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. In addition, piperacillin/tazobactam was also permitted for coverage of Gram-negative organisms if resistance to aztreonam was known or suspected. The Original Protocol had also allowed imipenem for Gram-negative coverage as well as aztreonam and/or metronidazole therapy; however, imipenem was removed as a treatment option in Protocol Amendment 1.

Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively. Study 0015 was conducted in 22 countries with 31% of the randomized and treated patients coming from the United States, while Study 0019 was conducted in 29 countries with a much lower percentage (14%) of the randomized and treated patients coming from the United States.

Patients were randomized in a 1:1 ratio with randomization stratified on the combination of a pre-specified country grouping (see Table 2 for the pre-specified country groupings), the presence or absence of diabetes, and ventilatory status of the patient.

Table 2: Country Groupings used in Stratified Randomization

Country Grouping	Study 0015	Study 0019
1	Australia	Australia
	Belgium	Canada
	Canada	France
	France	Israel
	Israel	Spain
	Italy	United States
	United Kingdom	
	United States	
2	Argentina	Argentina
	Brazil	Brazil
	Chile	Chile
	South Africa	South Africa
	Taiwan	
3	Croatia	Bulgaria
	Czech Republic	China
	Greece	Croatia
	India	Czech Republic
	Malaysia	Estonia
	Malta	Georgia
	Peru	Greece
	Poland	Korea
	Turkey	Lebanon
		Lithuania
		Mexico
		Philippines
		Poland
		Romania
		Russia
		Serbia/Montenegro
		Slovakia
		Thailand

Ukraine

Source: Clinical Overview, Table 2

The primary objective in each trial was to compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with Gram-positive HAP with an emphasis in patients with infections due to MRSA.

A key secondary objective was to pool the data from both trials (protocols 0015 and 0019), which were of identical design, to assess the superiority of telavancin to vancomycin in patients with MRSA infections.

Baseline evaluations were performed within 24 hours prior to treatment start and included pertinent medical history; an assessment of the signs and symptoms of the infection; determination of the Glasgow Coma Score; chest x-ray or computed tomography scan (CT scan) for evaluation of radiographic lung infiltrates; oxygen status as measured by arterial blood gas is strongly encouraged, but is required for patients who are ventilated and/or have an existing arterial line; collection of respiratory specimens for Gram stain and culture, blood culture, clinical laboratory tests, an X-ray to rule out osteomyelitis (if clinically indicated); and three 12-lead electrocardiograms (ECGs).

All patients were to have an End-of-Therapy (EOT) visit within 3 days following the last dose of study medication and a Follow-Up visit within 7 to 14 days after the EOT visit. The procedures at the EOT visit included: record signs/symptoms of pneumonia; obtain a respiratory specimen, assess clinical response; obtain chest x-ray or computed tomography scan (CT scan) for evaluation of radiographic lung infiltrates; recording of oxygen status as measured by arterial blood gas is strongly encouraged, but is required for patients who are ventilated and/or have an existing arterial line; and obtain respiratory specimen only if clinically indicated.

A Test-of-Cure (TOC) assessment (record signs/symptoms of pneumonia, obtain a respiratory specimen, assess clinical response, record all systemic antibiotics received after EOT, obtain blood and urine samples, and assess adverse events) was conducted at the Follow-Up visit for patients who were a clinical cure or had an indeterminate outcome at the EOT visit. Both the EOT and TOC evaluations included an assessment of the clinical signs and symptoms of the infection, with the assessment of the clinical response based on the comparison of a patient's signs and symptoms at the EOT or Follow-Up Visit, respectively, to those recorded at trial admission,

Inclusion criteria

1. Male and female patients ≥ 18 years old
2. Clinical signs and symptoms consistent with pneumonia acquired after at least 48 hours of continuous stay in an inpatient acute or chronic-care facility, or acquired within 7 days after being discharged from a hospitalization of ≥ 3 days duration
    - At least two of the following signs and symptoms must be present:
        - cough,
        - purulent sputum or other deep respiratory specimen,
        - auscultatory findings of pneumonia,

- dyspnea, tachypnea, or hypoxemia,
- identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples.

AND

- At least two of the following must also be present:
- fever (> 38°C) or hypothermia (rectal/core temperature < 35°C),
- respiratory rate > 30 breaths/min,
- pulse rate ≥ 120 beats/min,
- altered mental status,
- need for mechanical ventilation,
- elevated total peripheral WBC count > 10,000 cells/mm^3, > 15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count < 4500 cells/mm^3.

3. A chest radiograph with findings consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion) within 48 hours prior to randomization in the study
4. Availability of appropriate respiratory or sputum specimens for Gram stain and culture, and venous access for IV dosing
5. Willing to receive IV therapy for the duration of treatment
6. Informed consent can be obtained for participation in this study as defined by the local Institutional Review Board or Ethics Committee

Exclusion criteria

1. Received more than 24 hours of potentially effective systemic (IV/IM or PO) antibiotic therapy for Gram-positive pneumonia immediately prior to randomization, (unless documented to have not responded to at least 3 days of treatment or if the isolated pathogen for the current pneumonia was resistant in vitro to previous treatment). For patients with renal impairment who have received one or more doses of vancomycin during the last week prior to the enrollment, please contact the Study Physician Helpline to determine eligibility.
2. Respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture
3. Known infection with MSSA or S. pneumoniae and patient will require more than 24 hours of concomitant study medication therapy with an antibiotic for Gram-negative coverage that has activity versus MSSA or S. pneumoniae (e.g., piperacillin-tazobactam)
4. Known or suspected pulmonary disease that precludes evaluation of therapeutic response (e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs); cystic fibrosis or active tuberculosis
5. Known or suspected *Legionella pneumophila* pneumonia
6. Known or suspected infection with an organism that is not susceptible to medications permitted by the protocol.
7. Documented or suspected meningitis, endocarditis, or osteomyelitis
8. Refractory shock defined as supine systolic blood pressure < 90 mm Hg for > 2 hours with evidence of hypoperfusion or requirement for high-dose sympathomimetic agents (dopamine ≥ 10 μg/kg/min or norepinephrine ≥ 0.1 μg/kg/min)
9. Baseline QTc > 500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K+ or Mg++ blood levels that cannot be corrected

10. Severely neutropenic (absolute neutrophil count < 500/mm³) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or have HIV with CD4 count < 100/mm³ during the last 6 months
11. Requirement for concomitant administration of intravenous Sporanox® (itraconazole), Vfend® (voriconazole), Geodon® (ziprasidone), or any other medication containing a cyclodextrin solubilizer
12. a) Female patients of childbearing potential if they are pregnant, nursing, or unable to use a highly effective method of birth control during the study and for at least one complete menstrual cycle following the last dose of study medication. A negative serum pregnancy result must be documented prior to treatment. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or a vasectomized partner.
    b) Male patients must agree to use medically acceptable birth control for a least three months following last dose of study medication. A vasectomy or a condom used with a spermicide is a medically acceptable birth control method for males.
13. Prior enrollment in a clinical trial of telavancin
14. Known hypersensitivity to, or intolerance of, study medications or their formulation excipients
15. Treatment with another investigational medication within 30 days of study entry
16. Considered unlikely to survive at least 7 days due to underlying illness
17. Considered unlikely to comply with the study procedures or to return for scheduled post-treatment evaluations
18. Any other condition that in the opinion of an investigator, would confound or interfere with evaluation of safety or efficacy of the investigational medication, or prevent compliance with the study protocol

Endpoints

Primary Efficacy

The primary efficacy endpoint is clinical response at TOC. Patients who were failures at End-of-therapy were not to have a Test-of-cure evaluation. Consequently, for purpose of analysis, a clinical response of "failure" at the End-of-therapy assessment will be extrapolated to the Test-of-cure evaluation, even if a value is recorded on the CRF at Follow-up/Test-of-cure.

Any patient who dies on or after Study Day 3 and before the Test-of-cure evaluation—or if no Follow-up/Test-of-cure evaluation was done, within 28 days (inclusive) after last study medication—where the death is attributable to the HAP episode under study, will be imputed to be a "failure" with respect to Clinical Response at TOC, regardless of any value recorded on the CRF for Clinical Response at TOC.

Secondary Efficacy Endpoints

- By pathogen microbiological response at TOC

By-pathogen microbiological response at the Follow-up visit is defined for each unique baseline respiratory pathogen. The endpoint is evaluated using culture results, if available; otherwise,

Clinical Response is presumed to be indicative of microbiological response and is used as a surrogate.

- By patient microbiological response
- All-cause mortality

Deaths will be identified from the Death Report CRF. Deaths will be identified through the Follow-up/Test-of-cure evaluation. If no Follow-up visit was made, deaths that occur within 28 days after last study medication (that is, through Post-treatment Study Day 28P, inclusive) will be considered

- Mortality attributable to primary infection
- Duration of study medication treatment
- Time to resolution of fever, i.e. > 38° F
- Length of stay in ICU
- Number of days on mechanical ventilation, for patients on ventilation at randomization

Safety endpoints

- Adverse events
- QT and QTc intervals
- Laboratory results: Hematology, serum chemistry, and urinalysis

Sample Size

At the time of protocol development, the study's planned enrollment of 312 patients per arm was expected to provide 109 clinically evaluable patients per arm, with the assumption that at least 35% of enrolled patients would be clinically evaluable. If the population clinical cure rates for telavancin and vancomycin are both 60%, then a one-sided, 0.025-level test of the non-inferiority of telavancin relative to vancomycin, and employing a non-inferiority Δ-criterion of 20%, has 86% power.

Analysis Populations

1. All-Treated (AT) analysis population was comprised of patients who received any amount of study medication. Patients were to be analyzed according to the treatment group assigned by randomization
2. Modified All-Treated: The "Modified All-Treated" (MAT) analysis population was comprised of patients in the AT population who had a baseline respiratory pathogen identified
3. Per Protocol (PP): MAT patients who had at least one Gram-positive baseline respiratory pathogen
4. MRSA: MAT patients who had at least one MRSA identified at baseline
5. Modified All-Treated – ATS/IDSA (MAT — ATS/IDSA): MAT Patients who met ATS/IDSA pneumonia criteria at baseline
6. Clinically Evaluable: The "Clinically Evaluable" (CE) analysis population was to be comprised of patients in the All-Treated population who received the study medication assigned by the randomization schedule and who meets all of the following criteria:
    - The patient met the following protocol inclusion criteria (IC), or else was approved for enrollment by the study hotline monitor:
        - IC #2, which requires certain signs and symptoms consistent with pneumonia

    - IC #3, which requires a chest radiograph consistent with a diagnosis of pneumonia
    - IC #4, which requires the availability of appropriate specimens for Gram stain and culture, and venous access for dosing.
- The patient did not violate the following protocol exclusion criteria (EC), or else was approved for enrollment by the study hotline monitor:
    - EC #1, which excludes patients who have received more than a specified amount of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization.
    - EC #2, which excludes patients with respiratory tract specimens or sputum with only Gram-negative bacteria
    - EC #3, which excludes patients with MSSA or S. pneumoniae who also require more than a specified amount of concomitant antibiotic therapy for Gram-negative coverage that has activity versus MSSA or *S. pneumonia*
    - EC#4, which excludes patients with known or suspected pulmonary disease that precludes evaluation of therapeutic response, cystic fibrosis, or active tuberculosis
    - EC #5, which excludes patients with known or suspected *Legionella pneumophila* pneumonia
    - EC #6, which excludes patients who are known or suspected to be infected with an organism that is not susceptible to medications permitted by the protocol.
    - EC #7, which excludes patients with documented or suspected meningitis, endocarditis, or osteomyelitis
- The patient's identified analysis pathogen(s) were not solely Gram-negative pathogens. That is, either the patient had a Gram-positive analysis pathogen, or no analysis pathogen was identified.
- The patient did not have pneumonia due to *Stenotrophomonas maltophilia* or *Burkholderia cepacia* at Baseline.
- The patient did not have a persistent S. aureus bacteremia, defined as two or more *S. aureus*-positive blood cultures on different days between Study Day 1 and TOC, inclusive.
- The patient did not receive more than two days of vancomycin or teicoplanin between Study Day -4 and Study Day 1, inclusive. The rationale for excluding patients who have received prior treatment with vancomycin is to exclude prior treatment failures to vancomycin. Only intravenous vancomycin will be considered as a potential basis for exclusion from the CE population; oral administration will not be a basis for exclusion.
- The patient was treated with the study medication assigned by the randomization.
- The patient received at least 80% of intended doses of active study medication.
- The patient did not receive potentially effective concomitant systemic antibiotic therapy for more than 2 calendar days any time before the TOC assessment. The day of the TOC assessment is not counted for this criterion.
- The patient was a "failure" at End-of-therapy, or else was either a "cure" or a "failure" at Test-of-cure.
- If the patient was not a "failure" at End-of-therapy, then the Test-of-cure assessment was made between Study Day 6P and Study Day 28P inclusive.
- If the patient was a "cure," the patient received at least 5 days of active study medication.

- If the patient was a "failure," the patient received active study medication daily through Study Day 3.

Additionally, for patients who died on or after Study Day 3, where the death is attributable to the HAP episode under study, the receipt of PEAT will not exclude them from the CE population

7. Microbiologically Evaluable: The "Microbiologically Evaluable" (ME) analysis population was to be comprised of patients in the CE population who also have a Gram-positive baseline respiratory pathogen

The primary analysis was to test both non-inferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the non-inferiority analysis, both the AT and CE analysis populations were considered co-primary. For the superiority analysis, the AT population served as the primary population.

> *Reviewer's Comment:*
> *For efficacy analyses, the analysis populations should exclude patients who had only gram-negative pathogens cultured at baseline. This approach is followed because neither the test article nor the active comparator have activity against gram-negative pathogens so the inclusion of patients who have gram-negative pathogens recovered at baseline could confound the drug effect for gram-positive pathogens due to effect of the adjunctive therapy and potentially bias the results toward falsely concluding noninferiority.*

The primary efficacy analysis was to initially test for the clinical non-inferiority of telavancin relative to vancomycin using a difference in the rate of clinical response at TOC and employing a non-inferiority margin of 20%. The testing was to be performed by using a 2-sided 95% confidence interval for the difference in clinical response rates based on the normal approximation to the binomial distribution. If any cell size is less than 10, as might occur during a subgroup analysis, the confidence interval will be calculated using the adjustment presented by Agresti and Caffo to adjust for the sparse cell size. If noninferiority was established, then statistical superiority would be examined using the confidence interval approach to determine whether the lower bound of 2-sided 95% confidence interval was greater than zero.

The disposition of patients is shown in Table 3. In Study 0015, there was trend that more telavancin patients [175/381 (45.9%)] compared to vancomycin patients [150/380 (39.5%)] prematurely discontinued study medication (difference=6.5%; 95% CI=(-0.5%, 13,5%), p-value=0.07). This difference in premature discontinuations was not seen in Study 0019.

Looking at the discontinuation categories for Study 0015, two categories stood out. The first category was having two consecutive ECGs with QTc > 500 msec that resulted in study drug discontinuation. Eight telavancin patients (2%) discontinued study medication for this reason compared to one vancomycin patient (<1%) [odds ratio=8.1; exact 95% CI=(1.1, 361.6;); Fisher's exact p-value=0.04). Secondly, there were a marginally significant difference in the discontinuations due to adverse events where 6% of the telavancin patients discontinued study medication due to adverse events compared to 3% of the vancomycin patients [odds ratio=2.0; exact 95% CI=(0.9, 4.8); Fisher's exact p-value=0.07).

Table 3: Disposition of Patients for Studies 0015 and 0019

	Study 0015		Study 0019	
	Telavancin (N=381) N (%)	Vancomycin (N=380) N (%)	Telavancin (N=386) N (%)	Vancomycin (N=385) N (%)
Randomized	381 (100%)	380 (100%)	386 (100%)	385 (100%)
Received Study Drug	372 (98%)	374 (98%)	377 (98%)	380 (99%)
Randomized by Not Treated	9 (2%)	6 (2%)	9 (2%)	5 (1%)
Completed Course Of Study Therapy	206 (55%)	230 (61%)	228 (60%)	224 (59%)
Resolution of Signs and Symptoms in ≤ 21 days	204 (55%)	229 (61%)	224 (59%)	216 (57%)
Infection not resolved but patient received maximum allowable 21 days of treatment	2 (<1%)	1 (<1%)	4 (1%)	8 (2%)
Premature Discontinuation of Study Medication	166 (45%)	144 (39%)	149 (40%)	156 (41%)
Unsatisfactory Therapeutic Response, Did Not Receive Maximum Allowable 21 Days of Treatment	28 (8%)	36 (10%)	25 (7%)	24 (6%)
Death	38 (10%)	29 (8%)	33 (9%)	31 (8%)
Two Consecutive ECGs with QTc > 500 msec	8 (2%)	1 (<1%)	5 (1%)	2 (<1%)
Adverse Event	22 (6%)	11 (3%)	16 (4%)	15 (4%)
Patient Withdrew Consent	11 (3%)	12 (3%)	15 (4%)	15 (4%)
Major Protocol Deviation	4 (1%)	0	2 (<1%)	4 (1%)
Infection due to Gram-negative Organisms only	11 (3%)	9 (2%)	5 (1%)	2 (<1%)
Infection due to *Stenotrophomonas Maltophllia* or *Burkholderia Cepacia*	0	4 (1%)	1 (<1%)	1 (<1%)
Persistent S. aureus Bacteremia	0	0	0	2 (<1%)
Gram-positive Coverage No Longer Clinically Indicated	27 (7%)	18 (5%)	42 (11%)	45 (12%)
Documented Meningitis, Endocarditis, or Osteomyelitis	0	0	1 (<1%)	2 (<1%)
Required Non-study Antibiotics	6 (2%)	5 (1%)	2 (<1%)	6 (2%)
Other	11 (3%)	19 (5%)	2 (<1%)	7 (2%)

Source: Summary of Clinical Efficacy, Tables 14 and 15 (original application)
2 patients in Study 0019 were randomized to the vancomycin group by received telavancin instead.

The number of patients in each treatment group was evenly balanced in the AT, CE, MAT, and ME population, see Table 3. As mentioned earlier, for efficacy analyses, patients who had only gram-negative pathogens isolated at baseline should be excluded because their inclusion has the potential to bias the analyses towards demonstrating noninferiority.

Table 4: Analysis Populations

Population	Study 0015		Study 0019	
	Telavancin n (%)	Vancomycin n (%)	Telavancin n (%)	Vancomycin n (%)
AT	372 (100)	374 (100)	377 (100)	380 (100)
AT – ATS/IDSA	309 (83)	316 (84)	325 (86)	339 (89)
Modified AT (MAT)	257 (69)	247 (66)	303 (80)	282 (74)
MAT – at least 1 gram+ pathogen	187 (50)	180 (48)	224 (59)	206 (54)
MAT-at least 1 gram+ pathogen – ATS/IDSA	157 (42)	155 (41)	194 (51)	188 (49)
MAT – only gram+ pathogens	137 (37)	135 (36)	130 (34)	125 (33)
MAT – only gram+ pathogens – ATS/IDSA	115 (31)	113 (30)	110 (29)	111 (29)

MRSA	115 (31)	114 (30)	118 (31)	117 (31)
MRSA – ATS/IDSA	97 (26)	99 (26)	99 (26)	105 (28)
CE	141 (38)	172 (46)	171 (45)	170 (45)
ME	108 (29)	113 (30)	135 (36)	124 (33)

Source: Modified from Summary of Clinical Efficacy, Table 44, current submission

The demographics of the AT population are summarized in Table 5. For each trial, the two treatment groups appeared similar with respect to the many baseline demographic characteristics presented in the table. However, on average, there were fewer patients from US sites in Study 0019 (14%) than for Study 0015 (31%). In addition, patients in Study 0015 had an increased rate of renal impairment, renal problems, and diabetes than patients in Study 0019.

Table 5: Baseline Demographics (AT Population)

	Study 0015		Study 0019	
	TLV (N=372)	VANC (N=374)	TLV (N=377)	VANC (N=380)
US vs. Non-US				
US	117 (31)	113 (30)	60 (16)	46 (12)
Non-US	255 (69)	261 (70)	317 (84)	334 (88)
Age				
Mean ± SD	63 ± 19.2	64 ± 17.3	61 ± 17.8	62 ± 18.0
Min, Max	18, 99	19, 97	18, 100	18, 97
Age Distribution				
<65 years	170 (46)	162 (43)	182 (48)	184 (48)
≥65 years	202 (54)	212 (57)	195 (52)	196 (52)
Age Distribution				
<75 years	241 (65)	250 (67)	278 (74)	271 (71)
≥75 years	131 (35)	124 (33)	99 (26)	109 (29)
Sex				
Male	235 (63)	213 (57)	252 (67)	256 (67)
Female	137 (37)	161 (43)	125 (33)	124 (33)
Race				
Asian	91 (24)	87 (23)	81 (21)	91 (24)
Black, of African heritage	10 (3)	14 (4)	15 (4)	6 (2)
White	267 (72)	272 (73)	248 (66)	254 (67)
Other including Mixed Race	4 (1)	1 (<1)	33 (9)	29 (8)
Type of Pneumonia				
VAP	103 (28)	100 (27)	113 (30)	111 (29)
Late VAP (≥4 days on ventilation at diagnosis	91 (24)	81 (22)	98 (26)	90 (24)
HAP	269 (72)	274 (73)	264 (70)	269 (71)
APACHE II (complete scores)				
Mean ± SD	16 ± 6.2	17 ± 5.8	16 ± 5.7	17 ± 6.2
0 - 13 Points	80 (37)	72 (35)	60 (33)	63 (32)
14 - 19 Points	75 (35)	78 (38)	70 (38)	74 (37)
≥20 Points	59 (28)	56 (27)	52 (29)	63 (32)
N	214	206	182	200
Medical History				

Diabetes	118 (32)	114 (30)	85 (23)	77 (20)
Congestive Heart Failure	71 (19)	78 (21)	59 (16)	63 (17)
COPD	86 (23)	90 (24)	87 (23)	88 (23)
Chronic Renal Failure	32 (9)	35 (9)	11 (3)	17 (4)
Shock	14 (4)	23 (6)	15 (4)	18 (5)
ARDS	24 (6)	20 (5)	9 (2)	10 (3)
Acute Lung Injury (but not ARDS)	33 (9)	20 (5)	18 (5)	13 (3)
ICU				
ICU at Baseline	224 (60)	216 (58)	207 (55)	224 (59)
Body Mass Index (kg/m^2)				
Underweight < 18.5 (kg/m^2)	28 (8)	29 (8)	41 (11)	37 (10)
Normal Wt 18.5 - < 25 (kg/m^2)	150 (40)	163 (44)	172 (46)	189 (50)
Overweight 25 - < 30 (kg/m^2)	108 (29)	99 (26)	119 (32)	107 (28)
Obese 30 - < 40 (kg/m^2)	63 (17)	64 (17)	39 (10)	42 (11)
Morbidly Obese ≥40 (kg/m^2)	20 (5)	16 (4)	6 (2)	5 (1)
Missing	3 (<1)	3 (<1)	0	0
Baseline Serum Creatinine Clear				
Clearance (central lab unless missing)				
>80 mL/min	143 (38)	152 (41)	181 (48)	181 (48)
>50-80 mL/min	88 (24)	88 (24)	96 (25)	90 (24)
30-50 mL/min	80 (22)	83 (22)	62 (16)	68 (18)
<30 mL/min	61 (16)	51 (14)	38 (10)	41 (11)
Diabetes status at baseline				
Non-diabetic	272 (73)	274 (73)	308 (82)	315 (83)
Diabetic	100 (27)	100 (27)	69 (18)	65 (17)
Hemodialysis				
Patient on hemodialysis	11 (3)	9 (2)	3 (<1)	5 (1)
Acute renal failure	43 (12)	35 (9)	30 (8)	29 (8)
VAP	103 (28)	100 (27)	113 (30)	111 (29)
Late VAP (≥4 days on ventilator at diagnosis)	91 (24)	81 (22)	98 (26)	90 (24)
Radiologic characteristics				
Multilobar Involvement	238 (64)	229 (61)	235 (62)	231 (61)
Pleural Effusion	125 (34)	132 (35)	112 (30)	112 (29)
Prior antibacterial use (>24h prior to enrollment)	181 (49)	209 (56)	210 (56)	218 (57)
Pathogen resistant to prior antibacterial therapy	34 (19)	41 (20)	58 (28)	61 (28)
Failed prior antibacterial therapy for HAP	88 (49)	86 (41)	127 (60)	125 (57)

Source: ISE, Table 5-11; CSR, Supporting Tables 31, 33, and 34 (original application), SCE Table 45 (current submission)

Other baseline microbiological characteristics in the MAT population are provided in Table 6. The two treatment arms are similar for the baseline pathogens. It should be noted that only a relative small number of patients had *Streptococcus pneumoniae* recovered (telavancin: 29; vancomycin: 30). Additionally, only a few patients had *Enterococcus faecalis* or *Enterococcus faecium* recovered

Table 6: Baseline Gram-Positive Respiratory Pathogens (Micro AT Population)

	Study 0015		Study 0019	
Population	Telavancin (n=257)	Vancomycin (n=247)	Telavancin (n=303)	Vancomycin (n=282)
Gram-positive pathogens	181 (70%)	178 (72%)	220 (73%)	205 (73%)
Staphylococcus aureus	168 (65.4%)	170 (68.8%)	199 (65.7%)	178 (63.1%)
MRSA	111 (43.2%)	113 (45.7%)	117 (38.6%)	117 (41.5%)
MSSA	61 (23.7%)	57 (23.1%)	83 (27.4%)	63 (22.3%)
Streptococcus pneumoniae	15 (5.8%)	7 (2.8%)	14 (4.6%)	23 (8.2%)
Enterococcus faecalis	3 (1.2%)	6 (2.4%)	10 (3.3%)	13 (4.6%)
Enterococcus faecium	1 (0.4%)	0 (0.0%)	3 (1.0%)	1 (0.4%)
Gram-negative pathogens	118 (46%)	111 (45%)	171 (56%)	155 (55%)
Pseudomonas aeruginosa	43 (16.7%)	36 (14.6%)	67 (22.1%)	56 (19.9%)
Acinetobacter calcoaceticus	15 (5.8%)	18 (7.3%)	41 (13.5%)	34 (12.1%)
Klebsiella pneumoniae	14 (5.4%)	19 (7.7%)	26 (8.6%)	34 (12.1%)
Escherichia coli	18 (7.0%)	7 (2.8%)	18 (5.9%)	11 (3.9%)
Haemophilus influenzae	15 (5.8%)	9 (3.6%)	10 (3.3%)	8 (2.8%)
Stenotrophomonas maltophilia	8 (3.1%)	8 (3.2%)	18 (5.9%)	6 (2.1%)
Enterobacter cloacae	6 (2.3%)	9 (3.6%)	12 (4.0%)	9 (3.2%)
Proteus mirabilis	5 (1.9%)	9 (3.6%)	5 (1.7%)	6 (2.1%)
Serratia marcescens	7 (2.7%)	3 (1.2%)	4 (1.3%)	4 (1.4%)
Acinetobacter baumanii	3 (1.2%)	2 (0.8%)	4 (1.3%)	4 (1.4%)
Klebsiella oxytoca	2 (0.8%)	2 (0.8%)	3 (1.0%)	6 (2.1%)
Enterobacter aerogenes	3 (1.2%)	2 (0.8%)	3 (1.0%)	2 (0.7%)

Source: SCE, Table 53 (current submission)

The dosing in the study was designed to be for 7-21 days in length for both trials. As can be seen in Table 7, most patients (42%-44%) received 7-10 days of treatment.

Table 7: Days of Study Medication (AT population)

	0015		0019		Pooled	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
<3 Days	23 (6%)	15 (4%)	17 (5%)	17 (4%)	40 (5%)	32 (4%)
3-6 Days	77 (21%)	62 (17%)	52 (14%)	53 (14%)	129 (17%)	115 (15%)
7-10 Days	152 (41%)	172 (46%)	163 (43%)	160 (42%)	315 (42%)	332 (44%)
11-14 Days	79 (21%)	85 (23%)	95 (25%)	97 (26%)	174 (23%)	182 (24%)
15-21 Days	39 (10%)	38 (10%)	48 (13%)	47 (12%)	87 (12%)	85 (11%)
>21 Days	2 (<1%)	2 (<1%)	2 (<1%)	6 (2%)	4 (<1%)	8 (1%)
- Total -	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)

Source: ISE, Table 5-20

The pre-specified primary analysis was to evaluate non-inferiority based on the difference between the telavancin and vancomycin groups for the investigator's assessment of clinical response rates at the Test of Cure (TOC) visit using an NI margin of 20%. If noninferiority was demonstrated, then the superiority of telavancin to vancomycin for clinical response at the Test of Cure assessment would be evaluated. For the non-inferiority analysis, both the AT and CE

analysis populations were considered co-primary. For the superiority analysis, the AT population served as the primary population.

The results for investigator assessment of clinical response are given in Table 8. However, it is difficult to interpret the results of these noninferiority analyses for clinical response because the lack of historical data for this endpoint does not allow one to estimate the treatment effect of the active comparator. This estimate is an essential in determining a non-inferiority margin to be used in the interpretation of the results.

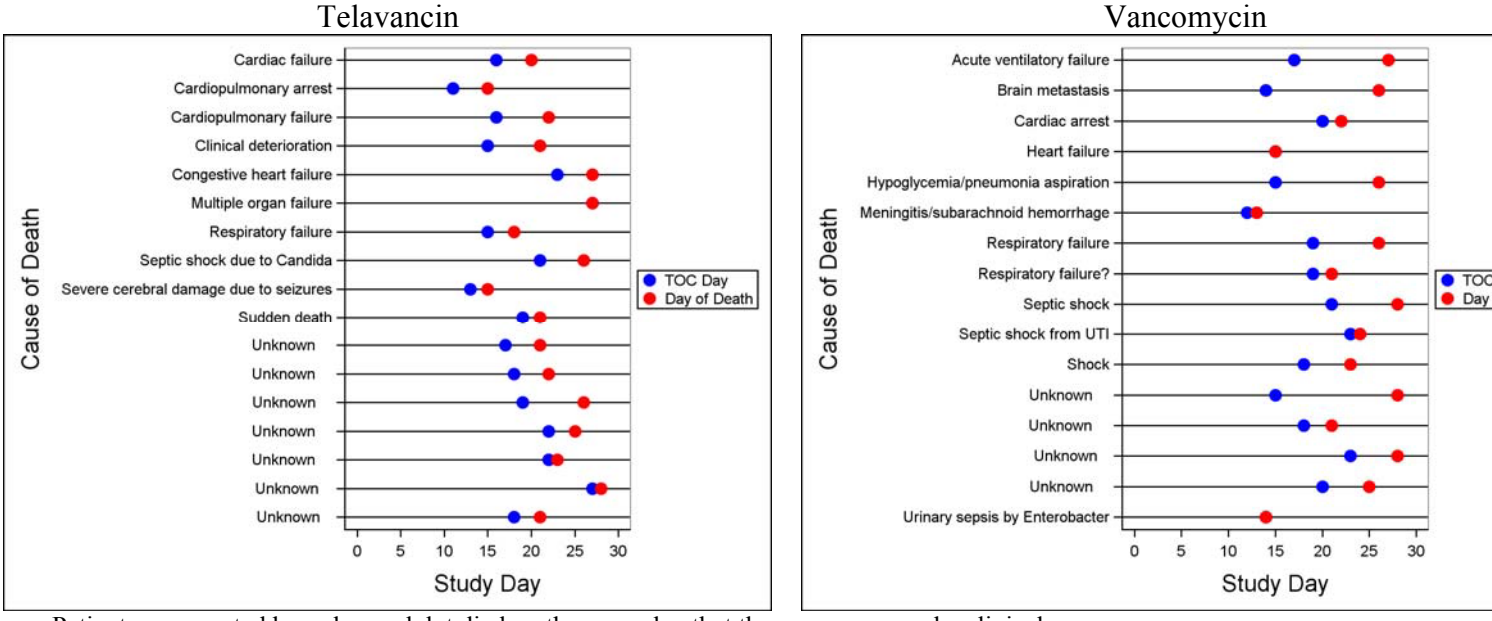
Table 8: Clinical Response at TOC

Population	0015			0019		
	Telavancin N (%)	Vancomycin N (%)	Difference (%) (95% CI)*	Telavancin N (%)	Vancomycin N (%)	Difference (%) (95% CI)*
All-Treated	214/372 (57.5)	221/374 (59.1)	-1.6 (-8.6, 5.5)	227/377 (60.2)	228/380 (60.0)	0.2% (-6.7, 7.2)
All-Treated — ATS/IDSA	182/309 (58.9)	184/316 (58.2)	0.7 (-7.0, 8.4)	194/325 (59.7)	202/339 (59.6)	0.1 (-7.3, 7.5)
MAT – at least 1 gram+ pathogen	108/187 (57.8)	106/180 (58.9)	-1.1 (-11.2, 8.9)	131/224 (58.5)	124/206 (60.2)	-1.7 (-10.9, 7.6)
MRSA	68/115 (59.1)	66/114 (57.9)	1.2 (-11.4, 13.9)	59/118 (50.0)	63/117 (53.8)	-3.8 (-16.4, 8.9)
Clinically Evaluable	118/141 (83.7)	138/172 (80.2)	3.5 (-5.2 , 11.9)	139/171 (81.3)	138/170 (81.2)	0.1 (-8.2 , 8.4)

*95% CI calculated based on Agresti-Caffo method

In the two trials, there were thirty-three patients who the investigator classified as clinical cures at the TOC assessment but who died within the 28-day window (Table 26 contains a patient listing and a graphical display is given in Figure 1). Most of the deaths occurred in close temporal proximity to the cure assessment and for many of the patients, based on investigator reported cause of death, it was not possible to have assurance that the deaths were unrelated to the nosocomial pneumonia. This phenomenon has been seen in several recent NP trials. Two possible explanations for this phenomenon are that the clinical response endpoint is not well defined and reliable or alternatively, there could be an issue with determining the mortality window that maximizes the number of deaths related to NP and minimizes the number of non-infection related deaths.

Figure 1: Patients who were TOC Clinical Cure and Died by Day 28 (Studies 0015 and 0019 AT Population)



Patients represented by only a red dot died on the same day that they were assessed a clinical cure
Cause of death was based on the investigator's determination

Table 9: Clinical Cures at TOC and Deaths by Day 28

	Pooled		Study 0015		Study 0019	
	Telavancin (N=749)	Vancomycin (N=754)	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=377)	Vancomy (N=38
Subjects who Died up to Day 28	178 (24%)	164 (22%)	95 (26%)	74 (20%)	83 (22%)	90 (24%)
Subjects with Cure at TOC	441 (59%)	449 (60%)	214 (58%)	221 (59%)	227 (60%)	228 (60%
Subjects with Both Cure at TOC and Death by Day 28	17	16	11	5	6	11

The distribution of the time between the TOC assessment of cure and the subsequent death within the 28-day windows is provided below:

Table 10: Time between TOC Assessment of Cure and Death

Time (Days) Between Cure and Death	Pooled		Study 0015		Study 0019	
	Telavancin (N=749)	Vancomycin (N=754)	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=377)	Vancomycin (N=380)
Mean (SD)	3.5 (1.91)	5.3 (4.36)	3.5 (2.02)	4.2 (4.97)	3.5 (1.87)	5.7 (4.22)
Median	4	5	4	2	4	5
(Min, Max)	(0, 7)	(0, 13)	(0, 7)	(1, 13)	(1, 6)	(0, 12)
n	17	16	11	5	6	11

Assay sensitivity is critical to support the conclusions of an adequate and well-controlled trial. Due to concern regarding potential inconsistencies for patients who were considered clinical cures but who subsequently died in close temporal proximity to the assessment, sensitivity

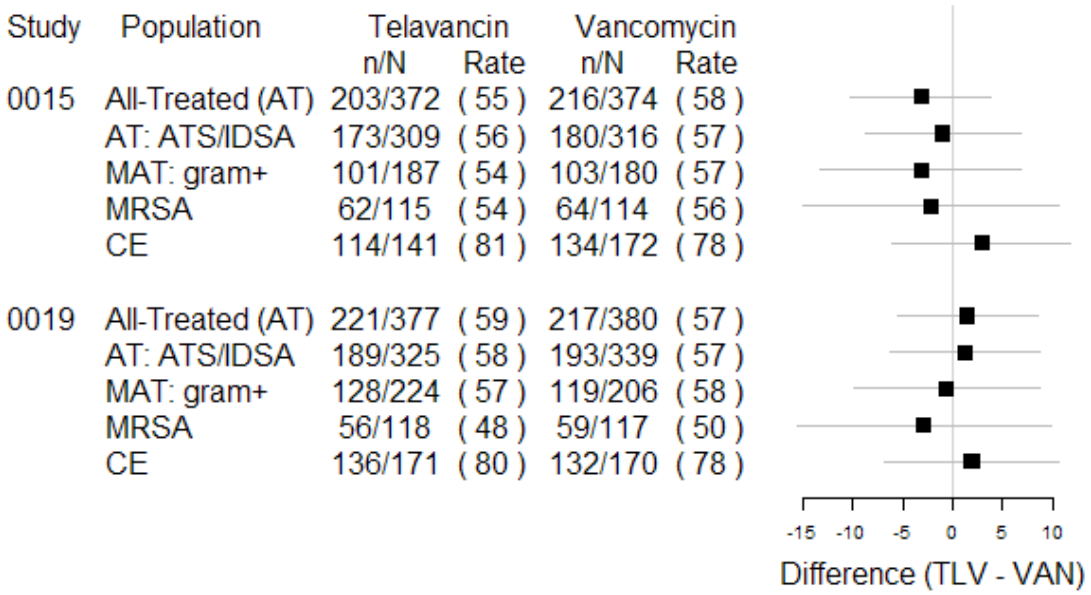
analyses were performed where patients who died by Study Day 28 were considered clinical failures. The results of these analyses are presented in Table 11 and Figure 2.

Table 11: Clinical Response at TOC (Deaths by Day 28 Considered Failures)

Population	0015			0019		
	Telavancin N (%)	Vancomycin N (%)	Difference (%) (95% CI)	Telavancin N (%)	Vancomycin N (%)	Difference (%) (95% CI)
All-Treated	372	374		377	380	
Cure	203 (54.6)	216 (57.8)	-3.2 (-10.3, 3.9)	221 (58.6)	217 (57.1)	1.5 (-5.5, 8.5)
All-Treated — ATS/IDSA	309	316		325	339	
Cure	173 (56)	180 (57)	-1 (-8.7, 6.8)	189 (58.2)	193 (56.9)	1.2 (-6.3, 8.7)
MAT – at least 1 gram+ pathogen	187	180		224	206	
Cure	101 (54)	103 (57.2)	-3.2 (-13.3, 6.9)	128 (57.1)	119 (57.8)	-0.6 (-9.9, 8.7)
MRSA	115	114		118	117	
Cure	62 (53.9)	64 (56.1)	-2.2 (-15, 10.6)	56 (47.5)	59 (50.4)	-3 (-15.6, 9.8)
Clinically Evaluable	141	172		171	170	
Cure	114 (80.9)	134 (77.9)	2.9 (-6.1, 11.8)	136 (79.5)	132 (77.6)	1.9 (-6.8, 10.6)

95% CI calculated based on Agresti-Caffo method

Figure 2: Clinical Response at TOC (Deaths Considered Failures)



95% CI calculated based on Agresti-Caffo method

We also looked at the effect of baseline creatinine clearance on clinical response at TOC and the findings are as follows:

Table 12: Clinical Response at TOC by Baseline Renal Function

Population	0015			0019		
	Telavancin N (%)	Vancomycin N (%)	Difference (%) (95% CI)	Telavancin N (%)	Vancomycin N (%)	Difference (%) (95% CI)
All-Treated (Cure)	372	374		377	380	
>80 mL/min	92/143	95/152	1.8	122/181	107/181	8.3
	(64.3)	(62.5)	(-9.1, 12.7)	(67.4)	(59.1)	(-1.7, 18)
>50-80 mL/min	50/88	58/88	-9.1	55/96	49/90	2.8
	(56.8)	(65.9)	(-23.1, 5.3)	(57.3)	(54.4)	(-11.3, 16.9)
30-50 mL/min	38/80	43/83	-4.3	33/62	42/68	-8.5
	(47.5)	(51.8)	(-19.4, 11.0)	(53.2)	(61.8)	(-25, 8.4)
<30 mL/min	23/61	20/51	-1.5	11/38	19/41	-17.4
	(37.7)	(39.2)	(-19.3, 16.3)	(28.9)	(46.3)	(-37.1, 4.1)
MAT – at least 1 gram+ pathogen (Cure)	187	180		224	206	
>80 mL/min	44/77	47/74	-6.4	76/111	64/104	6.9
	(57.1)	(63.5)	(-21.6, 9.2)	(68.5)	(61.5)	(-5.8, 19.5)
>50-80 mL/min	26/47	27/38	-15.7	31/60	22/44	1.7
	(55.3)	(71.1)	(-34.8, 5)	(51.7)	(50)	(-17.5, 20.7)
30-50 mL/min	21/39	19/43	9.7	14/33	20/34	-16.4
	(53.8)	(44.2)	(-11.9, 30.3)	(42.4)	(58.8)	(-38.5, 7.5)
<30 mL/min	10/24	10/25	1.7	7/20	13/24	-19.2
	(41.7)	(40.0)	(-25, 28.1)	(35)	(54.2)	(-45.3, 10.3)

Based on central lab serum creatinine measurements unless missing where local lab measurements are used
95% CI calculated based on Agresti-Caffo method

Based on an Agency review of the literature (Sorbello et al., 2010) and the discussion at the 2009 NP workshop co-sponsored by the Agency, the clearest evidence of treatment effect was based on all-cause mortality. However, the historical literature did not provide a uniform timepoint for the assessment of mortality. The mortality reporting window should be of adequate length such that the outcome of interest reflects the attributable clinical effect of the drug rather than being confounded by the underlying comorbidities. In addition, ideally, the timing of the assessment should be prospectively defined to avoid any kind of post-hoc selection. However, at the present time there is not a clear consensus on the appropriate timing of assessment. Discussion at the workshop focused on the timepoint of 28 days after randomization/initiation of therapy. This is why the Agency analyses will focus on 28-day all-cause mortality.

Based on the literature review (Sorbello et al., 2010) and the large active control treatment effect, found in the Agency meta-analyses, it was felt that a 10% noninferiority margin was justifiable based on clinical judgment. Note there were concerns with using an NI margin of greater than 10% for a mortality endpoint because this would equate to considering a new treatment to be noninferior to a comparator when mortality could be increased by greater than 10%.

In the original NDA, there was incomplete survival information for the 28-day period in a large proportion of the patients (Study 0015: 34.9%; Study 0019: 28.5%). This occurred primarily because the protocols for 0015 and 0019 required that safety data through the follow-up visit (7-14 after EOT) be reported for each patient. Because the duration of treatment was 7-21 days with most patients receiving 7-10 days of study drug (see Table 7), a large number of patients were not followed up to Day 28. The Applicant retrospectively went back and determined survival

status. In the new submission, the percentage of patients with incomplete survival information for the 28-day period has substantially decreased (Study 0015: 6%; Study 0019: 5%).

The distribution of the last day that patients were known to be alive is shown below:

Table 13: Last Day Patient is Known to be Alive for those Missing 28-day Survival Information

	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

After review of the original NDA and recovery of much of the incomplete mortality data, incomplete data was reduced to 6% in Study 0015 and 5% in Study 0019. Patients with missing data at Day 28 were designated as censored observations.

Table 14: Vital Status at Day 28 by Study – AT Population

	Study 0015		**Study 0019**		**Total**	
	TLV (N=372)	**VAN (N=374)**	**TLV (N=377)**	**VAN (N=380)**	**TLV (N=749)**	**VAN (N=754)**
	Number of Patients (%)					
Dead	95 (25.5%)	74 (19.8%)	83 (22.0%)	90 (23.7%)	178 (23.8%)	164 (21.8%)
Alive	258 (69.4%)	272 (72.7%)	277 (73.5%)	270 (71.1%)	535 (71.4%)	542 (71.9%)
Censored	19 (5.1%)	28 (7.5%)	17 (4.5%)	20 (5.3%)	36 (4.8%)	48 (6.4%)

Adapted from Applicant's ISE addendum Table 4-1

The results based on 28-day all-cause mortality rates for Study 0015 and Study 0019 for various analyses populations are given in Figure 3. The results for the AT population for Study 0015 are concerning because 1) telavancin mortality rate is almost significantly (p=0.06) higher than vancomycin (treatment difference: 5.8%; 95% CI: (-0.3%, 11.9%) in Study 0015; and 2) the upper bound for Study 0015 is markedly higher than the NI margin of 10%.

The 28-day all-cause mortality results for the AT and the Agency defined primary analysis population of patients who had at least one gram-positive pathogen isolated at baseline are presented in Figure 3. In addition, the results for the Applicant defined primary population of treated patients who met ATS/IDSA criteria at baseline as well as the patients who had MRSA isolated at baseline are also presented.

In Study 0015, telavancin is tending do to a little worse than vancomycin for all-cause mortality in the AT, AT-ATS/IDSA. ≥1 gram+, and MRSA populations. It should be noted that the upper bound is higher than the 10% NI margin for all of the populations except for the AT-ATS/IDSA. Of particular concern is that the lower bound of the 95% CI in the AT population is just below zero showing that the mortality was almost statistically significantly higher for the telavancin patients then the vancomycin patients. Note this was not seen in Study 0019.

In Study 0019, the mortality rates are more similar between groups and the upper bound of the 95% CI was less than or equal to the 10% for all of the populations except for the MRSA population.

The results from the two trials appear to be different. It should be noted that there were more patients enrolled in Study 0015 from the US. In addition, Study 0015 enrolled more patients with baseline renal impairment and risk factors for renal injury.

Figure 3: 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)
	MAT: 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)	339	(24.1)	-1.1 (-7.7, 5.4)
	MAT: gram+	224	(24.3)	206	(22.3)	2.0 (-6.1, 10)
	MRSA	118	(33.3)	117	(30.3)	3.0 (-9.0, 15..0)

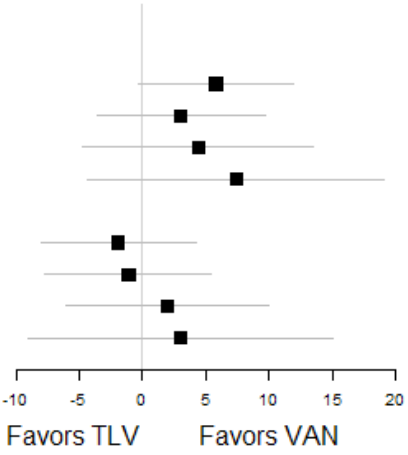
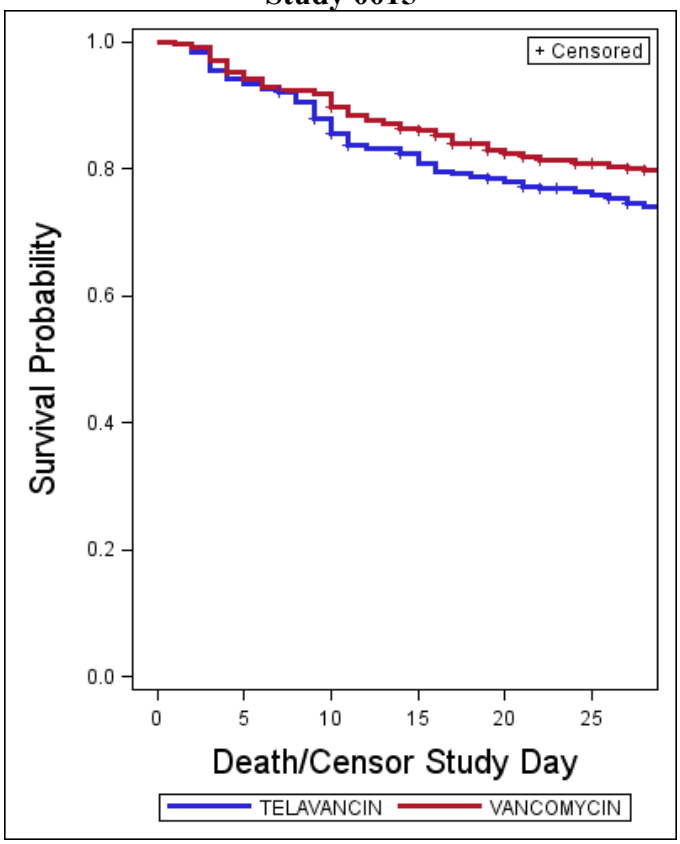


Table 15 contains the Kaplan-Meier survival curves in the AT population. The telavancin group is represented by the blue curve and the vancomycin group by the red curve. In Study 0015, the curves begin to diverge at 7-10 after the initiation of study drug with the telavancin curve falling below the vancomycin curve. For Study 0019, the curves are relatively close together.

Table 15: K-M Survival Curves (AT Population)

Study 0015



Study 0019

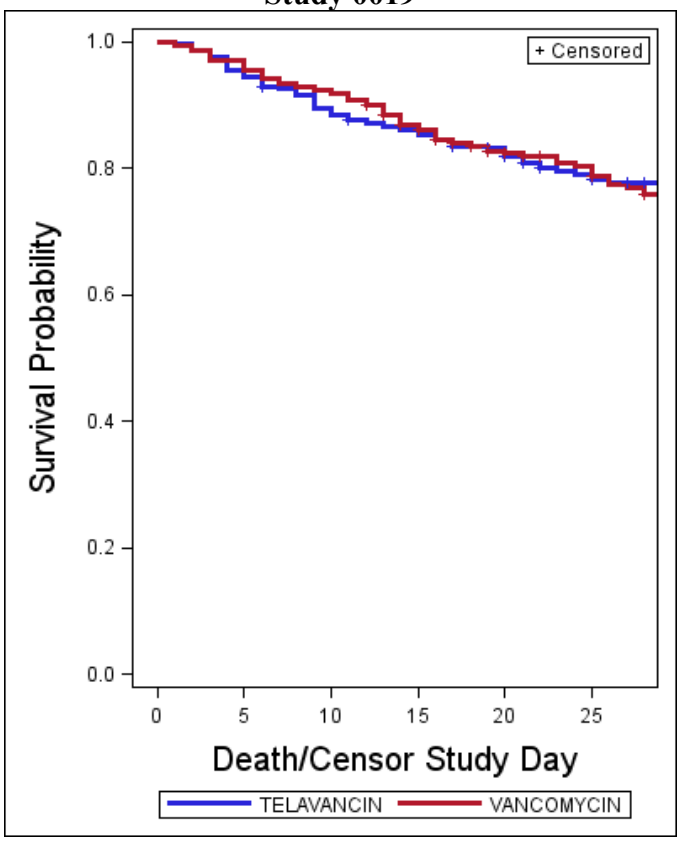
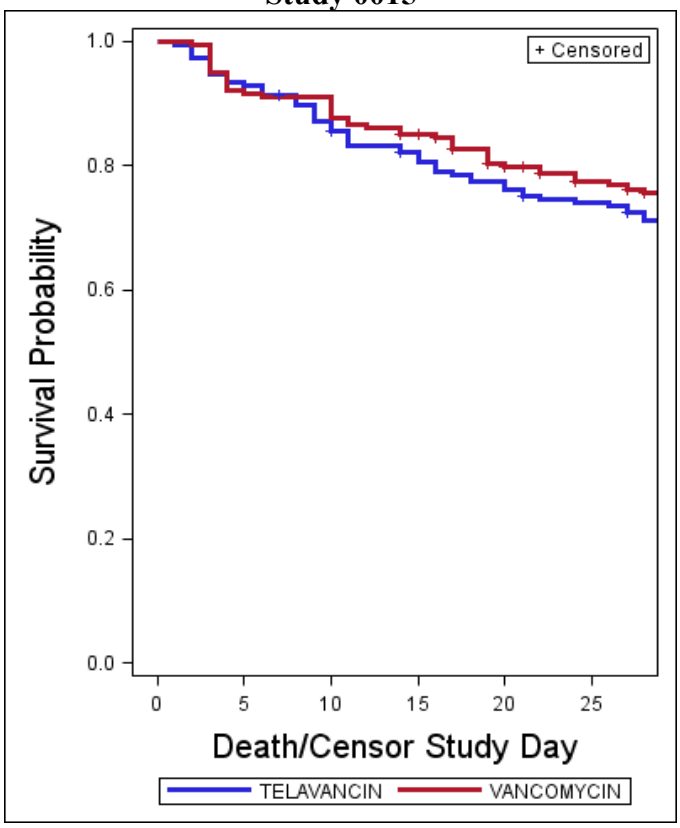


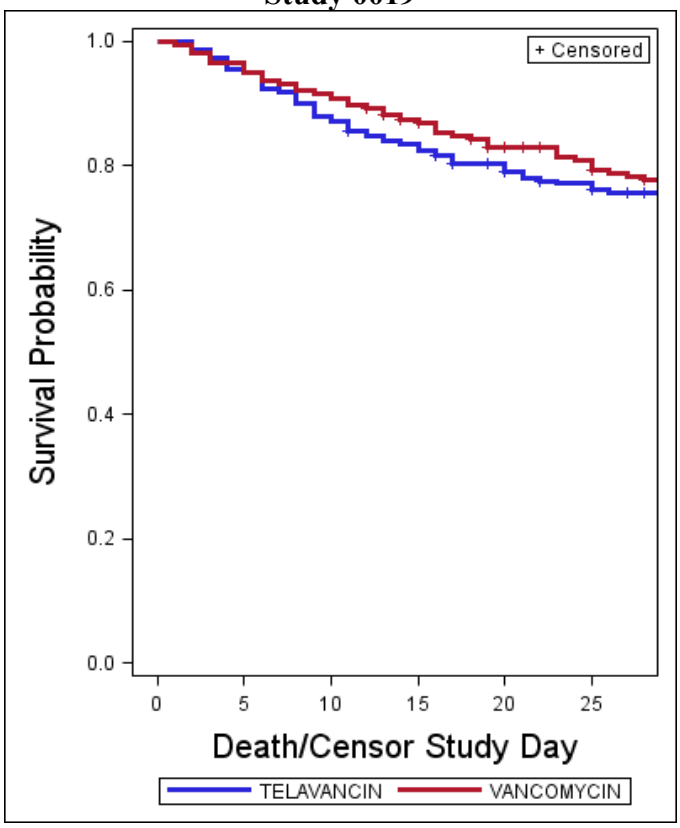
Table 16 contains the Kaplan-Meier survival curves in the patients who had at least one gram-positive pathogen isolated at baseline. The blue curve represents the telavancin group and the red curve represents the vancomycin group. In both studies, the curves begin to diverge at 7-10 after the initiation of study drug with the telavancin curve falling below the vancomycin curve. However, in Study 0015, the curves continue to stay separated through Day 28 while for Study 0019, the curves come together by Day 28 with the vancomycin patients suffering more late deaths

Table 16: K-M Survival Curves (≥1 baseline gram+ pathogen)

Study 0015



Study 0019



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. The prior evidence of renal effects are the renal findings that were seen in the complicated skin and skin structure infection (cSSSI) application (NDA 22-110), where there was a finding of decreased efficacy among patients with moderate/severe pre-existing renal impairment (baseline CrCl ≤50 mL/min) included in the Warnings and Precautions section of the current telavancin label. In addition, concerns for nephrotoxicity based on new onset or worsening renal impairment occurred in the both the cSSSI (NDA 22-110) application as well as the current HAP/VAP application. Finally, renal toxicity was seen in the preclinical studies.

Baseline variables that either measure renal function or are risk factors for renal injury were tested for a homogeneous treatment effect across the levels of the variables. The results are given in Table 17. The possible effect modifiers that were identified are baseline creatinine clearance in Study 0019 , congestive heart failure in Study 0015, and receipt of nephrotoxic drugs at baseline in both studies.

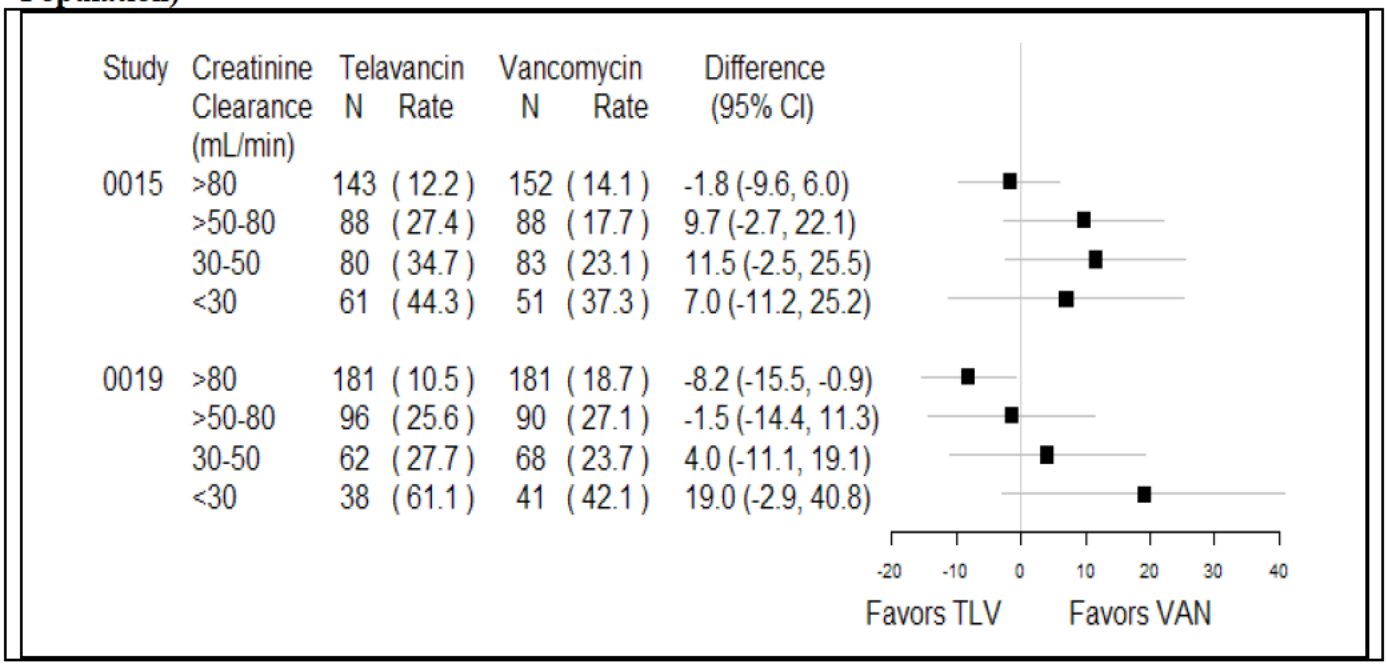
Table 17: Potential Effect Modifiers for 28-day All-Cause Mortality (AT Population)

	p-value*	
	Study 0015	Study 0019
Baseline creatinine clearance	0.25	**0.08**
History of diabetes	0.72	0.76
Age (<65, ≥65)	0.84	0.58
Congestive heart failure	**0.08**	0.82
Baseline nephrotoxic medications	**0.06**	**0.08**

* p-value for baseline creatinine clearance is based on a Cochran's Q test with 3 degrees of freedom and an interaction contrast test for the other risk factors.

Figure 4 contains the 28-day all-cause mortality results in the all-treated population by baseline creatinine clearance. In Study 0015, the results tend to favor vancomycin for patients with baseline creatinine clearance < 80 ml/min. For Study 0019, the treatment effect of telavancin relative to vancomycin decreases as baseline renal function worsens. Note, this is the same relationship seen in the cSSSI trials for the clinical response at TOC endpoint.

Figure 4: 28-day Mortality (K-M estimates) stratified by baseline creatinine clearance (AT Population)



(b) (4)

there is a real concern of a mortality imbalance for patients who had a baseline creatinine clearance ≤50 mL/min.

Figure 5 presents the 28-day all-cause mortality results for patients who had at least 1 gram+ pathogen isolated at baseline stratified by baseline creatinine clearance. The results are similar to those in the all-treated population. In study 0015, the results again tend to favor vancomycin for patients with baseline creatinine clearance < 80 ml/min and similar to the AT analyses, in study 0019, the treatment effect of telavancin relative to vancomycin decreases as baseline renal function worsens.

Figure 5: 28-day Mortality (K-M estimates) stratified by baseline creatinine clearance (≥1 baseline gram+ pathogen Population)

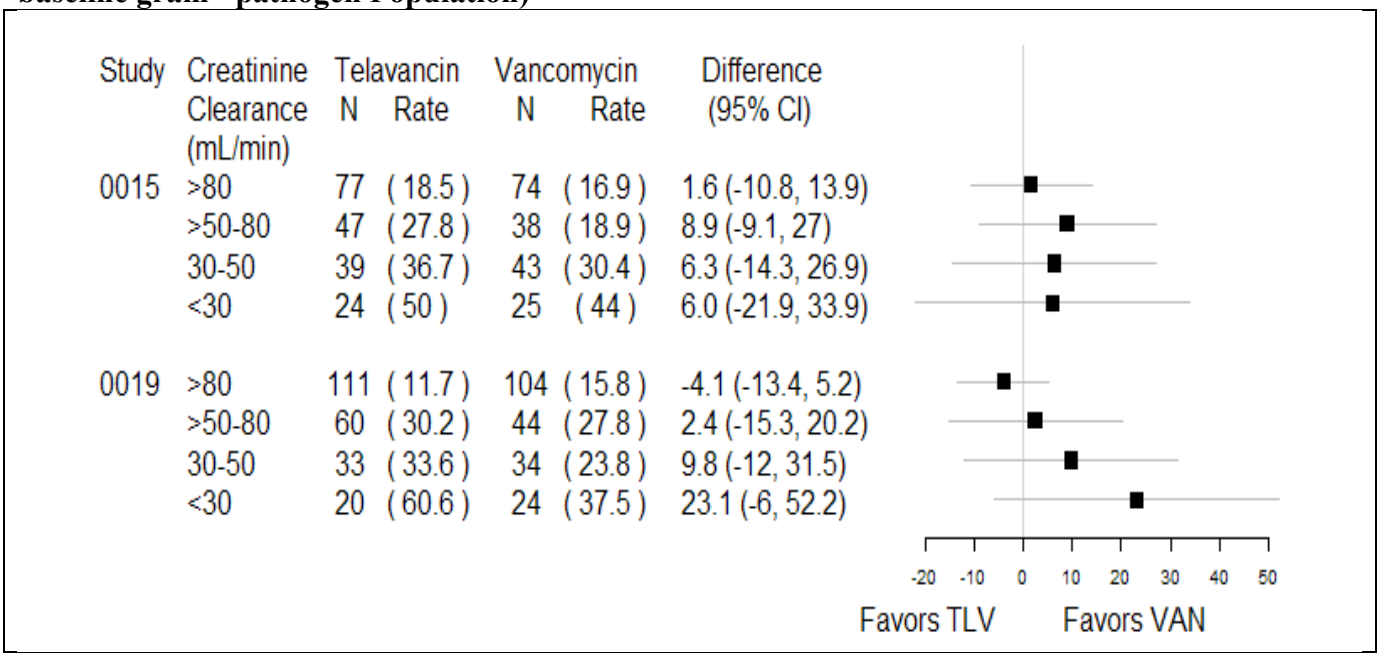
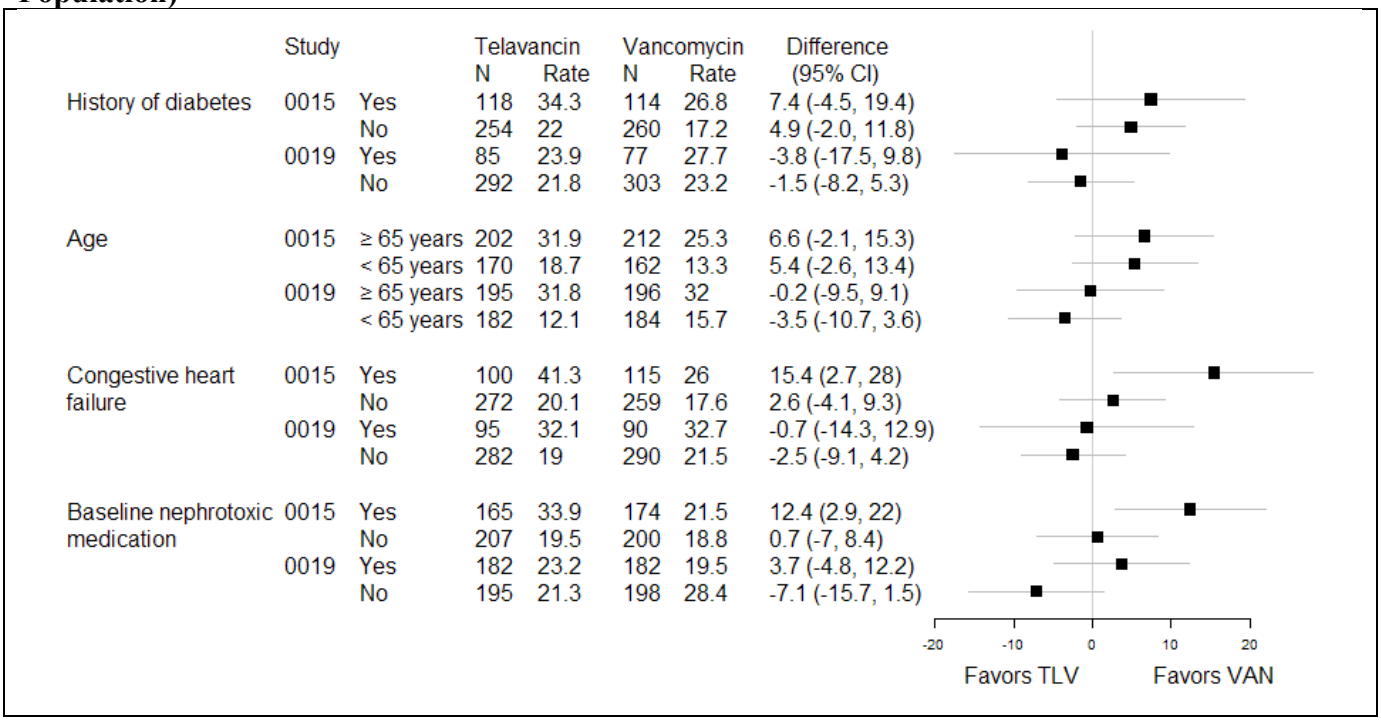


Figure 6 presents the analyses of 28-day all-cause mortality stratified by other risk factors for renal injury in the AT population. In analyses stratified by a baseline history of diabetes, the treatment differences do not vary based on the history of diabetes in either of the trials. Similarly, in the analyses stratified by age, where age groups are classified by those ≥65 years of age and those <65 years, the treatment difference also does not vary across the age strata in either of the trials. In contrast, in the analyses stratified by a history of congestive heart failure for Study 0015, there is a differential treatment effect across the strata where the analyses strongly favor vancomycin for patients with a history of congestive heart failure and the mortality rates appear to be similar for patients without a history of congestive heart failure. This is not seen in Study 0019 where the two treatments appear similar regardless of the history of congestive heart disease. Finally, in the analyses stratified by the receipt of baseline nephrotoxic medications, there is a differential treatment effect in both trials where, patients who received baseline nephrotoxic medications fared worse on telavancin relative to vancomycin. In contrast, the relative treatment effect in patients who did not receive baseline nephrotoxic medications differed from those who did. This occurred in both trials.

Figure 6: 28-Day All-Cause Mortality — Other Risk Factors for Renal Injury (AT Population)



3.3 Evaluation of Safety

The patients analyzed for safety are presented in Table 18.

Table 18: Safety Population

Study Group	TLV 10 mg/kg	Vanc
Study 0015	372	374 [1]
Study 0019	379	378 [2]
TOTAL (Studies 0015 and 0019)	751	752 [3]

[1] Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin
[2] Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin
[3] Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin
Source: ISS, Table 3-3

Renal treatment-emergent adverse events (TEAE) stratified by baseline creatinine are presented in Table 19. It can be seen for both trials that patients with baseline creatinine > 1.2 mg/dL have more TEAEs in the telavancin group than the vancomycin group. This did not occur in patients with a baseline creatinine≤1.2 mg/dL.

Table 19: Treatment-emergent Renal Adverse Events

	Study 0015		Study 0019	
Baseline Creatinine category	Telavancin (N=372)	Vancomycin (N=374)	Telavancin (N=379)	Vancomycin (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 Patient count with renal TEAE	38 (10.2)	30 (8.0)	37 (9.8)	29 (7.7)

Renal treatment-emergent adverse events by Preferred Term are presented in Table 20. Acute renal failure was the most common TEAE and was higher for telavancin patients in Study 0015. This imbalance was not seen in Study 0019. Additionally, there were more telavancin patients who had increased blood creatinine during the trial in Study 0015. Again, this imbalance was not seen in Study 0019.

Table 20: Renal Treatment-Emergent Adverse Events by Preferred Term

Preferred Term	Study 0015		Study 0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
BLOOD CREATININE INCREASED	11 (3.0)	6 (1.6)	7 (1.8)	6 (1.6)
RENAL FAILURE ACUTE	18 (4.8)	10 (2.7)	16 (4.2)	18 (4.8)
RENAL FAILURE CHRONIC	2 (0.5)	1 (0.3)	2 (0.5)	0 (0.00)
RENAL IMPAIRMENT	2 (0.5)	3 (0.8)	6 (1.6)	4 (1.1)
RENAL INSUFFICIENCY	5 (1.3)	8 (2.1)	7 (1.8)	3 (0.8)
RENAL TUBULAR ACIDOSIS	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)

The 28-day all-cause mortality results with patients classified by the treatment they received are presented in Table 21. These results are similar to those presented in Figure 3 because there were only two patients in Study 0019 who did not receive the treatment they were randomized to.

Table 21: 28-day all-cause mortality K-M estimates

Population	Study 0015 Mortality (N)					Study 0019 Mortality (N)				
	TLV	VAN	Diff	95% CI		TLV	VAN	Diff	95% CI	
AT	25.9% (372)	20.1% (374)	5.8%	-0.3%	**11.9%**	22.3% (377)	24.2% (380)	-1.9%	-8.0%	**4.2%**
≥1 gram+	28.7% (187)	24.3% (180)	4.4%	-4.7%	**13.5%**	24.3% (224)	22.3% (206)	2.0%	-6.1%	**10.0%**
Only gram+	27.5% (137)	25.8% (135)	1.7%	-8.9%	**12.3%**	18.5% (130)	24.5% (125)	-6.0%	-16.1%	**4.2%**
MRSA	31.7% (115)	24.3% (114)	7.4%	-4.3%	**19.1%**	33.3% (118)	30.3% (117)	3.0%	-9.0%	**15.0%**
Only MRSA	34.8% (79)	25.0% (91)	9.8%	-4.1%	**23.8%**	25.6% (59)	38.3% (66)	-12.7%	-29.0%	**3.6%**

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

The 28-day all-cause mortality rates stratified by age, gender, and race are provided in Table 22. The mortality treatment effect did not differ markedly across these three factors.

Table 22: 28-day all-cause mortality by Age, Gender, and Race (AT Population)

	Study 0015			Study 0019		
	Mortality Rate (N)		Diff (95% CI)	Mortality Rate (N)		Diff (95% CI)
	TLV	VAN	TLV-VAN	TLV	VAN	TLV-VAN
Age						
<65	18.7 (170)	13.3 (162)	5.4 (-2.6, 13.4)	12.1 (182)	15.7 (184)	-3.5 (-10.7, 3.6)
≥65	31.9 (202)	25.3 (212)	6.6 (-2.1, 15.3)	31.8 (195)	32 (196)	-0.2 (-9.5, 9.1)
Gender						
Female	23.7 (137)	22.3 (161)	1.5 (-8.2, 11.2)	25.2 (125)	26.7 (124)	-1.6 (-12.5, 9.4)
Male	27.2 (235)	18.5 (213)	8.6 (0.9, 16.4)	20.8 (252)	22.9 (256)	-2.1 (-9.4, 5.2)
Race						
American Indian / Alaska Native	0 (2)	0 (0)		19.6 (31)	26.6 (29)	-7 (-29.1, 15.1)
Asian	22 (91)	16.1 (87)	5.9 (-5.6, 17.4)	23.8 (81)	20.9 (91)	2.9 (-9.6, 15.4)
Black, of African Heritage	32.5 (10)	14.3 (14)	18.2 (-17.3, 53.7)	20 (15)	16.7 (6)	3.3 (-32.7, 39.4)
Hawaiian / Pacific Islander	0 (1)	0 (0)		0 (2)	0 ()	
White	27.4 (267)	21.4 (272)	6 (-1.3, 13.3)	22.4 (248)	25.3 (254)	-2.9 (-10.4, 4.6)
Mixed	0 (1)	100 (1)				

TLV = Telavancin and VAN = Vancomycin

4.2 Other Special/Subgroup Populations

The 28-day all-cause mortality results broken out by US vs. non-US patients are presented in Table 23, it can be seen that the treatment difference for 28-day all-cause mortality does not differ markedly between US and non-US patients for the all-treated population in either trial (Interaction contrast: Study 0015: p-value=0.59; Study 0019: p-value=0.62). In the ≥1 baseline gram+ population, the treatment difference for 28-day all-cause mortality rates appear to possibly differ between US and non-US patients in Study 0015. However, because the number of US patients is small in this subpopulation, the standard error is large and US vs. non-US was not identified as a effect modifier based on the lack of a statistically significant result for the test of a homogeneous treatment effect between US and non-US patients (Interaction contrast: Study 0015: p-value=0.30; Study 0019: p-value=0.96). It should be noted that US patients constitute 31% of the patients in Study 0015 and 14% of the patients in Study 0019.

Although the test for a homogeneous treatment effect between the US and non-US in the Division's primary analysis population (≥1 baseline gram-positive pathogen) was not a statistically significant, it is concerning that almost the entire mortality imbalance is driven by the US sites.

Table 23: 28-day Mortality Rates (Kaplan-Meier estimates) by US/Non-US for the AT and ≥1 baseline gram+ pathogen populations

Population	Study	US/ Non-US	Telavancin		Vancomycin		Difference (TLV – VAN)		
			N	Mortality Rate (%)	N	Mortality Rate (%)	Estimate	95% CI	
AT	0015	US	117	27.3	113	19.0	8.4	-2.6	19.4
AT	0015	Non-US	255	25.3	261	20.5	4.7	-2.5	12.0
AT	0019	US	60	21.7	46	19.9	1.9	-13.8	17.5
AT	0019	Non-US	317	22.3	334	24.7	-2.4	-9.0	4.2
≥1 gram+	0015	US	58	35.3	52	23.4	11.9	-5.2	28.9
≥1 gram+	0015	Non-US	129	25.8	128	24.6	1.1	-9.6	11.8
≥1 gram+	0019	US	32	21.9	20	20.3	1.6	-21.3	24.4
≥1 gram+	0019	Non-US	192	24.7	186	22.5	2.2	-6.5	10.8

To explore whether the effect of baseline creatinine clearance varied depending whether the patient was enrolled in the US or ex-US, stratified analyses by US/non-US and baseline creatinine clearance were conducted. The results are presented for both the all-treated and ≥1 baseline gram-positive pathogen populations. In Study 0015, the mortality is markedly higher for telavancin relative to vancomycin patients for US patients with a baseline creatinine clearance ≤50 ml/min. This was not seen for the non-US patients in Study 0015. The analyses for Study 0019 must be interpreted carefully because of the small number of US patients, which results in very small cell sizes. In Study 0019, mortality appears to be increased for US patients with baseline creatinine clearance <80 ml/min although the same sizes are very small. This was not seen for non-US patients where the only telavancin patients with increased mortality were those with baseline creatinine clearance <30 ml/min.

Table 24: All-treated patients: 28-day all-cause mortality by US/Non-US and baseline creatinine clearance

Study	US / Non-US	Baseline Creatinine Clearance (ml/min)	Telavancin		Vancomycin		Difference (TLV-VAN)	
			N	Mortality Rate (%)	N	Mortality Rate (%)	Estimate	95% CI
0015	US	>80	48	6.4	46	8.7	-2.3	(-13.0, 8.4)
0015	US	>50-80	25	24.4	25	21.9	2.5	(-21.7, 26.6)
0015	US	30-50	28	49.0	29	27.9	21.1	(-4.3, 46.6)
0015	US	<30	16	56.3	13	30.8	25.5	(-9.5, 60.4)
0015	Non-US	>80	95	15.1	106	16.3	-1.2	(-11.4, 9.0)
0015	Non-US	>50-80	63	28.6	63	16.2	12.4	(-2.1, 26.9)
0015	Non-US	30-50	52	27.4	54	20.5	6.9	(-9.4, 23.2)
0015	Non-US	<30	45	40.0	38	39.5	0.5	(-20.6, 21.7)
0019	US	>80	34	8.8	21	20.0	-11.2	(-31.3, 8.9)
0019	US	>50-80	13	23.8	9	11.1	12.7	(-18.6, 44.1)
0019	US	30-50	9	44.4	12	16.7	27.8	(-10.9, 66.5)
0019	US	<30	4	75.0	4	50.0	25.0	(-39.8, 89.8)

0019	Non-US	>80	147	11.0	160	18.6	-7.6	(-15.6, 0.3)
0019	Non-US	>50-80	83	25.8	81	28.9	-3.1	(-16.9, 10.7)
0019	Non-US	30-50	53	24.9	56	25.3	-0.4	(-16.8, 16.0)
0019	Non-US	<30	34	59.4	37	41.3	18.1	(-5.1, 41.2)

Table 25: >=1 baseline gram+ pathogen by US/non-US and baseline creatinine clearance

Study	US/ Non-US	Baseline Creatinine Clearance (ml/min)	Telavancin N	Telavancin Mortality Rate (%)	Vancomycin N	Vancomycin Mortality Rate (%)	Difference (TLV – VAN) Estimate	Difference (TLV – VAN) 95% CI
0015	US	>80	22	9.1	21	4.8	4.3	(-12.4, 19.4)
0015	US	>50-80	15	34.0	9	23.8	10.2	(-27.7, 48.0)
0015	US	30-50	13	61.5	13	46.2	15.4	(-22.5, 53.3)
0015	US	<30	8	62.5	9	33.3	29.2	(-16.4, 74.7)
0015	Non-US	>80	55	22.1	53	21.4	0.7	(-15.1, 16.4)
0015	Non-US	>50-80	32	25.0	29	17.5	7.5	(-13.0, 28.0)
0015	Non-US	30-50	26	23.6	30	23.6	0.0	(-22.5, 22.5)
0015	Non-US	<30	16	43.8	16	50.0	-6.3	(-40.8, 28.3)
0019	US	>80	22	9.1	11	18.2	-9.1	(-34.9, 16.7)
0019	US	>50-80	4	25.0	5	20.0	5.0	(-50.0, 60.0)
0019	US	30-50	5	60.0	2	50.0	10.0	(-71.5, 91.5)
0019	US	<30	1	100.0	2	0.0	100.0	.
0019	Non-US	>80	89	12.4	93	15.5	-3.1	(-13.2, 7.1)
0019	Non-US	>50-80	56	30.6	39	28.7	1.9	(-16.9, 20.7)
0019	Non-US	30-50	28	28.9	32	22.2	6.7	(-15.6, 29.0)
0019	Non-US	<30	19	57.9	22	40.9	17.0	(-13.3, 47.2)

5 SUMMARY AND CONCLUSIONS

Clinical Response at TOC endpoint

The trials used an active controlled noninferiority design with a primary endpoint of clinical response at TOC in the AT and CE populations using a 20% noninferiority margin. After the initiation of the trials but prior to the submission of the application, the Agency published a Draft Guidance in October 2007 entitled "Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval", which states that "Sponsors should re-evaluate all ongoing or completed NI studies that will be submitted to a new drug application for antibacterial indications to ensure there is adequate scientific rationale for the effect size of the active control and the proposed NI margin that is used."

Also, prior to the submission of the application, the lack of a historical evidence of active comparator treatment effect for the clinical response endpoint was discussed at two venues. The first was at the July 2008 meeting of the AIDAC convened to discuss NDA 22-171 (doripenem

for injection) for the treatment of HAP/VAP. This issue was also discussed at the March 31 - April 1, 2009, workshop (co-sponsored by FDA, IDSA, ATS, SCCM and ACCP). At both of these meetings, the Agency presented historical data for all-cause mortality in HAP/VAP and found that an NI margin that could be justified based on this data for all-cause mortality but not for clinical response.

Because of the draft guidance as well as the two meetings discussed above, the Applicant was informed at the pre-NDA meeting that they would have to provide justification for the NI margin they used in their trials.

In the submission, the Applicant did not provide compelling evidence of a historical evidence of treatment effect for the active comparator using the clinical response endpoint. For this reason, the Division considered 28-day all-cause mortality as the primary endpoint for the submission.

Based on an Agency review of the literature and the discussion at the workshop, the clearest evidence of treatment effect was based on all-cause mortality. However, the historical literature did not provide a uniform timepoint for the assessment of mortality. The mortality reporting window should be of adequate length such that the outcome of interest reflects the attributable clinical effect of the drug rather than being confounded by the underlying comorbidities. In addition, ideally, the timing of the assessment should be prospectively defined to avoid any kind of post-hoc selection. However, at the present time there is 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.
As described in the HABP/VABP Draft Guidance, the effect of antibacterial therapy on all-cause mortality was based on historical evidence of the sensitivity of drug effect (HESDE), and using a recent review of historical evidence, the Guidance recommends an M1 conservatively estimated at 20% and (to preserve 50% of the treatment effect on all-cause mortality) a non-inferiority margin of 10%.

28-day all-cause mortality

Because both treatment groups have only gram-positive activity, the Division decided that the primary efficacy analyses should be performed in patients who had at least one gram-positive pathogen isolated at baseline. In this population using a 10% NI margin, noninferiority of telavancin to vancomycin for 28-day all-cause mortality was demonstrated for Study 0019 [difference = 2.0% (telavancin: 24.3%; vancomycin: 22.3%); 95% CI = (-6.1%, 10.0%)] but not for Study 0015 [difference = 4.4% (telavancin: 28.7%; vancomycin: 24.3%); 95% CI = (-4.7%, 13.5%)]. It is important to note that noninferiority was demonstrated only in Study 0019 based on 10% noninferiority (NI) margin. However, at the November 2011 AIDAC meeting, there was a recommendation that only a single successful HAP/VAP trial was needed if there are other supportive evidence available, which in this case would be the two successful cSSSI trials that led to approval of the cSSSI indication.

Pooling of trials

Even though the trials used identical protocols, there are concerns in pooling the two trials to assess mortality because of the differential treatment effects for the AT population seen in Figure

3. This is possibly due to differences between the trials in baseline characteristics and co-morbid conditions, some of which may be potential effect modifiers. The cross-study differences in potential risk factors for mortality (such as diabetes mellitus and renal impairment/failure) could seriously impact the comparability of the distributions across the two trials. There are more patients in Study 0015 with chronic renal failure, baseline CrCl<50 mL/min, serum creatinine >1.2 mg/dL, hemodialysis, diabetes mellitus, acute respiratory distress syndrome, HCAP, torsades de pointes, history of atrial fibrillation, and history of myocardial infarction. In contrast, there were more patients in Study 0019 with serum creatinine ≤1.2 mg/dL, immunocompromised, HAP, organ failure at baseline, and history of left ventricular hypertrophy compared to Study 0015. Because of these concerns, these trials were not pooled in the Agency's analysis to assess all-cause mortality.

Mortality imbalance seen in Study 0015

A major issue with this application is that for Study 0015 there was a nearly statistically significant increase in 28-day all-cause mortality in telavancin relative to vancomycin. Even though this finding was not replicated, there are serious safety concerns because of this finding. Of note, is that, even though the two trials used identical protocols, there were more patients in Study 0015 who had baseline renal impairment or risk factors for renal injury.

The adequacy of gram-negative coverage is an issue because it is one of the factors that the Applicant is using to explain the observed mortality increase seen for the telavancin arm relative to the vancomycin arm in Study 0015. They argue there were more telavancin treated patients with a baseline gram-negative pathogen who received inadequate or no gram-negative coverage compared to the number of vancomycin patients. It should be noted that this was not a pre-planned analysis and that these factors should be balanced due to randomization and any apparent imbalances are accounted for by the Type I error and are likely due to chance. Thus, I do not find their argument compelling.

Effect modification by baseline renal function and risk factor for renal injury

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. The prior evidence of renal effects are the renal findings that were seen in the complicated skin and skin structure infection (cSSSI) application (NDA 22-110), where there was a finding of decreased efficacy among patients with moderate/severe pre-existing renal impairment (baseline CrCl ≤50 mL/min) included in the Warnings and Precautions section of the current telavancin label. In addition, concerns for nephrotoxicity based on new onset or worsening renal impairment occurred in the both the cSSSI (NDA 22-110) application as well as the current HAP/VAP application. Finally, renal toxicity was seen in the preclinical studies.

Baseline variables that either measure renal function or are risk factors for renal injury were tested for a homogeneous treatment effect across the levels of the variables. The results are given in Table 17. The possible effect modifiers that were identified are baseline creatinine clearance in Study 0019, congestive heart failure in Study 0015, and receipt of nephrotoxic drugs at baseline in both studies.

Figure 4 contains the 28-day all-cause mortality results in the all-treated population by baseline creatinine clearance. In Study 0015, the 28-day all-cause mortality tended to be higher for telavancin patients with baseline creatinine clearance < 80 ml/min. For Study 0019, the treatment effect of telavancin relative to vancomycin decreases as baseline renal function worsens. Note, this is the same relationship seen in the cSSSI trials for the clinical response at TOC endpoint.

Differential treatment effect for all-cause mortality between US and. non-US sites

Although the test of a homogeneous treatment effect between the US and non-US (Interaction contrast: Study 0015: p-value=0.59; Study 0019: p-value=0.62) in the Division's primary analysis population (≥1 baseline gram+ pathogen) was not a statistically significant, it is concerning that almost the entire mortality imbalance in Study 0015 is driven by the US sites (Table 23). This result was not replicated in Study 0019 but it should be noted that US patients constituted much smaller proportion of the population in Study 0019 (14%) than for Study 0015 (31%).

To further explore the apparent trend in Study 0015 of increased telavancin mortality in the US sites, analyses were performed stratified by both US/non-US and the baseline creatinine clearance (AT: Table 24; ≥1 baseline gram-positive pathogen: Table 25). In Study 0015, the mortality is markedly higher for telavancin relative to vancomycin patients for US patients with a baseline creatinine clearance ≤50 ml/min. This was not seen for the non-US patients in Study 0015. The analyses for Study 0019 must be interpreted carefully because of the small number of US patients, which results in very small cell sizes. In Study 0019, mortality appears to be increased for US patients with baseline creatinine clearance <80 ml/min although the sample sizes are very small. This was not seen for non-US patients where the only telavancin patients with increased mortality were those with baseline creatinine clearance <30 ml/min.

It is also important to note that there are only two drugs approved to treat HAP/VAP or lower respiratory tract infections due to MRSA as opposed to infections due to MSSA where there are additional treatment options, i.e. beta-lactams.

Advisory Committee Meeting

The AIDAC did not support a finding that there was substantial evidence of safety and effectiveness for telavancin in the treatment of NP (Yes: 6; No: 9). However, the AIDAC voted overwhelmingly (Yes: 13; No; 2) that the results provided substantial evidence of safety and effectiveness of televancin for the treatment of NP when other alternatives are not suitable, Many of the members recommended limiting use for only MRSA while some also recommended use in MSSA if other treatment options were not suitable, e.g. in patients with a severe beta-lactam allergy. Additionally, many of the members also voiced serious concerns on the observed mortality imbalance for patients with baseline renal impairment and felt that use should be limited in this population.

Conclusion

In conclusion, there is evidence that telavancin is effective in the treatment of HAP/VAP in specific patient groups. However, there are serious concerns for increased mortality in patients with baseline renal impairment, especially for those with a baseline CrCl ≤50 mL/min.. This is consistent with the renal findings that were seen in the complicated skin and skin structure infection (cSSSI) application (NDA 22-110), where there was a finding of decreased efficacy among patients with moderate/severe pre-existing renal impairment (baseline CrCl ≤50 mL/min) included in the Warnings and Precautions section of the current telavancin label. In addition, concerns for nephrotoxicity based on new onset or worsening renal impairment occurred in both the cSSSI (NDA 22-110) application as well as the current HAP/VAP application. Finally, renal toxicity was seen in the preclinical studies. Given the concerns of increased mortality for patients with a baseline estimated CrCl≤50 mL/min and the relatively few number of treatment options for nosocomial pneumonia caused by *S. aureus* along with the incidence of increasing resistance to these antibacterials, I recommend that the label include a statement on the finding of increased mortality for telavancin treated patients with baseline CrCl ≤50 ml/min with use limited to situations where other treatment options are not available.

6 REFERENCES

Sorbello A, Komo S, Valappil T. Non-inferiority Margin for Clinical Trials of Antibacterial Drugs for Nosocomial Pneumonia. *Drug Information Journal* 2010; 44:165-176.

7 APPENDIX

Table 26: Subjects with both clinical response of cure and all-cause mortality by Day 28 — All Treated (AT) analysis set

Study Medication	Subject ID	TOC Study Day	Death Study Day	Days between Cure and Death	Cause of Death as cited by Investigator
Vancomycin	0015-01014-4132	(b) (6)	(b) (6)	2	Cardiac arrest
Telavancin	0015-02011-4566			2	Severe cerebral damage due to seizures
Telavancin	0015-02024-4216			3	Respiratory failure
Vancomycin	0015-06016-4399			3	Unknown
Vancomycin	0015-07001-4486			1	Septic shock from urinary tract infection
Telavancin	0015-07002-4069			4	Congestive heart failure
Vancomycin	0015-09004-4640			13	Unknown
Telavancin	0015-12016-4649			0	Multiple organ failure
Vancomycin	0015-18001-4652			2	(Respiratory failure?)
Telavancin	0015-33016-4457			3	Unknown
Telavancin	0015-38024-4787			4	Unknown
Telavancin	0015-38148-4114			6	Clinical deterioration
Telavancin	0015-38270-4747			4	Unknown
Telavancin	0015-38271-4112			1	Unknown
Telavancin	0015-38271-4124			4	Cardiopulmonary arrest
Telavancin	0015-38348-4709			7	Unknown
Telavancin	0019-01019-6032			4	Cardiac failure
Vancomycin	0019-01019-6339			5	Shock
Vancomycin	0019-01019-6341			7	Septic shock
Telavancin	0019-01021-6340			5	Septic shock due to *Candida albicans*
Vancomycin	0019-01022-6059			11	Hypoglycemia/pneumonia aspiration
Vancomycin	0019-01022-6624			1	Meningitis/subarachnoid hemorrhage
Vancomycin	0019-05003-6069			0	Urinary sepsis by *Enterobacter cloacae*
Vancomycin	0019-05003-6626			10	Acute ventilatory failure
Vancomycin	0019-06005-6693			5	Unknown
Telavancin	0019-12009-6203			2	Sudden death
Vancomycin	0019-18004-6717			12	Brain metastasis
Telavancin	0019-18012-6382			1	Unknown
Telavancin	0019-22006-6582			3	Unknown
Vancomycin	0019-25024-6639			0	Heart failure
Vancomycin	0019-40000-6092			5	Unknown
Vancomycin	0019-40006-6811			7	Respiratory failure
Telavancin	0019-44003-6751			6	Cardiopulmonary failure

Source: ISE (current submission), Listing 8

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/s/

SCOTT S KOMO
01/18/2013

THAMBAN I VALAPPIL
01/18/2013

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22407
Drug Name:	Telavancin
Indication(s):	Nosocomial pneumonia
Applicant:	Theravance, Inc.
Date(s):	Stamp Date: July 12, 2012
	PDUFA Date: January 12, 2013
Biometrics Division:	Division of Biometrics IV
Statistical Reviewer:	Daniel Rubin, Ph.D.
Concurring Reviewers:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective Products
Clinical Team:	Medical Officer: Benjamin Lorenz, M.D.
	Clinical Team Leader: Eileen Navarro, M.D.
Project Manager:	Christopher Davi

1 Introduction

Primary statistical review of this application is deferred to Dr. Scott Komo the assigned statistical reviewer for this NDA. The present document is meant to supplement Dr. Komo's review, and perform several analyses bearing upon the assay sensitivities of the trials under consideration for differentiating effective and ineffective therapy, the choice of endpoint, the analysis population, and noninferiority margins.

Telavancin is a lipoglycopeptide antibacterial drug that is under review for the indication of treating nosocomial pneumonia. This application contains evidence from two confirmatory phase 3 trials: Study 0015 and Study 0019. Each was a randomized, double-blind, multinational, active-controlled noninferiority clinical trial. The two trials were conducted simultaneously over 2005-2007 according to identical protocols, and each trial compared treatment with telavancin to the active control drug, vancomycin.

Over the course of the two trials, many subjects were enrolled who had Gram-negative bacterial pathogens at baseline. In real time this was not known to investigators because of the time required for bacterial cultures to grow, and neither telavancin nor the active comparator vancomycin had activity against these pathogens. In accordance with the protocols, subjects were given Gram-negative therapy at baseline at investigator discretion, which depending on circumstances and date of protocol amendments was imipenem, aztreonam, piperacillin/tazobactam, or another drug with Gram-negative activity. The Applicant's study report summarized the protocol amendment as follows: "Imipenem for Gram-negative coverage was removed as a treatment option. Aztreonam is still the preferred antibiotic for Gram-negative coverage. Piperacillin/tazobactam remains an alternative antibiotic for those sites with a high rate of aztreonam resistance."

However, due to investigator discretion many subjects with a Gram-negative baseline pathogen were not given adjunctive Gram-negative coverage at baseline. In order to estimate what treatment effects would have been seen with a hypothetical placebo arm, outcomes for subjects with Gram-negative baseline pathogens were analyzed by this reviewer according to the provision of adjunctive Gram-negative coverage.

It should be kept in mind that in trying to estimate the effect of Gram-negative coverage for subjects with Gram-negative pathogens, this reviewer was examining antibacterial treatment effects relative to delayed therapy rather than a true placebo. Investigators were alerted to the need for rescue therapy from microbiological results within approximately 48-72 hours, while with a hypothetical placebo arm the rescue therapy might have been delayed longer until deterioration of signs and symptoms. However, FDA reviewers have previously based noninferiority margin justifications on similar comparisons of the effect of delayed or inadequate nosocomial pneumonia therapy[1].

This reviewer pooled Study 0015 and Study 0019. This is not meant to contradict Dr. Alfred Sorbello, who in his review of the original filing of this NDA stated that "it is

[1] Sorbello A., Komo S., Valappil T. Noninferiority margin for clinical trials of antibacterial drugs for nosocomial pneumonia. *Drug Information Journal*, 2009;44:165-176

evident that the populations were substantially different based on pre-treatment characteristics and co-morbid conditions such that pooling for mortality analysis was not advisable and that the mortality data for each study should be assessed individually." Rather, as this review is somewhat exploratory, pooling of the two trials was done to increase statistical power.

So as not to infringe upon Dr. Komo's assessment of telavancin's safety and efficacy, all analyses in this document also pool the telavancin and vancomycin arms, with the exception of brief comments in Section 6 regarding telavancin and nephrotoxicity.

Section 2 describes the data sources used. Section 3 then discusses the baseline disposition of subjects who had a Gram-negative baseline pathogen, and compares the dispositions of those who did and did not receive Gram-negative coverage at baseline. As the decision to provide coverage was not randomized, factors are considered that may have confounded the comparability of the two groups. Section 4 analyzes mortality and clinical response results among subjects with a Gram-negative baseline pathogen, and provides estimated treatment differences between those subjects who did and did not receive coverage. Section 5 then provides a detailed discussion of statistical analyses meant to address the lack of randomization, including univariate cross-tabulations and multivariate analysis using both propensity score models and outcome regression models. Section 6 contains comments on the nephrotoxicity of telavancin, and Section 7 summarizes the results and conclusions.

2 Data Sources

Because mortality status was originally censored for many subjects, a request was made by FDA reviewers for the Applicant to collect missing mortality data. All-cause mortality and the timing thereof is captured in the admort.xpt dataset rather than the datasets provided in the original NDA submission, and is available to FDA reviewers as a SAS transport files at the following link to the Electronic Document Room:
\\Cdsesub1\evsprod\NDA022407\0105\m5\datasets\ise\analysis

For other variables needed to replicate this reviewer's analyses, the necessary datasets are available to FDA reviewers in the Electronic Document Room at the following links:
\\Cdsesub1\evsprod\NDA022407\0000\m5\datasets\0015\analysis
\\Cdsesub1\evsprod\NDA022407\0000\m5\datasets\0019\analysis

Variables in this reviewer's analyses were taken from the adsl.xpt or adcov.xpt datasets, with the exception of variables for baseline respiratory rate (BLRESP) and body temperature (BLTEMP), which were taken from the adsigsym.xpt dataset. Presence of a Gram-negative baseline pathogen was captured in GNEGBASE. An indicator of no baseline Gram-negative coverage was captured in the Applicant's variable GNNON. Equivalently, this can be derived by the disjunction of variables GNAZT (aztreonam), GNPIP (piperacillin), GNIMI (imipenem), and GNOTH (other).

3 Baseline Disposition of Subjects with a Gram-negative Baseline Pathogen

The table below summarizes baseline characteristics of subjects enrolled in Study 0015 or Study 0019 who had a Gram-negative baseline pathogen, according to receipt of baseline Gram-negative coverage. In assessing these two groups an important consideration is that Gram-negative coverage was not randomized. Hence, a difference in outcomes did not necessarily imply a casual effect of therapy because the comparison groups may have differed in other ways. The direction of possible confounding was not immediately obvious to this reviewer from the table: although subjects who received coverage were younger and had fewer mixed infections, they were also more likely to be ventilated.

Table 1: Baseline status of subjects with a Gram-negative (GN) baseline pathogen

Baseline Characteristic	GN Coverage (n = 382)	No GN Coverage (n = 180)
Study		
0015	163/382 (42.7)	69/180 (38.3)
0019	219/382 (57.3)	111/180 (61.7)
Country		
United States	66/382 (17.3)	24/180 (13.3)
Other	316/382 (82.7)	156/180 (86.7)
Male	265/382 (69.4)	129/180 (71.7)
White	242/382 (63.4)	104/180 (57.8)
Age in years, mean ± SE	**60.8 ± 1.0**	**64.1 ± 1.3**
APACHE II score, mean ± SE	16.2 ± 0.3	15.5 ± 0.5
Ventilation	**219/382 (57.3)**	**82/180 (45.6)**
Hospitalized in past 6 months	176/382 (46.1)	83/180 (46.1)
Antibiotics over past 3 months	181/382 (47.4)	91/180 (50.6)
Multiple lobes	232/382 (60.7)	117/180 (65.0)
Immunocompromised	10/382 (2.6)	3/180 (1.7)
Bacteremia	48/382 (12.6)	22/180 (12.2)
Pulmonary co-morbidity	258/382 (67.5)	128/180 (71.1)
Cardiac co-morbidity	204/382 (53.4)	105/180 (58.3)
Acute renal failure	32/382 (8.4)	22/180 (12.2)
Chronic renal failure	23/382 (6.0)	9/180 (5.0)
CrCl (mL/min), mean ± SE	82.3 ± 2.5	76.4 ± 3.5
Diabetes	65/382 (17.0)	34/180 (18.9)
Smoking history	199/382 (52.1)	107/180 (59.4)
Mixed infection	**172/382 (45.0)**	**98/180 (54.0)**
>24h prior therapy	203/382 (53.1)	106/180 (58.9)
Vital Signs, mean ± SE		
Temperature (degrees C)	38.6 ± 0.1	38.8 ± 0.1
Breaths/minute	25.5 ± 0.4	26.4 ± 0.5
Pulse (beats/min)	101.6 ± 1.1	100.0 ± 1.5
Systolic BP (mm Hg)	129.6 ± 1.1	128.6 ± 1.7

Bold = difference between groups was statistically significant at two-sided $\alpha = 0.05$ level.

4 Unadjusted Results for All-Cause Mortality and Clinical Response

The next table presents results on all-cause mortality and clinical response for subjects with a Gram-negative baseline pathogen, according to whether or not subjects received Gram-negative coverage. As a first cut the raw unadjusted results are presented without attempting to control for possible confounding. In the table survival was imputed for censored subjects, and this choice had little impact on results at early times due to the limited number of subjects involved [e.g., 5/562 (<1%) at Day 14]. The results suggested that there was a mortality benefit to providing Gram-negative coverage at baseline to subjects who had a Gram-negative baseline pathogen.

Table 2: All-cause mortality and clinical response in subjects with a Gram-negative (GN) baseline pathogen, according to Gram-negative coverage at baseline

GN Population	GN Coverage (n = 382)	No GN Coverage (n = 180)	Difference (95% CI)
All-cause mortality			
Day 7	15/382 (3.9)	25/180 (13.9)	-10.0 (-16.0, -5.1)
Day 14	40/382 (10.5)	37/180 (20.6)	-10.1 (-17.2, -3.8)
Day 21	65/382 (17.0)	46/180 (25.6)	-8.5 (-16.2, -1.4)
Day 28	84/382 (22.0)	50/180 (27.8)	-5.8 (-13.8, 1.7)
Clinical cure			
EOT	183/382 (47.9)	92/180 (51.1)	-3.2 (-12.0, 5.6)
TOC	192/382 (50.3)	92/180 (51.1)	-0.8 (-9.6, 8.0)

Effects appeared to be largest slightly earlier than the Day 28 timepoint previously recommended by FDA reviewers, and precision around the estimates was also greater at the earlier times. At later times there was greater variability in estimating the drug effect on mortality due to patients who were dying of their underlying illness. Although differences at Day 7, 14, and 21 reached nominal statistical significance, the magnitude of mortality effects was smaller than in the Sorbello meta-analysis, in which cross-study comparisons estimated mortality rates to be 20% (95% CI: 18% to 23%) under antibacterial treatment and 62% (95% CI: 52% to 71%) under delayed or inadequate therapy.

In addition to all-cause mortality, another endpoint that has previously been used in nosocomial pneumonia trials is clinical response. In fact, Study 0015 and Study 0019 originally prespecified clinical response endpoints for primary analysis. Traditionally, this endpoint defines clinical cure as resolution of signs and symptoms of the disease to the extent that no additional therapy is needed in the overall opinion of the investigator, and it is assessed at both an end-of-therapy (EOT) visit and several weeks afterwards at a test-of-cure (TOC) visit. Clinical response endpoints have been criticized for several reasons.

First, there is a dearth of evidence with which to justify a noninferiority margin for the clinical response endpoint in nosocomial pneumonia.

Second, the endpoint may not meet the standard in the Code of Federal Regulations that adequate and well-controlled trials needed for drug approval under the 1962 amendments to Food, Drug, and Cosmetic Act should have "well-defined and reliable" outcome measures [21CFR314.126(b)(6)], meaning the protocol for the study and the report of the results should explain the variables measured, the methods of observation, and the criteria used to assess response. It is often unclear what signs and symptoms investigators are assessing, and the fact that many mark the clinical outcome as indeterminate suggest that investigators themselves are often unsure of the endpoint's meaning.

Third, treatment effects on the endpoint may reflect effects on biomarkers such as WBC counts and body temperature that are used by clinicians for diagnosis, prognosis, and patient management. These should be considered surrogate endpoints, since it is not clear that treatment effects imply a beneficial effect on patient feeling, function, or survival, which is the ultimate objective of providing therapy.

Unlike the mortality endpoint, for subjects with a Gram-negative baseline pathogen there was no estimated benefit of Gram-negative coverage on clinical cure rates. One possible explanation could be that the Gram-negative coverage was not the therapy under investigation, so rescue therapy that was provided in part to cover the needed spectrum of activity did not necessarily trigger the failure definition. However, the fact that cure rates did not differ between a treated group and an untreated group that died at a significantly higher rate implies to this reviewer that caution should be exercised in basing noninferiority conclusions from Study 0015 and Study 0019 on clinical cure rates.

5 Analysis of Confounding

A limitation of the unadjusted results was that Gram-negative baseline coverage was not randomized. Therefore, a difference in outcomes between the two comparison groups could have underestimated or overestimated the effect of therapy if the groups were systematically different. This section therefore considers adjustments for confounding.

5.1 Complement Analysis

Before moving to the more traditional cross-tabulations and regressions used to adjust for confounding in nonrandomized comparisons, it is useful to consider a thought experiment. If the mortality benefit previously observed was driven by confounding rather than the causal effect of Gram-negative coverage, then subjects in Study 0015 and Study 0019 who received coverage were systematically different from those who did not in ways other than through the coverage itself. Under such a pattern one might expect to see a similar artifact association between receipt of Gram-negative coverage and lower mortality even for subjects who *did not* have a Gram-negative baseline pathogen, where the coverage had no activity. Table 3 below analyzes such all-cause mortality rates. The first results are for those in the all treated (AT) group, or the intent-to-treat population of randomized subjects who received any dose of study drug, but where this reviewer excluded subjects with Gram-negative baseline pathogens. This was the complement of the population already considered in this review.

Objections could be made that, due to the poor sensitivity of microbiological diagnostics, many culture-negative subjects may have had undetected Gram-negative pathogens, or that Gram-negative therapy may have had overlapping coverage against Gram-positive organisms. To address these limitations the table also shows results for subjects with confirmed MRSA at baseline who did not have an identified Gram-negative baseline co-pathogen. The two objections here were less relevant because the Gram-positive etiology was more specifically known for subjects with confirmed MRSA, and overlapping anti-MRSA activity was less likely.

Table 3: All-cause mortality by Gram-negative coverage in subjects *without* a Gram-negative baseline pathogen, among the all-treated and MRSA populations

All-Cause Mortality	GN Coverage	No GN Coverage	Difference (95% CI)
AT Pop – GN Pop			
Day 7	30/452 (6.6)	40/489 (8.2)	-1.5 (-4.9, 1.9)
Day 14	72/452 (15.9)	69/489 (14.1)	1.8 (-2.8, 6.4)
Day 21	96/452 (21.2)	84/489 (17.2)	4.1 (-1.0, 9.1)
Day 28	112/452 (24.8)	96/489 (19.6)	5.1 (-0.2, 10.5)
MRSA Pop – GN Pop			
Day 7	10/118 (8.5)	20/185 (10.8)	-2.3 (-9.0, 5.1)
Day 14	22/118 (18.6)	34/185 (18.4)	0.3 (-8.4, 9.7)
Day 21	32/118 (27.1)	42/185 (22.7)	4.4 (-5.4, 14.7)
Day 28	41/118 (34.7)	49/185 (26.5)	8.3 (-2.2, 19.0)

Among subjects who did not have a Gram-negative pathogen at baseline, the above table shows, if anything, higher mortality rates for the subjects who received Gram-negative coverage. This provides some evidence that the antibacterial mortality benefit seen earlier in Table 2, for the population of subjects who did have a Gram-negative baseline pathogen, may actually have been underestimated due to selection factors because subjects receiving coverage may have had greater severity of illness.

5.2 Univariate Cross-Tabulation

Among subjects with Gram-negative baseline pathogens, Table 4 below presents cross-tabulations of Day 14 all-cause mortality with baseline covariates that were either significantly imbalanced between coverage groups, were hypothesized to be effect modifiers, or were otherwise of interest. The "adjusted" estimate for a specific baseline variable weighted the stratum-specific mortality rate by the total number of subjects in the stratum over both coverage groups; this attempted to estimate the overall effect of providing or withholding coverage while controlling for confounding due to this variable.

Adjusted treatment effect estimates were similar to unadjusted estimates, with point estimates near 10% and the differences showing nominal statistical significance. The most notable finding from subgroup and interaction analysis was the suggestion that the largest antibacterial treatment effect on mortality, and hence the greatest sensitivity for differentiating effective and ineffective therapy, was for subjects in relatively severe condition (e.g., high APACHE II scores or poor renal function).

Table 4: Day 14 all-cause mortality in subjects with a Gram-negative baseline pathogen

Baseline Characteristic	GN Coverage (n = 382)	No GN Coverage (n = 180)	Difference (95% CI)
Age (years)			
≥65	24/188 (12.8)	27/102 (26.5)	-13.7 (-24.0, -4.4)
<65	16/194 (8.2)	10/78 (12.8)	-4.6 (-14.3, 2.9)
Adjusted	10.6	19.9	-9.3 (-15.8, -2.8)
Ventilation			
Yes	26/219 (11.9)	17/82 (20.7)	-8.9 (-19.6, 0.0)
No	14/163 (8.6)	20/98 (20.4)	-11.8 (-21.6, -3.3)
Adjusted	10.3	20.6	-10.2 (-17.0, -3.5)
Mixed infection			
Yes	18/172 (10.5)	26/98 (26.5)	-16.1 (-26.4, -6.7)
No	22/210 (10.5)	11/82 (13.4)	-2.9 (-12.6, 4.7)
Adjusted	10.5	19.7	-9.2 (-15.7, -2.8)
Study			
0015	18/163 (11.0)	16/69 (23.2)	-12.1 (-24.1, -2.0)
0019	22/219 (10.0)	21/111 (18.9)	-8.9 (-17.9, -1.1)
Adjusted	10.5	20.7	-10.2 (-16.9, -3.5)
APACHE II score			
≥14	36/263 (13.7)	34/107 (31.8)	-18.1 (-28.2, -8.8)
<14	4/119 (3.4)	3/73 (4.1)	-0.7 (-8.4, 4.9)
Adjusted	10.2	22.3	-12.2 (-18.9, -5.4)
Prior therapy			
≤24 hours	16/179 (8.9)	18/74 (24.3)	-15.4 (-26.9, -5.7)
>24 hours	24/203 (11.8)	19/106 (17.9)	-6.1 (-15.4, 1.9)
Adjusted	10.5	20.8	-10.3 (-17.0, -3.6)
Bacteremia			
Yes	10/48 (20.8)	9/22 (40.9)	-20.1 (-43.1, 2.2)
No	30/334 (9.0)	28/158 (17.7)	-8.7 (-16.0, -2.5)
Adjusted	10.5	20.6	-10.2 (-16.7, -3.6)
Renal function			
CrCl ≤ 50 mL/min	19/115 (16.5)	23/60 (38.3)	-21.8 (-35.9, -8.2)
CrCl > 50 mL/min	21/267 (7.9)	14/120 (11.7)	-3.8 (-11.3, 2.2)
Adjusted	10.6	20.0	-9.4 (-15.8, -3.1)
Enriched*			
Subgroup #1	15/130 (11.5)	17/46 (37.0)	-25.4 (-40.7, -11.5)
Subgroup #2	15/141 (10.6)	17/65 (26.2)	-15.5 (-28.2, -4.6)

* Enriched subgroup #1 required ≤24 hours of prior therapy and APACHE II score ≥14. Enriched subgroup #2 required ≤24 hours of prior therapy and either age ≥50 years or bacteremia, and was motivated by a previous analysis[2]. The fact that these two enriched subgroups had the same number of deaths within each coverage group was coincidental.

[2] Fleming T and Powers J. Issues in noninferiority trials: the evidence in community-acquired pneumonia. *Clinical Infectious Diseases,* 2008;47:S108-120.

5.3 Multivariate Adjustments

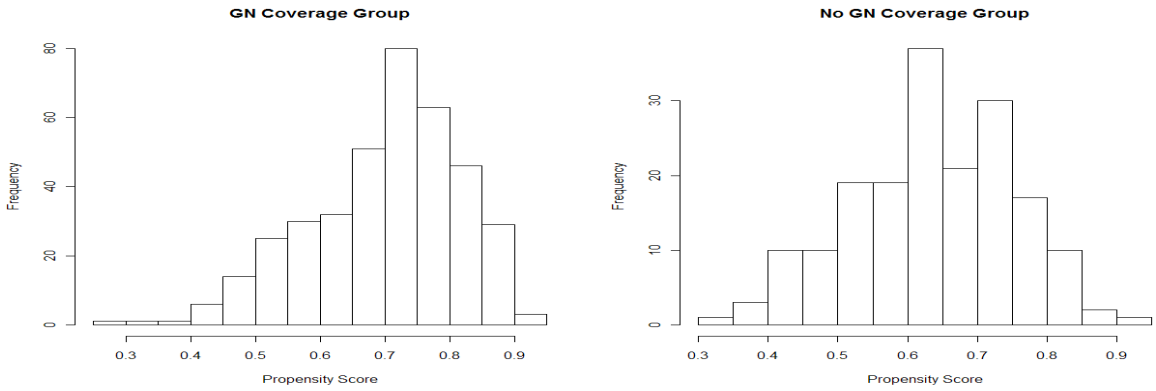
While the cross-tabulations are useful for examining one variable at a time, they quickly run out of data when simultaneously adjusting for multiple confounders, and in non-randomized comparisons the traditional approach is to instead apply regression modeling. Within the population of subjects with Gram-negative baseline pathogens, this reviewer considered several different regression-based estimators for the causal effect of providing Gram-negative coverage at baseline, using the 25 baseline variables in Table 1 as the set of confounders.

While these approaches allow more than one covariate to be considered at a time, the results can be sensitive to model specification, and with non-randomized comparisons it is impossible to adjust for unmeasured confounders. Consequently, these models are best viewed as rough approximations for how complicated processes actually occur. Thus, multivariate adjustments in this section are meant to supplement the analyses of confounding in the previous two subsections rather than override them.

Among subjects with a Gram-negative baseline pathogen, there were missing covariate values for 31/562 (5.5%) subjects. This reviewer imputed missing covariate values based on the average of non-missing values of these covariates.

The first multivariate adjustment conducted by this reviewer applied propensity scores. In this approach a logistic regression model was fit for regressing the conditional probability of receiving Gram-negative coverage on the 25 baseline covariates in Table 1. The causal effect of Gram-negative coverage on mortality was then estimated by inverse probability of treatment weighting[3]. Because the estimated propensity scores ranged only from 0.29 to 0.91, this technique did not encounter the problem where a small number of subjects dominate estimator weights due to inverse weighting by quantities close to zero. Figure 1 below displays how propensity scores were distributed within coverage groups.

Figure 1: The propensity score distributions for subjects with Gram-negative (GN) baseline pathogens, who did and did not receive GN coverage.



[3] Hernan M and Robins J. Estimating causal effects from epidemiological data. *Journal of Epidemiology & Community Health*, 2006;60(7):578-586.

The second multivariate adjustment considered was outcome regression. In this approach a logistic regression model was fit for regressing the conditional probability of Day 14 all-cause mortality as a function of baseline Gram-negative coverage and the aforementioned 25 baseline variables. The fitted logistic regression model was then used to estimate the causal effect of dispensing or withholding baseline Gram-negative coverage through the standardization (or "G-computation") method[4].

The third and final approach was to perform doubly robust estimation[5]. This method estimated causal effects by combining the fit of the propensity score model with the fit of the outcome regression model, and had the beneficial theoretical property that only one of the two regression models needed to be well-specified.

The bootstrap method was then applied with 10,000 resamples to estimate standard errors for each of the three multivariate adjustment techniques, where in each resample the imputation for missing baseline covariate values was redone. Confidence intervals were formed through the normal approximation. The table below shows results for the three multivariate adjustment techniques.

Table 5: Multivariate regression adjustments for estimating the effect of baseline Gram-negative coverage on Day 14 mortality in subjects with a Gram-negative (GN) pathogen.

Multivariate Adjustment	GN Coverage	No GN Coverage	Difference (95% CI)
Inverse PS weighting	10.7	18.4	-7.7 (-14.6, -0.9)
Standardization	11.1	19.2	-8.1 (-14.5, -1.8)
Doubly robust estimation	10.8	17.8	-7.0 (-13.6, -0.4)

The estimated treatment effects of around 8% were similar to the unadjusted result, and reached nominal statistical significance. Furthermore, the three methods gave similar results even though the propensity score method and outcome regression method were based on fitting statistical models for two different conditional probability distributions.

6 Comments on telavancin and nephrotoxicity

One issue in this review is the appearance of a safety signal related to nephrotoxicity. It was somewhat surprising that a nephrotoxicity signal would appear in a vancomycin-controlled trial, because vancomycin itself is a nephrotoxic drug. However, the table below shows that in the all-treated population (AT Population, an intent-to-treat analysis group of randomized subjects who received a dose of study drug) of the pooled trials, telavancin led to significantly higher mortality in subjects with baseline creatinine clearance ≤50 mL/min. The table also shows minimal difference in the excess mortality between groups with CrCl ≤30 mL/min and 30<CrCl≤50 mL/min. Additionally, a similar nephrotoxicity signal was seen in the registration trials of telavancin that led to its

[4] Snowden J, Rose S, and Mortimer K. Implementation of G-computation on a simulated data set: demonstration of a causal inference technique. *American Journal of Epidemiology*, 2011;173.
[5] Bang H and Robins J. Doubly robust estimation in missing data and causal inference models. *Biometrics*, 2005;61:692-972

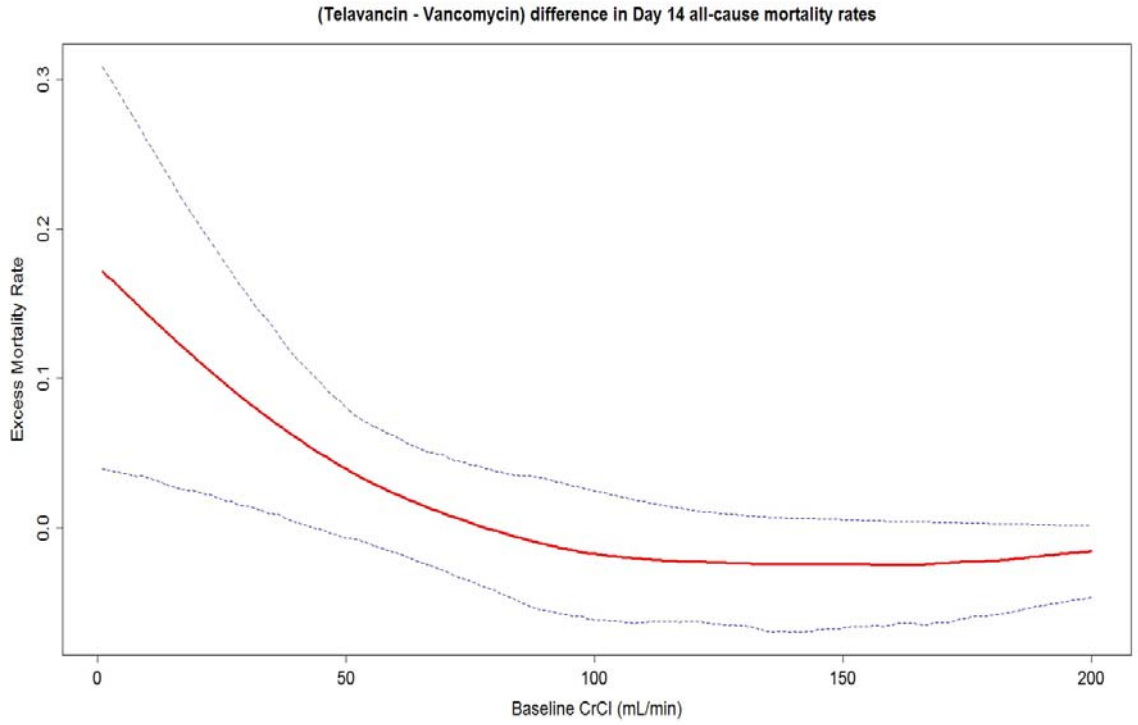
FDA approval for the treatment of complicated skin and skin structure infections. The table does not show evidence of a mortality signal for subjects who had baseline renal function of CrCL>50 mL/min. If the indication is granted, an important consideration in labeling will concern handling of subjects with baseline renal dysfunction.

Table 6: Baseline renal function and Day 14 mortality of telavancin and vancomycin; AT Population; Pooled Study 0015 and Study 0019

Baseline CrCl (mL/min)	Telavancin	Vancomycin	Difference (95% CI)
CrCl≤30	34/98 (34.7)	26/96 (27.1)	7.6 (-5.4, 20.4)
30< ClCr≤50	34/157 (21.7)	22/154 (14.3)	7.4 (-1.2, 16.0)
CrCl≤50	68/255 (26.7)	48/250 (19.2)	7.5 (0.1, 14.8)
50<ClCr≤80	32/202 (15.8)	20/203 (14.8)	1.1 (-6.0, 8.2)
CrCl>80	17/292 (5.8)	23/301 (7.6)	-1.8 (-6.0, 2.3)

This reviewer also fit a generalized additive model with a logistic link in the AT Population of the pooled studies that regressed Day 14 all-cause mortality on treatment status (telavancin or vancomycin), baseline renal function (with loess smoothing), and treatment by CrCl interaction (again with loess smoothing of CrCl). Figure 2 below plots the estimate of telavancin's excess mortality as a function of baseline CrCl. Pointwise 95% upper and lower confidence limits were formed with the bootstrap, similar to Efron (2005, Figure 5)[6]. This plot also suggests a nephrotoxicity-related mortality signal.

Figure 2: Estimated excess mortality as a function of baseline creatinine clearance



[6] Efron B. Bayesians, frequentists, and scientists. *Journal of the American Statistical Association*, 2005;100:1-5.

However, the analysis of Gram-negative coverage in this review also suggests that the nephrotoxicity safety issue is intertwined with the efficacy analysis in a complicated manner. From Table 4, there appears to be a large antibacterial mortality effect relative to placebo only in subjects with poor renal function. Note that baseline creatinine clearance is a marker for patient severity: in the AT population subjects with CrCl≤50 mL/min had an average age of 74 years, compared to 57 years for subjects with CrCl>50 mL/min. Therefore, while the difference in mortality rates between telavancin and vancomycin is only apparent in subjects with poor renal function, this reviewer notes that these may be exactly the subjects in whom there is the sensitivity to detect mortality differences between antibacterial drugs.

7 Summary and Conclusions

Results and conclusions from the analyses in this review can be summarized as follows:

- For subjects with Gram-negative baseline pathogens, withholding Gram-negative coverage was associated with higher mortality. This provided some evidence for the assay sensitivities of the trials under review for detecting ineffective therapy through mortality differences.
- The estimated antibacterial mortality benefit was much smaller than the 42% estimate in the Sorbello meta-analysis that has been used by FDA reviewers to justify noninferiority margins. A potential bias in previous analyses of subjects who received delayed or inadequate therapy due to drug resistance was that these subjects likely had greater severity of illness at baseline[7]. However, analyses in this review may have underestimated antibacterial effects since "No Gram-negative coverage" still reflected delayed therapy rather than a placebo.
- A limitation of this analysis was that baseline Gram-negative coverage was not randomized. Although univariate and multivariate regression adjustments gave similar results to the raw unadjusted results, the groups that did and did not receive coverage may have differed in ways not fully encapsulated by Table 1.
- For subjects with a Gram-negative pathogen at baseline there was no estimated benefit of adjunctive Gram-negative coverage on clinical cure rates even though this coverage was associated with significantly lower mortality. This reviewer therefore recommends caution in basing noninferiority conclusions from Study 0015 and Study 0019 on clinical response results.
- There is some evidence that the Day 28 mortality endpoint may be less sensitive for detecting ineffective therapy than when defined earlier, such as at Day 14.
- Exploratory subgroup analysis suggested the largest antibacterial treatment effect on mortality appeared to be for subjects in relatively severe condition at baseline (e.g., high APACHE II scores or poor renal function), and that antibacterial mortality effects were largely attenuated in complementary subgroups of patients in less severe condition. This reviewer therefore recommends caution in basing efficacy conclusions on mortality results in subjects with normal renal function.

[7] Rosenberger L, LaPar D, and Sawyer R. Infections caused by multidrug resistant organisms are not associated with overall, all-cause mortality in the surgical intensive care unit: the 20,000 foot view. *Journal of the American College of Surgeons*, 2012;214(5):747-755.

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-407 / 0000
Drug Name:	Telavancin for Injection (10 mg/kg IV q24h)
Indication(s):	Nosocomial Pneumonia
Applicant:	Theravance Inc.
Date(s):	6/30/10
Review Priority:	Class 2 Resubmission
Biometrics Division:	DBIV
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products (DAIOP)
Clinical Team:	Benjamin Lorenz, MD
	Janice Pohlman MD, MPH
Project Manager:	Christopher Davi, MS

Keywords: active control/non-inferiority

Table of Contents

1 CONCLUSIONS AND RECOMMENDATOINS

The Applicant did not provide substantial evidence that telavancin is effective for the treatment of nosocomial pneumonia (NP). While the applicant attempted to address the issues specified in the 11/23/09 complete response letter, this reviewer does not find that the issues have been adequately addressed.

Specifically, analyses including the additional 28-day all-cause mortality data, did not demonstrate noninferiority using a 10% NI margin in the microbiological all-treated (MAT) population that excluded patients who had only gram-negative pathogens isolated at baseline. Additionally, there are potential safety concerns because in the all-treated population for Study 0015, the telavancin mortality rate is almost statistically significantly ($p<0.05$) higher than vancomycin (treatment difference: 5.8%; 95% CI: (-0.3%, 11.9%). In addition, the Applicant did not provide a compelling argument to pool patients across the two trials. The baseline differences in patients between the two trials make pooling of patients across the two trials a concern. Finally, the Applicant's attempt to conduct subgroup analyses in the patients who met the criteria in the IDSA/ATS guideline still suffers from issues in the conduct of the trials that were identified by the Medical Officer during the first cycle review. These subgroup analyses had findings that are similar to those of the primary analyses, i.e., MAT excluding patients who had only gram-negative pathogens isolated at baseline. It should be noted for the subgroup analyses that neither trial demonstrated noninferiority using a 10% NI margin.

The Applicant conducted two Phase 3 trials (0015 and 0019), with identical protocols, in patients with NP. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours. Treatment duration was to be from 7 to 21 days. Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively. Study 0015 was conducted in 22 countries with 31% of the randomized and treated patients coming from the United States, while Study 0019 was conducted in 29 countries with a much lower percentage (14%) of the randomized and treated patients coming from the United States.

The Applicant initial submission (dated 1/23/09) was not approved and the Agency sent a complete response letter on 11/23/09. The Applicant subsequently submitted a response on 12/22/09. However, the response was deemed to be incomplete on 1/25/10.

While the proportion of patients with missing 28-day all-cause mortality status has been substantially reduced in this submission (Study 0015: 35% to 6%; Study 0019: 28% to 5%), there is still some missing data. The Applicant proposed to treat these patients as censored observations. Because most of patients are missing because they had their test-of-cure (TOC) visit prior to Day 28 and were not followed later per the protocol, the assumption that these patients were noninformative dropouts may be a reasonable assumption.

Because both treatment groups have only gram-positive activity, the Division decided that the primary efficacy analyses should be performed in the micro AT (MAT) population which

excluded patients who had only gram-negative pathogens isolated at baseline. In Table 6, it can be seen that the estimated difference in 28-day all-cause mortality rates for Study 0015 is 4.4% (telavancin: 28.7%; vancomycin: 24.3%) with a corresponding 95% CI of (-4.7%, **13.5%**). For Study 0019, the estimated difference in 28-day all-cause mortality rates is 2.0% (telavancin: 24.3%; vancomycin: 22.3%) with a corresponding 95% CI of (-6.1%, **10.0%**). It is important to note that that the upper bound for Study 0015 is markedly higher than the NI margin of 10% and thus noninferiority is not demonstrated using a 10% NI margin.

Also concerning is that in Study 0015, the 28-day all-cause mortality is higher in the telavancin treated patients (25.9%) than for those who received vancomycin (20.1%) with an estimated increase of 5.8% (Table 4) and a 95% CI of (-0.3%, 11.9%). This is an almost statistically significant ($p<0.05$) increase in 28-day all-cause mortality. However, this result was not duplicated in Study 0019.

Further analyses suggest that baseline renal function is potentially related to the increase in 28-day all-cause mortality seen for telavancin. Using a Cox proportional hazards model with treatment and acute renal failure as predictors, there was a significant interaction ($p<0.10$) between treatment and baseline acute renal failure in the all-treated population for both of the trials suggesting that the treatment effect varies depending on whether the patient had acute renal failure at baseline. This can be seen in Table 10 where there is at least a 20% increase for both trials in mortality for telavancin compared to vancomycin in patients with acute renal failure at baseline as compared to minimal or no increase in patients who did not have acute renal failure at baseline. In addition, for Study 0019, the mortality difference between telavancin and vancomycin increased as baseline renal function decreased (Table 12). Furthermore, for Study 0019, in patients with chronic renal failure, the estimated mortality difference is 31% with a 95% CI of (-4.6%, 66.7%) while patients who do not have chronic renal failure at baseline have an estimated mortality difference of -2.6% with a 95% CI of (-8.8%, 3.5%), see Table 14

There are several additional issues with this review. The first issue is that this reviewer does not agree with the Applicant's strategy to demonstrate efficacy by comparing the telavancin arm from the current trials to a historical control, i.e., the patients who received in adequate or delayed treatment for NP from historical studies. The well known concern with the use of historical controls is the issue of baseline comparability of the patients. The information provided by the Applicant does not adequately address this concern.

The second issue is the pooling of patients across the two trials. The Applicant provided a rationale to pool patients but this reviewer does not agree with their argument. Although the protocols for the two trials were identical and conducted concurrently, Dr. Alfred Sorbello, the medical reviewer for the initial submission, found several differences between the two trials in the distribution of potential risk factors for mortality, e.g. diabetes mellitus and renal impairment/failure). There were more patients in Study 0015 with chronic renal failure, baseline CrCl<50 mL/min, serum creatinine >1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, HCAP, torsades, history of atrial fibrillation, and history of myocardial infarction. It is evident that the populations were substantially different based on pre-treatment

characteristics and co-morbid conditions such that pooling for mortality analysis was not advisable and that the mortality data for each study should be assessed individually.

Another issue was the Applicant's inclusion of post-hoc selected prognostic risk factors for mortality in their analyses. This is problematic because it is a data-driven analysis and can bias the results. Furthermore, the Applicant's assertion that there is a need to include these factors to account for imbalance is questionable because the trials were randomized so any imbalances between the two treatment arms are due to chance. The effect of any apparent observed imbalances is accounted for with the type I error. We view the analyses that include prognostic factors as exploratory. It should be noted that these prognostic factors were not included in the initial pre-specified primary analysis of clinical response at TOC.

Another issue in analyzing the trials was that substantial proportion of the patient who received adjunctive agents to provide gram-negative coverage. Specifically, for patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria in addition to the Gram-positive pathogens for which study medication therapy are used, aztreonam and/or metronidazole therapy, respectively, should be used. Piperacillin-tazobactam or imipenem may be administered for Gram-negative coverage only if aztreonam is not appropriate due to an unacceptable level of resistance among Gram-negative bacteria

Some of these agents also had overlapping gram-positive activity so their use could potentially confound the efficacy analysis for the trials. Two sensitivity analyses were performed. The first analysis was in the subgroup of MRSA patients who did not receive any adjunctive agents that had MRSA activity. The second analysis was in the subgroup of microbiological all-treated patients who did not have only a gram-negative organism isolated at baseline and who did not receive any adjunctive agents with gram-positive activity. The results of these analyses, presented in Table 19 and Table 21, are similar to those for of the primary analysis and do not provide evidence that the adjunctive agents with overlapping gram-positive coverage had a large effect.

Finally, there was a concern identified in the review of the first cycle submission, that the inclusion criteria did not provide a high likelihood that the patients had NP. This is imperative in a non-inferiority analysis because in a noninferiority study, lack of assurance that the patients have the disease under study could bias the results towards a finding of noninferiority. Rather than conducting new trials as recommended in the complete response letter, the Applicant chose to perform subgroup analyses in patients who met the criteria specified in the IDSA/ATS guideline. However, there are still concerns with these subgroup analyses. The first issue is that independent confirmation of the investigator's interpretation of the chest radiographs was not required and often not performed. Additionally, temperature readings based on axillary measurement are used for a large number of patients. This is concerning because of questions on the accuracy of the axillary method. Finally quality assessments of the endotracheal aspirates were not provided.

Bearing in mind the limitations for the subgroups, the analyses in this subgroup (CXR+2F) had finding that are similar to those of the primary analyses. It should be noted for CXR+2F analyses that neither trial demonstrated noninferiority using a 10% NI margin.

All of these issues provide further uncertainty in the interpretation of the results of Studies 0015 and 0019.

2 SUBMISSION OVERVIEW

This NDA was submitted in support of telavancin for injection for the proposed indication of treatment of NP. The submission contains the Applicant's response to the complete response letter issued by the Agency on 11/23/09. The Applicant subsequently submitted a response on 12/22/09. However, the response was deemed to be incomplete on 1/25/10.

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is the treatment of nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant strains) and *Streptococcus pneumoniae*.

The proposed dosing regimen for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days.

Telavancin is eliminated primarily by the kidney. The dosage is adjusted for patients with renal impairment. For patients with moderate (creatinine clearance [CrCL] 30-50 mL/min) impairment, the dosage is decreased to 7.5 mg/kg every 24 hours. In contrast, for those with severe (CrCL 10-30 mL/min) renal impairment, the dosage is decreased to 10 mg/kg every 48 hours. Finally, there are no dosage recommendations for patients with end-stage renal disease (CrCL <10 mL/min), including patients receiving hemodialysis.

Telavancin was studied previously for the treatment of complicated skin and skin structure infections (cSSSI). Three clinical trials (202b, 0017, and 0018) were conducted in patients with cSSSI at the same dosage (10 mg/kg) as the current submission. The dosage was increased from 7.5 mg/kg to 10 mg/kg during the Phase 3 trials based on the results of the results of Study 202b. Another study, 202a, was conducted at the lower the 7.5 mg/kg dosage. Telavancin was approved to treat patients with cSSSI at the 10 mg dose on 11 September 2009.

The Applicant conducted two Phase 3 trials (0015 and 0019), with identical protocols, in patients with NP. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours. Treatment duration was to be from 7 to 21 days. Because both the test and comparator drugs do not have activity against gram-negative pathogens, a substantial number of patients received empiric gram-negative coverage. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. In addition, piperacillin/tazobactam was also permitted for coverage of Gram-negative organisms if resistance to aztreonam was known or suspected. The Original Protocol had also allowed imipenem for Gram-negative coverage as well as aztreonam and/or metronidazole therapy; however, imipenem was removed as a treatment option in Protocol Amendment 1.

Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively. Study 0015 was conducted in 22 countries with 31% of the randomized and treated patients coming from the United States, while Study 0019 was conducted in 29 countries with a much lower percentage (14%) of the randomized and treated patients coming from the United States.

Patients were randomized in a 1:1 ratio with randomization stratified on the combination of a pre-specified country grouping (see Table 1 for the pre-specified country groupings), the presence or absence of diabetes, and ventilatory status of the patient.

Table 1: Country Groupings used in Stratified Randomization

Country Grouping	Study 0015	Study 0019
1	Australia	Australia
	Belgium	Canada
	Canada	France
	France	Israel
	Israel	Spain
	Italy	United States
	United Kingdom	
	United States	
2	Argentina	Argentina
	Brazil	Brazil
	Chile	Chile
	South Africa	South Africa
	Taiwan	
3	Croatia	Bulgaria
	Czech Republic	China
	Greece	Croatia
	India	Czech Republic
	Malaysia	Estonia
	Malta	Georgia
	Peru	Greece
	Poland	Korea
	Turkey	Lebanon
		Lithuania
		Mexico
		Philippines
		Poland
		Romania
		Russia
		Serbia/Montenegro
		Slovakia
		Thailand
		Ukraine

Source: Clinical Overview, Table 2

Additional details can be found in my review of the first cycle submission (received date: 1/26/09).

The 11/23/09 complete response letter cited the following deficiencies:

1. Submit all available all-cause mortality data and account fully for any censored information. In addition, provide a listing of the patients by trial in which mortality status is not known up to the end of the mortality reporting window. The listing should include study number, subject ID, randomized treatment group, actual treatment group, and last Study Day that mortality status is known. A tabulation of the subjects whose mortality status is unknown should also be provided by trial and treatment group, as well as a summary that presents the distribution of the Study Day where censoring occurs by trial and treatment group.
2. Provide a scientific rationale for pooling all-cause mortality data across the two clinical trials. The rationale should address the consistency of the treatment difference for telavancin relative to vancomycin across the trials given the difference in the distribution of baseline prognostic factors for mortality between the two trials and the proportion of subjects whose mortality status is censored.
3. In design of the new clinical trials for the NP indication, consider the following:
    a. The study population should contain patients with a high likelihood of having the disease of interest. Therefore, the inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever > 38°C, leukocytosis or leukopenia, and purulent lower respiratory tract secretions.
    b. Chest radiograph interpretation should be performed by a blinded healthcare provider, preferably a radiologist or pulmonologist, not directly involved in assessment of the patient for enrollment or during subsequent care.
    c. Uniform criteria should be applied to identify the quality of sputum and endotracheal aspirate specimens for culture and subsequent pathogen identification.
    d. The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

In order to address the first deficiency, the Applicant provided additional 28-day all-cause mortality data that substantially reduced the percentage of patients with missing mortality data (Study 0015: 35% to 6%; Study 0019: 28% to 5%). The analysis of this data to included in Section 3.

To address the second deficiency, the Applicant provided a rationale to pool patients across the two trials. This rationale was not found to be convincing and is discussed in Section 4.

Rather than conducting new clinical trials as recommended in the third point, the Applicant instead chose to conduct sensitivity analyses using the criteria specified in the complete response letter. The results of these analyses are discussed in Section 3.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

The trials were designed using a primary efficacy endpoint of clinical response at Test of Cure (TOC) with an NI margin of 20%. However, the Division subsequently informed that Applicant on 6/9/2009 that assessment of the noninferiority of telavancin compared with vancomycin

would depend on the analysis of the all-cause mortality data. The reason for the change in the primary endpoint was as reported in Sorbello et al (DIJ, 2010), there are no published data on clinical response or non-mortality related endpoints for NP to estimate the placebo response rate.

28-Day All-cause Mortality

In the original NDA, there was incomplete survival information for the 28-day period in a large proportion of the patients (Study 0015: 34.9%; Study 0019: 28.5%). This occurred primarily because the protocols for 0015 and 0019 required that safety data through the follow-up visit (7-14 after EOT) be reported for each patient. Because the duration of treatment was 7-21 days, a large number of patients were not followed up to Day 28. The Applicant retrospectively went back and determined survival status. In the new submission, the percentage of patients with incomplete survival for the 28-day period has substantially decreased (Study 0015: 6%; Study 0019: 5%).

The results for all-cause mortality at Day 28 are presented below:

Table 2: Summary of 28-day all-cause mortality (AT Population)

	0015		0019	
	Telavancin (n=372)	Vancomycin (n=374)	Telavancin (n=377)	Vancomycin (n=380)
Deaths Between Start of Study Drug and Study Day 28	95 (25.5%)	74 (19.8%)	83 (22.0%)	90 (23.7%)
Alive	258 (69.4%)	272 (72.7%)	277 (73.5%)	270 (71.1%)
Lost of follow-up	19 (5.1%)	28 (7.5%)	17 (4.5%)	20 (5.3%)

Source: ISE, Table 4-1

Note: 2 patients in Study 0019 were randomized to the vancomycin group but received telavancin, 1 patient was alive at the end of the 28-day study window while the other patient died on Day 3.

The censored patients in the above table represent patients whose survival status is not known through Day 28. The Applicant proposed to treat these patients as censored observations. Because most of patients are missing because they had their TOC visit prior to Day 28 and were not followed later per the protocol, the assumption that these patients were noninformative dropouts may be a reasonable assumption.

The distribution of the last day that the patient was known to be alive is presented below:

Table 3: Lost of follow-up: study day last known to be alive

	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

The results for the AT population in Table 4 are concerning because 1) telavancin mortality rate is almost statistically significantly ($p<0.05$) higher than vancomycin (treatment difference: 5.8%; 95% CI: (-0.3%, 11.9%) in Study 0015; and 2) the upper bound for Study 0015 is markedly

higher than the NI margin of 10% specified in the Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment published on 11/2010.

Table 4: Estimated 28-Day All-Cause Mortality (AT Population)

Study	Treatment	Estimated K-M Mortality at 28 Days (%)	Diff (%) (TLV - VAN) 95% CI
0015	TLV	25.9	5.8
	VAN	20.1	(-0.3, **11.9**)
0019	TLV	22.3	-1.9
	VAN	24.2	(-8.0, **4.42**)

Deaths occurring after Day 28 are censored
Adapted from ISE addendum, Table 4-2

Because both treatment groups have only gram-positive activity, the Division decided that the primary efficacy analyses should be performed in the micro AT (MAT) population which excluded patients who had only gram-negative pathogens isolated at baseline. In Table 6, it can be seen that the estimated difference in 28-day all-cause mortality rates for Study 0015 is 4.4% (telavancin: 28.7%; vancomycin: 24.3%) with a corresponding 95% CI of (-4.7%, **13.5%**). For Study 0019, the estimated difference in 28-day all-cause mortality rates is 2.0% (telavancin: 24.3%; vancomycin: 22.3%) with a corresponding 95% CI of (-6.1%, **10.0%**) as given in Table 6. It is important to note that that the upper bound for Study 0015 is markedly higher than the NI margin of 10%.

Table 5: 28-Day All-Cause Mortality (Micro AT (MAT) excluding patients w/only gram-negative pathogens isolated at baseline.

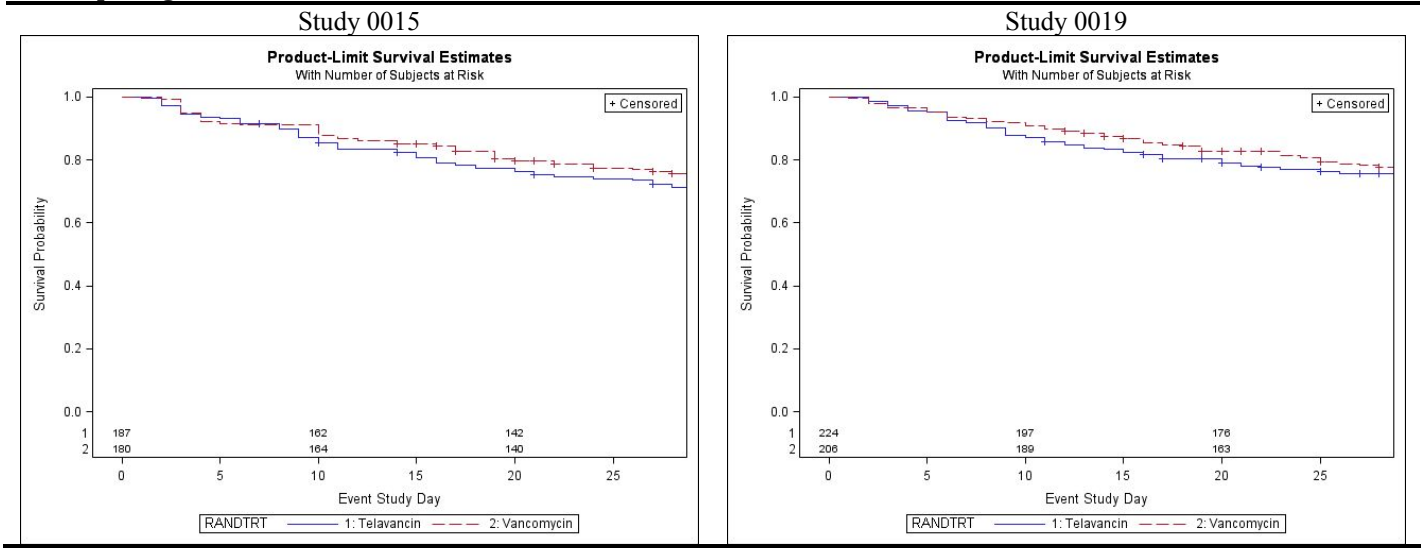
	0015		0019	
	Telavancin (n=187)	Vancomycin (n=180)	Telavancin (n=224)	Vancomycin (n=206)
Deaths Between Start of Study Drug and Study Day 28	53 (28.3)	43 (23.9)	54 (24.1)	45 (21.8)
Alive	128 (68.4)	123 (68.3)	161 (71.9)	148 (71.8)
Lost of follow-up	6 (3.2)	14 (7.8)	9 (4.0)	13 (6.3)

Table 6: Estimated 28-Day All-Cause Mortality (MAT excluding patients w/only gram-negative pathogens isolated at baseline

Study	Treatment	Estimated K-M Mortality at 28 Days (%)	Diff (%) (TLV - VAN) 95% CI
0015	TLV	28.7	4.4
	VAN	24.3	(-4.7, 13.5)
0019	TLV	24.3	2.0
	VAN	22.3	(-6.1, 10)

Lost to follow-up and deaths occurring after Day 28 are censored

Figure 1: Kaplan-Meier curve of All-cause Mortality for MAT patients excluding those w/only gram-negative pathogens isolated at baseline.



3.2 EVALUATION OF SAFETY

The following tables provided below as very similar to those provided in Table 2 and Table 4 with the exception that the two patients in Study 0019 who were randomized to the vancomycin group but received telavancin will be categorized with the telavancin group. Of these two patients, one was alive at the end of the 28-day study window while the other patient died on Day 3.

Table 7: Summary of 28-day all-cause mortality (AT Population)

	0015		0019	
	Telavancin (n=372)	Vancomycin (n=374)	Telavancin (n=379)	Vancomycin (n=378)
Deaths Between Start of Study Drug and Study Day 28	95 (25.5%)	74 (19.8%)	84 (22.2%)	89 (23.5%)
Alive	258 (69.4%)	272 (72.7%)	278 (73.4%)	269 (71.2%)
Lost of follow-up	19 (5.1%)	28 (7.5%)	17 (4.5%)	20 (5.3%)

Source: modified from ISE addendum, Table 4-1
Patients classified as treated

Table 8: Estimated 28-Day All-Cause Mortality (AT Population)

Study	Actual Treatment	Estimated K-M Mortality at 28 Days (%)	Diff (%) (TLV - VAN) 95% CI
0015	TLV	25.9	5.8
	VAN	20.1	(-0.3, **11.9**)
0019	TLV	22.4	-1.6
	VAN	24.0	(-7.7, **4.5**)

Lost to follow-up and deaths occurring after Day 28 are censored
Adapted from ISE addendum, Table 4-2

For Study 0015, the 28-day all-cause mortality is higher in the telavancin treated patients (25.9%) than for those who received vancomycin (20.1%) with an estimated increase of 5.8% and a 95% CI of (-0.3%, 11.9%). This is an almost statistically significant ($p<0.05$) increase in 28-day all-cause mortality. However, this result was not duplicated in Study 0019 and the cause may be related to the higher proportional of patients with renal dysfunction at baseline in Study 0015. The discussion of differences in baseline characteristics is discussed in other sections of the review.

Effect of baseline renal dysfunction

Based on concerns with renal toxicity and lack of efficacy found in the complicated skin and skin trials (NDA 22-110), analyses were performed that examined the effect of various measures of baseline renal dysfunction.

Effect of history of acute renal failure

Using a Cox proportional hazards model with treatment and acute renal failure as predictors, there was a significant interaction ($p<0.10$) between treatment and baseline acute renal failure in the all-treated population for both of the trials suggesting that the treatment effect varies depending on whether the patient had acute renal failure at baseline. This can be seen in Table 9 where there is at least a 20% increase in mortality for telavancin compared to vancomycin in patients with acute renal failure at baseline as compared to minimal or no decrease in patients who did not have acute renal failure at baseline.

Table 9: 28-day all-cause mortality (AT population) — patients classified as Treated

History of Acute Renal Failure	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Yes	43	35	30	29
Deaths Between Start of Study Drug and Study Day 28	22 (51.2)	8 (22.9)	19 (63.3)	13 (44.8)
Alive	21 (48.8)	26 (74.3)	9 (30.0)	16 (55.2)
Censored	0	1 (2.9)	2 (6.7)	0
No	329	339	349	349
Deaths Between Start of Study Drug and Study Day 28	73 (22.2)	66 (19.5)	65 (18.6)	76 (21.8)
Alive	237 (72.0)	246 (72.6)	269 (77.1)	253 (72.5)
Censored	19 (5.8)	27 (8.0)	15 (4.3)	20 (5.7)

Table 10: Kaplan-Meier estimates of 28-day all-cause mortality (AT population)

Acute Renal Failure at baseline	Study 0015			Study 0019		
	Estimated K-M Mortality at 28 Days (%)		Diff (%) (TLV - VAN) 95% CI	Estimated K-M Mortality at 28 Days (%)		Diff (%) (TLV - VAN) 95% CI
	TLV	VAN		TLV	VAN	
Yes	51.2	22.9	28.3 (7.9, **48.7**)	65.1	44.8	20.3 (-4.8, **45.3**)
No	22.5	19.8	2.7 (-3.6, **8.9**)	18.8	22.2	-3.4 (-9.5, **2.6**)

Patients classified as treated

Effect of baseline creatinine clearance on 28-day all-cause mortality

Another important potential effect modifier for telavancin may be baseline creatinine clearance. The interaction term in the Cox proportional hazards model was significant ($p<0.10$) for Study 0019 but not for Study 0015 suggesting for Study 0019 that the treatment effect varied by baseline renal function. The results for these analyses are presented below:

Table 11: 28-day cause mortality (AT Population) by baseline creatinine clearance

Baseline creatinine clearance	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
>80 mL/min	143	152	181	181
Deaths Between Start of Study Drug and Study Day 28	17 (11.9)	21 (13.8)	19 (10.5)	33 (18.2)
Alive	114 (79.7)	120 (79.0)	156 (86.2)	136 (75.1)
Censored	12 (8.4)	11 (7.2)	6 (3.3)	12 (6.6)
>50 – 80 mL/min	88	88	97	89
Deaths Between Start of Study Drug and Study Day 28	24 (27.3)	15 (17.0)	25 (25.8)	23 (25.8)
Alive	63 (71.6)	63 (71.6)	65 (67.0)	61 (68.5)
Censored	1 (1.1)	10 (11.4)	7 (7.2)	5 (5.6)
30 – 50 mL/min	80	83	63	67
Deaths Between Start of Study Drug and Study Day 28	27 (33.8)	19 (22.9)	17 (27.0)	16 (23.9)
Alive	47 (58.8)	59 (71.1)	43 (68.2)	49 (73.1)
Censored	6 (7.5)	5 (6.0)	3 (4.8)	2 (3.0)
<30 mL/min	61	51	38	41
Deaths Between Start of Study Drug and Study Day 28	27 (44.3)	19 (37.2)	23 (60.5)	17 (41.5)
Alive	34 (55.7)	30 (58.8)	14 (36.8)	23 (56.1)
Censored	0	2 (3.9)	1 (2.6)	1 (2.4)

Table 12: Kaplan-Meier estimates of 28-day cause mortality (AT Population) by baseline creatinine clearance

Baseline Creatinine Clearance	Study 0015			Study 0019		
	Estimated K-M Mortality at 28 Days (%)		Diff (%) (TLV - VAN) 95% CI	Estimated K-M Mortality at 28 Days (%)		Diff (%) (TLV - VAN) 95% CI
	TLV	VAN		TLV	VAN	
>80	18.5	16.9	1.6 (-10.8, **13.9**)	11.7	15.8	-4.1 (-13.4, **5.2**)
>50-80	27.8	18.9	0.089 (-9.1, **27.0**)	30.2	27.8	2.4 (-15.3, **20.2**)
30-50	36.7	30.4	6.3 (-14.3, **26.9**)	33.6	23.8	9.8 (-12.0, **31.5**)
<30	50.0	44.0	6.0 (-21.9, **33.9**)	60.6	37.5	23.1 (-5.9, **52.2**)

Effect of baseline chronic renal failure on 28-day all-cause mortality

There was a significant interaction ($p<0.10$) between treatment and baseline chronic renal failure in the all-treated population for Study 0019 suggesting that the treatment effect varied depending on whether the patient had chronic renal failure at baseline. This can be seen in Table 14, where in patients with chronic renal failure, the estimated mortality difference is 31% with a 95% CI of (-4.6%, 66.7%) while patients who do not have chronic renal failure at baseline have an estimated mortality difference of -2.6% with a 95% CI of (-8.8%, 3.5%).

Table 13: 28-day all-cause mortality by chronic renal failure status at baseline

History of Chronic Renal Failure	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Yes	32	35	11	17
Deaths Between Start of Study Drug and Study Day 28	11 (34.4)	9 (25.7)	6 (54.6)	4 (23.5)
Alive	20 (62.5)	24 (68.6)	5 (45.4)	13 (76.5)
Censored	1 (3.1)	2 (5.7)	0	0
No	340	339	368	361
Deaths Between Start of Study Drug and Study Day 28	84 (24.7)	65 (19.2)	78 (21.2)	85 (23.6)
Alive	238 (70.0)	248 (73.2)	273 (74.2)	256 (70.9)
Censored	18 (5.3)	26 (7.7)	17 (4.6)	20 (5.5)

Table 14: 28-day all-cause mortality by baseline chronic renal failure status (AT Population)

Chronic Renal Failure at baseline	Study 0015			Study 0019		
	Estimated K-M Mortality at 28 Days (%)		Diff (%) (TLV - VAN) 95% CI	Estimated K-M Mortality at 28 Days (%)		Diff (%) (TLV - VAN) 95% CI
	TLV	VAN		TLV	VAN	
Yes	35.0	25.7	9.3 (-12.8, **31.4**)	54.6	23.5	31.0 (-4.6, **66.7**)
No	25.0	19.5	5.5 (-0.8, **11.8**)	21.4	24.1	-2.6 (-8.8, **3.5**)

4 STATISTICAL ISSUES AND FINDING

There are several issues with this review that will be discussed in this section. The first issue is that this reviewer does not agree with the Applicant's strategy to demonstrate efficacy by comparing the telavancin arm from the current trials to a historical control, i.e., the patients who received inadequate or delayed treatment for NP from historical studies. The well known concern with the use of historical controls is the issue of baseline comparability of the patients. The information provided by the Applicant does not adequately address this concern.

The second issue is the pooling of patients across the two trials. The Applicant provided a rationale to pool patients but this reviewer does not agree with their argument. Although the protocols for the two trials were identical and conducted concurrently, Dr. Alfred Sorbello, the medical reviewer for the initial submission, found several differences between the two trials in the distribution of potential risk factors for mortality, e.g. diabetes mellitus and renal impairment/failure). There were more patients in Study 0015 with chronic renal failure, baseline CrCl<50 mL/min, serum creatinine >1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, HCAP, torsades, history of atrial fibrillation, and history of myocardial infarction. It is evident that the populations were substantially different based on pre-treatment characteristics and co-morbid conditions such that pooling for mortality analysis was not advisable and that the mortality data for each study should be assessed individually.

Another issue was the Applicant's inclusion of post-hoc selected prognostic risk factors for mortality in their analyses. This is problematic because it is a data-driven analysis and can bias the results. Furthermore, the Applicant's assertion that there is a need to include these factors to

account for imbalance is questionable because the trials were randomized so any imbalances between the two treatment arms are due to chance. The effect of any apparent observed imbalances is accounted for with the type I error. We view the analyses that include prognostic factors as exploratory. It should be noted that these prognostic factors were not included in the initial primary analysis of clinical response at TOC.

Another issue in analyzing the trials was that substantial proportion of the patient who received adjunctive agents to provide gram-negative coverage. Specifically, for patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria in addition to the Gram-positive organisms for which study medication therapy are used, aztreonam and/or metronidazole therapy, respectively, should be used. Piperacillin-tazobactam or imipenem may be administered for Gram-negative coverage only if aztreonam is not appropriate due to an unacceptable level of resistance among Gram-negative bacteria

Some of these agents also had overlapping gram-positive activity so their use could potentially confound the efficacy analysis for the trials. Two sensitivity analyses were performed. The first analysis was in the subgroup of baseline MRSA patients who did not receive any adjunctive agents that had MRSA activity. The second analysis was in the subgroup of microbiological all-treated patients who did not have only a gram-negative organism isolated at baseline and who did not receive any adjunctive agents with gram-positive activity. The results of these analyses, presented in Table 19 and Table 21, are similar to those for of the primary analysis and do not provide evidence that the adjunctive agents with overlapping gram-positive coverage had a large effect.

Finally, there was a concern identified in the review of the first cycle submission, that the inclusion criteria did not provide a high likelihood that the patients had NP. This is imperative in a non-inferiority analysis because in a noninferiority study, lack of assurance that the patients have the disease under study could bias the results towards a finding of noninferiority. Rather than conducting new trials as recommended in the complete response letter, the Applicant chose to perform subgroup analyses in patients who met the criteria specified in the IDSA/ATS guideline. However, there are still concerns with these subgroup analyses. The first issue is that independent confirmation of the investigator's interpretation of the chest radiographs was not required and often not performed. Additionally, temperature readings based on axillary measurement are used for a large number of patients. This is concerning because of questions on the accuracy of the axillary method. Finally quality assessments of the endotracheal aspirates were not provided.

Bearing in mind the limitations for the subgroups, the analyses in this subgroup (CXR+2F) had finding that are similar to those of the primary analyses. It should be noted for CXR+2F analyses that neither trial demonstrated noninferiority using a 10% NI margin.

The detailed discussion of these issues follows:

Analysis strategy

The Applicant took a different approach than usual to demonstrate the effect of telavancin in the two Phase 3 trials. Their approach involved superiority analyses comparing the telavancin arm from Studies 0015 and 0019 to an imputed placebo using the historical data of studies that

looked at the effect of inadequate or delayed treatment of NP. They stated that they took this approach because there are no placebo controlled studies with the active comparator to demonstrate a historical treatment effect for the comparator. The historical studies they used were the ten identified by Sorbello et al. (DIJ, 2010) and two additional studies that they indentified.

A second analysis compared vancomycin to the putative placebo with the intention to demonstrate assay sensitivity. Finally, an analysis that pooled the data across the two trials (Studies 0015 and 0019) and controlled for prognostic factors provided an estimate of the relative effect of telavancin compared to vancomycin.

The main issue with the analysis strategy is the use of a historical control group to demonstrate effectiveness. There are well known issues with the use of a historical control group. These are specified in ICH E10 Guideline: Choice of Control Group and Related Issues in Clinical Trials. The guideline points out that the ability to minimize bias is a major issue with these types of trials. It is difficult to establish comparability of the treatment and control groups, which is essential to fulfill the major purpose of the control group, i.e. the ability to discriminate patient's outcomes caused by treatment from outcomes caused by other factors. Control groups in a randomized study need to meet certain criteria to be entered into the study, criteria that are generally more stringent and identify a less sick population than is typical of external control groups. In addition, patient management is often not well characterized for the external control group and thus difficult to assess the comparability to the current trial.

As noted, the lack of randomization and blinding, and the resultant problems with lack of assurance of comparability of test group and control group, make the possibility of substantial bias inherent in this design and impossible to quantify.

Some approaches to design and conduct of externally controlled trials could lead them to be more persuasive and potentially less biased. A control group should be chosen for which there is detailed information, including, where pertinent, individual patient data regarding demographics, baseline status, concomitant therapy, and course on study. The control patients should be as similar as possible to the population expected to receive the test drug in the study and should have been treated in a similar setting and in a similar manner, except with respect to the study therapy. Study observations should use timing and methodology similar to those used in the control patients.

Externally controlled trials are most likely to be persuasive a) when the study endpoint is objective, b) when the outcome on treatment is markedly different from that of the external control and a high level of statistical significance for the treatment-control comparison is attained, c) when the covariates influencing outcome of the disease are well characterized, and d) when the control closely resembles the study group in all known relevant baseline, treatment (other than study drug), and observational variables. Even in such cases, however, there are documented examples of erroneous conclusions arising from such trials.

The externally controlled study cannot be blinded and is subject to patient, observer, and analyst bias; these are major disadvantages. It is possible to mitigate these problems to a degree. However, one cannot resolve such problems fully, as treatment assignment is not randomized and comparability of control and treatment groups at the start of treatment, and comparability of treatment of patients during the trial, cannot be ensured or well assessed. It is well documented that externally controlled trials tend to overestimate efficacy of test therapies. It should be recognized that tests of statistical significance carried out in such studies are less reliable than in randomized trials.

Comparability of patients

The Applicant proposed to look at twelve studies of patients who received inadequate or delayed therapy. Because of the lack of information on baseline data in these twelve studies, they were only able to find two studies, Koleff and Luna, whose baseline age and APACHE II score were presented and were similar to the telavancin trials. However, there is limited information on the other baseline characteristics of these patients in the historical studies. In addition, all of the patients in the historical trials were VAP patients while in the telavancin trials, only 28% (Study 0015) and 30% (Study 0019) were VAP patients. This is concerning when the 28-day all-cause mortality is analyzed by baseline VAP status where in Study 0019, the mortality rate is markedly higher for VAP patients than for non-VAP patients. Thus, the lower proportion of patients with VAP in the telavancin trials compared to the historical studies is concerning with regards to comparability.

Table 15: 28-day all-cause mortality by baseline VAP status excluding MAT patients who had only gram-negative pathogens isolated at baseline

VAP status at baseline	Telavancin	
	0015	0019
Yes	60	77
Deaths Between Start of Study Drug and Study Day 28	18 (30.0)	25 (32.5)
Alive	39 (65.0)	51 (66.2)
Censored	3 (5.0)	1 (1.3)
No	127	147
Deaths Between Start of Study Drug and Study Day 28	35 (27.6)	29 (19.7)
Alive	89 (70.1)	110 (74.8)
Censored	3 (2.4)	8 (5.4)

Table 16: 28-day all-cause mortality by baseline VAP status excluding MAT patients who had only gram-negative pathogens isolated at baseline

VAP status at baseline	Telavancin est. K-M Mortality Rate at 28 Days (%)	
	0015	0019
Yes	30.5	32.4
No	27.8	19.9

There was a differential distribution of baseline pathogens between the telavancin trials and the historical studies. In the telavancin trials, approximately 40% of the patients had MRSA at

baseline compared with approximately 20% in the historical studies. In contrast, *P. aeruginosa* and *Acinetobacter spp* were recovered in 20% to 30% and 5% to 28%, respectively of patients in the historical studies, compared with up to 11% to 18% in the telavancin trials.

The Applicant provided publications to support their hypothesis that the mortality associated with *S. aureus* (especially MRSA) as a pneumonia pathogen appears to be at least as high as other respiratory pathogens including *P. aeruginosa*. However, these findings are not consistent with earlier findings that found highly pathogenic Gram-negative organisms such as *P. aeruginosa* are associated with the highest rates of morbidity and mortality. This uncertainty in the effect of the baseline infecting organism is concerning given the differential distribution of infecting baseline organisms between the historical studies and the telavancin trials.

Adjunctive gram-negative coverage

Another issue in analyzing the trials was that a substantial proportion of the patient received adjunctive agents to provide gram-negative coverage. Specifically, for patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria in addition to the Gram-positive organisms for which study medication therapy is used, aztreonam and/or metronidazole therapy, respectively, should be used. Piperacillin-tazobactam or imipenem may be administered for Gram-negative coverage only if aztreonam is not appropriate due to an unacceptable level of resistance among Gram-negative bacteria. Each site must select one of these agents for use in all patients for whom aztreonam is not appropriate. However, as piperacillin-tazobactam and imipenem have activity against MSSA and *Streptococcus pneumoniae*, patients with those organisms, who require more than 24 hours of treatment with one of these medications, should not be enrolled. If the patient is already enrolled, the piperacillin-tazobactam or imipenem must be discontinued after no more than 24 hours of therapy. Otherwise, the patient must be discontinued from the study. Finally, therapy with metronidazole is unnecessary if either piperacillin-tazobactam or imipenem are administered, as these agents have activity against anaerobic bacteria.

Table 17: Patients who received adjunctive antimicrobial agents for initial gram-negative

Antimicrobial	Study 0015		Study 0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Aztreonam	160	167	160	169
Piperacillin/tazobactam*	42	36	23	33
Imipenem	4	0	5	2

* In Study 0015, 1 telavancin subject received piperacillin alone

To investigate the effect of adjunctive agents given to provide gram-negative coverage, two sensitivity analyses were performed. The first analysis was in the subgroup of MRSA patients who did not receive any adjunctive agents that had MRSA activity. The second first analysis was in the subgroup of microbiological all-treated patients who did not have only a gram-negative organism isolated at baseline and who did not receive any adjunctive agents with gram-positive activity. The results of these analyses, presented in Table 19 and Table 21, are similar to those for of the primary analysis and do not provide evidence that the adjunctive agents with overlapping gram-positive coverage had a large effect.

Table 18: 28-Day All-Cause Mortality (MAT including only patients MRSA at baseline) excluding patients who received adjunctive agents w/MRSA activity

	0015		0019	
	Telavancin (n=115)	Vancomycin (n=114)	Telavancin (n=118)	Vancomycin (n=116)
Deaths Between Start of Study Drug and Study Day 28	36 (31.3)	27 (23.7)	39 (33.0)	34 (29.3)
Alive	76 (66.1)	75 (65.8)	75 (63.6)	77 (66.4)
Lost of follow-up	3 (2.6)	12 (10.5)	4 (3.4)	5 (4.3)

1 vancomycin patient received a concomitant agent w/MRSA activity and was excluded

Table 19: Estimated 28-Day All-Cause Mortality (MAT including only patients MRSA at baseline) excluding patients who received concomitant agents w/MRSA activity

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

Table 20: 28-Day All-Cause Mortality (MAT including only patients w/gram-positive pathogens isolated at baseline) excluding patients who received adjunctive agents w/gram-positive activity

	0015		0019	
	Telavancin (n=164)	Vancomycin (n=163)	Telavancin (n=130)	Vancomycin (n=125)
Deaths Between Start of Study Drug and Study Day 28	47 (28.7)	39 (23.9)	47 (23.4)	38 (20.5)
Alive	112 (68.3)	110 (67.5)	146 (72.6)	134 (72.4)
Lost of follow-up	5 (3.0)	14 (8.6)	8 (4.0)	13 (7.0)

Table 21: Estimated 28-Day All-Cause Mortality (MAT excluding patients w/only gram-negative pathogens isolated at baseline patients who received adjunctive agents w/gram-positive activity

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

Deaths occurring after Day 28 are censored

Inclusion of prognostic risk factors in the analysis

The Applicant performed analysis of patients pooled across the two trials controlling for prognostic risk factors. Their rationale to include prognostic risk factors was that there are multiple prognostic factors of mortality outcomes in nosocomial pneumonia and that imbalance among these factors could skew results for unadjusted treatment comparisons, i.e. telavancin vs. vancomycin. Thus they included multiple prognostic factors using adjusted proportional hazard regression estimates of the log hazard ratio.

The Applicant states that there are multiple predictive factors of mortality outcomes in NP. They have included these predictive factors because of imbalance among these factors, which they feel could skew results. Thus, comparison of telavancin and vancomycin is based on adjusted proportional hazard regression estimates of the log hazard ratio based on combining data from both studies. They combined data from Studies 0015 and 0019 because it provides a more precise estimate of hazard ratios for comparison of treatments using all available data. Their argument is that regulatory guidance (ICH E9) suggests combining studies under certain circumstances, which they feel are present for the assessment of these studies. Their argument is that there is no *a priori* reason to expect a qualitative interaction in the treatment effect between two identical studies. However, observed differences between mortality outcomes could be related to the distribution of predictive factors between treatment groups. Using proportional hazards regression allows identification of predictive variables and potential treatment-effect modifiers and for adjustment of the hazard rate for differences in their occurrence in the study groups. This regression approach was employed when the mortality endpoint became the primary efficacy variable of interest in recognition of the severely ill patients enrolled with concomitant illnesses that may also have caused death independent of the pneumonia. The study randomization was not stratified by these co-morbidities. The regression analysis could not be prespecified because the endpoint was changed after NDA submission. This regression analysis is specific to the patients enrolled in these studies and may not be generalizable across other NP studies

Reviewer's comment:
The proposal for the comparison between telavancin and vancomycin to include post-hoc selected variables assumed to predict mortality is problematic because it is a data-driven analysis and can bias the results and potentially inflate the overall type-I error rate. Furthermore, the need to include these factors to account for imbalance is questionable because the trials were randomized so any imbalances between the two treatment arms are due to chance. The effect of any apparent observed imbalances is accounted for with the type I error. We view the analyses that include prognostic factors as exploratory. It should be noted that these prognostic factors were not included in the initial primary analysis of clinical response at TOC.

Pooling of patients across the two trials
The Applicant performed analysis of patients across the two trials controlling for prognostic risk factors. They provided a rationale to pool patients across the trials as specified in the complete response letter. However, there are two issues with this analysis. The first being the patients in the two trials differed in their baseline characteristics.

Justifications for combining evidence from the two telavancin studies include the following:
- The protocols were identical in all respects.
- The studies were conducted concurrently.
- The statistical analysis plan called for combining the studies for the analysis of an efficacy endpoint (clinical response in patients with MRSA).
- There was no difference between treatment groups for 30 of 31 baseline characteristics; the lone exception was baseline vasopressor use (ISE addendum, Appendix 8).

- Confidence intervals for the all-cause mortality rates overlap (ISE addendum, Table 4-2 and Table 4-13).
- Multivariate regression analysis suggests that multiple variables are related to vital status.
- There is not a statistically significant interaction between study and treatment ($p = 0.45$, Appendix 2 of the Statistical Report in Appendix 3). This result supports combining Studies 0015 and 0019 for more precise estimation of results. After adjustment for significant factors predictive of mortality, an interpretable model was obtained that statistically segregated risk between the two treatment groups.

Reviewer's comments:
Although the protocols for the two trials were identical and conducted concurrently, Dr. Alfred Sorbello, the medical reviewer for the initial submission, found several differences between the two trials in the distribution of potential risk factors for mortality, e.g. diabetes mellitus and renal impairment/failure). He found there were more patients in Study 0015 with chronic renal failure, baseline CrCl<50 mL/min, serum creatinine >1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, HCAP, torsades, history of atrial fibrillation, and history of myocardial infarction. In contrast, there were more patients in Study 0019 with serum creatinine ≤1.2 mg/dL, immunocompromise, HAP, organ failure at baseline, and history of left ventricular hypertrophy compared to Study 0015, and the differences were statistically significant. It is evident that the populations were substantially different based on pre-treatment characteristics and co-morbid conditions such that pooling for mortality analysis was not advisable and that the mortality data for each study should be assessed individually.

The Applicant's assertion that there was no difference between treatment groups for 30 of 31 baseline characteristics pooled across the two trials is irrelevant. This balance between treatment arms simply shows that the randomization worked. It does not demonstrate that the patients in the two trials are similar and could be pooled.

Baseline Characteristic	Pooled TLV and VAN Treatment Arms Study 0015 N=746 n (%)	Pooled TLV and VAN Treatment Arms Study 0019 N=757 n (%)	95% CI for Risk difference (Study 0015-Study 0019)
Acute renal failure	78	59	2.8 (-0.1, 5.7)
Chronic renal failure	67	28	5.3 (2.8, 7.7)*
Baseline CrCl<50 mL/min	276	209	9.4 (4.7, 14.1)*
Serum creatinine ≤1.2 mg/dL†	531 (71.2)	596 (78.7)	-7.6 (-11.9, -3.2)*
Serum creatinine >1.2 mg/dL†	192 (25.7)	142 (18.8)	7.0 (2.8, 11.2)*
Hemodialysis	20 (2.7)	8 (1.1)	1.6 (0.3, 3.0)*
Diabetic status (yes)	200 (26.8)	134 (17.7)	9.1 (4.9, 13.3)*
History of diabetes mellitus	232 (31.1)	162 (21.3)	9.6 (5.3, 14.1)*
Any pulmonary co-morbidity	478	517	-4.2 (-9.0, 0.6)
COPD	194	192	0.6 (-3.8, 5.1)
ARDS	44	19	3.4 (1.4, 5.4)*
Pulmonary edema	68	75	-0.8 (-3.8, 2.2)
VAP	203	224	-2.4 (-6.9, 2.2)
HAP	500	592	-11.2 (-15.7, -6.7)*
HCAP	243	164	10.9 (6.4, 15.4)*
Baseline signs/symptoms SIRS	623	633	-0.1 9-3.9, 3.6)
Sepsis/septic shock/MOF at any time	135	110	3.6 (-0.2, 7.3)
Immunocompromised	11	34	-3.0 (-4.7, -1.3)*
Torsades	425	342	11.8 (6.8, 16.8)*
Organ failure at baseline	136	183	-5.9 (-10.1, -1.8)*
ICU at baseline	440	431	2.0 (-2.9, 7.0)
History of atrial fib	148	113	4.9 (1.1, 8.7)*
History of CHF	149	122	3.9 (-0.03, 7.7)
History of MI	109	80	4.0 (0.7, 7.4)*
History of left ventricular hypertrophy	28	56	-3.6 (-6.0, -1.3)*
History other cardiac diseases	295	312	-1.7 (-6.6, 3.3)
Bacteremia	71	69	0.4 (-2.5, 3.3)

n=subject count; CrCl=creatinine clearance; *statistically significant;
HAP=hospital-acquired pneumonia; HCAP=healthcare-associated pneumonia;
TLV=telavancin; VAN=vancomycin; †at baseline

Issue whether patients had NP at baseline

The clinical reviewer from the first cycle submission, Dr. Alfred Sorbello, identified the following issues with the specificity of the diagnosis of NP at baseline:

- Inclusion criteria do not provide a high probability that all enrolled patients had NP
  The inclusion criteria were not consistent with the recommendations of the 1998 FDA Draft Guidance for Industry: "Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment" and also not consistent with the recommendations in the ATS/IDSA Guidelines for the management of Hospital-acquired Pneumonia. According to the 1998 FDA Draft Guidance on Antibacterial Drugs for Nosocomial Pneumonia, fever (100.4 ºF), leukocytosis, and two of the following clinical findings are required inclusion criteria for clinical trials: cough, new or change in sputum production, auscultatory change (rales), dyspnea, tachypnea (respiratory rate ≥30/min), or hypoxemia <60 on room air (1). According to the ATS/IDSA Guidelines, Clinical Strategy for NP should include evidence of a new or progressive chest x-ray infiltrate with at least two of the following three clinical features: Fever >38 ºC (100.4 ºF), leukocytosis or leucopenia, and purulent secretions. As described in the guidelines document "Although sensitivity for the presence of pneumonia is increased if one criterion is used, this occurs at the expense of specificity, leading to significantly more antibiotic treatment"(2). As fever, leukocytosis, and purulent respiratory specimens were not required for

eligibility criteria for this study (and Study 0019), patients enrolled without fever, purulent respiratory specimens, or leukocytosis may not have had the disease of interest. This is a critical issue, as 21 CFR 314.126(b)(3) specifically stipulates that one of the characteristics of an adequate and well-controlled study is that "the method of selection of patients provides adequate assurance that they have the disease or condition being studied." Based on the inclusion criteria employed in this clinical trial, it is not possible to have adequate assurance that all study patients have either NP or VAP.

- Chest radiographs
  The inclusion criterion regarding radiographic findings "consistent with a diagnosis of pneumonia" was problematic in such patients as they may have other non-infectious illnesses (such as atelectasis, congestive heart failure, pulmonary embolism with infarct, pulmonary contusion, and chemical aspiration) that may produce x-ray findings that may mimic pneumonia (3). Confirmation of the Investigators' interpretation of chest radiographs by a radiologist was not required. The lack of radiologists' confirmation of the chest x-ray findings that were reported by Investigators adds to the dilemma of assessing whether enrolled patients actually had the disease being studied. In addition to concerns about the enrollment of patients with noninfectious disorders as described above, it is likely that some patients enrolled in this clinical trial may have purulent tracheobronchitis rather than NP or VAP as a consequence of the lack of stringent inclusion criteria. Purulent tracheobronchitis may produce clinical signs similar to those associated with HAP and VAP and may require treatment with intravenous antibiotics (2).
- Microbiological specimens
  Quality assessments for endotracheal aspirates were not provided. According to the ATS/IDSA guidelines document, a reliable tracheal Gram stain can be used to direct initial empiric antimicrobial therapy and may increase the diagnostic value of the clinical pulmonary infection score (CPIS) (2). In the absence of interpretive criteria, all bacteria isolated from endotracheal aspirate cultures could be considered potential pathogens, which confound distinguishing true pathogens from colonizers. Rejection criteria for endotracheal aspirates have been published in the scientific literature (4). Errors in interpretation of endotracheal aspirates could result in incorrect assessments of the number of isolates considered microbiologically evaluable for efficacy assessment, which could increase the probability of erroneously concluding noninferiority between the two treatment arms in the clinical trial.
- Use of axillary temperatures
  The FDA Medical Officer determined that axillary temperatures were the most frequently employed modality for body temperature measurement in both Studies 0015 and 0019 as can be seen in the table below.

Table 6: FDA Medical Officer Table of the Modes of Temperature Measurement by selected Study Visit for Pooled Treatment Groups, AT Population, Study 0015

Study Visit	Temperature measurement modality	Study 15 Pooled TLV and VAN n (%)
Pre-treatment	Axillary	266 (47.3)
	All others combined	296
Day 4	Axillary	236 (37.6)
	All others combined	392
Day 7	Axillary	194 (38.7)
	All others combined	307
Day 10	Axillary	110 (41.0)
	All others combined	158
Day 20	Axillary	15 (62.5)
	All others combined	9
EOT	Axillary	247 (33.1)
	All others combined	499
FU/TOC	Axillary	178 (33.6)
	All others combined	351

TLV=telavancin; VAN=vancomycin; n=subject count
EOT=end of therapy; FU/TOC=follow-up/test of cure

The FDA Medical Officer further noted that the Applicant retained use of axillary temperatures despite recommendations against their use in publications that provide guidelines for evaluating new fever in critically ill adults. In response to an information request from the Division dated April 30, 2009, the Applicant stated that "during initiation of the studies, it became evident that standard clinical practice at numerous investigative sites was to determine body temperature using the axillary method. However, the protocol inadvertently was not updated to reflect this practice, which Theravance did acknowledge and allow." In addition, the Applicant cited a publication (8) and indicated that "while axillary temperatures did not correlate well with core temperature, this was because the axillary temperature readings averaged 1ºC below the core readings, ranging as much as 4ºC below core temperature. Therefore, we chose to conservatively adjust the axillary temperature readings by adding 1ºC." In the opinion of this FDA Medical Officer, the approach described above appears arbitrary, is not supported by scientific evidence from other publications, and is not consistent with current medical practice guidelines. The use of axillary temperatures introduces considerable uncertainty in the evaluation of eligible patients for enrollment and in the reliability of APACHE II scores and CPIS scores used for assessment of severity of illness and likelihood of VAP, respectively. Nasal and bladder temperatures were reported for some study patients, although there was no specific provision in the protocol permitting such methods of body temperature assessment and no published scientific data was provided by the Applicant to substantiate their use as surrogates for core body temperatures.

The FDA Medical Officer also noted that the APACHE II algorithm specifically requires rectal temperatures for determination of the temperature component of the score. Furthermore, the CPIS algorithm does not specify the method for temperature measurements. Modifying the axillary temperatures as above and then using the modified value as representative of core/rectal temperature creates substantial uncertainty in the severity of illness as reflected by APACHE II scores and the likelihood of having VAP based on the CPIS scores as reported at baseline and at subsequent study visits. By adding one degree Celsius to axillary temperatures, the magnitude of increase can be as much as 3 points in the APACHE II scores and 2 points in the CPIS scores. Thus, this approach for

analysis purposes tends to depict the study population as having a higher severity of illness and a greater likelihood for VAP than is actually true. The reference journal article provided in the Applicant's Clinical Study Report does not specifically support the modification of recorded axillary temperatures for analysis purposes; instead, the article indicates that axillary temperatures are not reliable and should not be used as a measure of core body temperature.

To address some of the issues identified with the inclusion criteria used to enroll patients, the Applicant identified a subgroup ["Chest X-Ray Plus Two Features" (CXR+2F)] that met guidelines of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA), which was referenced by the Agency as a population to consider in the design of future studies in NP in the CR letter. This population is defined by the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) at baseline. There are still issues with this subgroup. This sensitivity analyses are still prone to the some of the issues identified earlier:

- Independent confirmation of investigator's interpretation of the chest radiograph was not required
- Fever could be identified using axillary temperature

The results for this subpopulation are presented in Table 22and Table 23. These results are similar to those of the primary analysis and it should be noted that both trials do not demonstrate noninferiority using a 10% NI margin. For Study 0015, the estimated treatment difference was 2.0% with a 95% CI of (-7.9%, **11.9%**). Similarly, in Study 0019, the estimated treatment difference was 2.0% with a 95% CI of (-6.5%, **10.6%**).

CXR+2F and excluding patients who have only gram-negative pathogen cultured at baseline

Table 22: 28-day all-cause mortality in the CXR+2F population excluding patients with only gram-negative pathogens cultured at baseline

	0015		0019	
	Telavancin (n=157)	Vancomycin (n=155)	Telavancin (n=194)	Vancomycin (n=188)
Deaths Between Start of Study Drug and Study Day 28	43 (27.4)	39 (25.2)	47 (24.2)	41 (21.8)
Alive	109 (69.4)	105 (67.7)	139 (71.7)	134 (71.3)
Lost of follow-up	5 (3.2)	11 (7.1)	8 (4.1)	13 (6.9)

Table 23: Estimated 28-Day All-Cause Mortality in the CXR+2F population excluding patients with only gram-negative pathogens cultured at baseline

Study	Treatment	Estimated K-M Mortality at 28 Days (%)	Diff (%) (TLV - VAN) 95% CI
0015	TLV	27.7	2.0
	VAN	25.6	(-7.9, **11.9**)
0019	TLV	24.4	2.0
	VAN	22.3	(-6.5, **10.6**)

All of the preceding issues provide further uncertainty in the interpretation of the results of Studies 0015 and 0019.

REFERENCES

Sorbello A, Komo S, Valappil T. Non-inferiority Margin for Clinical Trials of Antibacterial Drugs for Nosocomial Pneumonia. *Drug Information Journal* 2010; 44:165-176.

5 SIGNATURES/DISTRIBUTION LIST (Optional)

Primary Statistical Reviewer: Scott Komo, DrPH

Concurring Reviewer(s): Thamban Valappil, PhD

Statistical Team Leader: Thamban Valappil, PhD

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/s/

SCOTT S KOMO
12/13/2010

THAMBAN I VALAPPIL
12/13/2010

Statistical Review

NDA#: 22-407 / SDN 036
Name of drug: Vibativ (telavancin)
Sponsor: Theravance
Indication: Nosocomial pneumonia
Dates: 5/11/10
Statistical Reviewer: Scott Komo, DrPH
Clinical Reviewer: Janice Pohlman, MD, MPH
Project Manager: J Christopher Davi, MS

SUMMARY

This submission contains the meeting package for a May 25, 2010 meeting. The responses for selected questions are included in this review.

1. The draft statistical analysis plan (Appendix 1) proposes a three-step approach to analysis of the mortality data in Studies 0015 and 0019. Please comment on the acceptability of this approach. Which of the analysis objectives can be used to support a conclusion regarding the efficacy of telavancin?

Comment: There are several concerns with your proposal:

a. Relying on a historical control based on inadequate/delayed therapy studies without a thorough evaluation as to the comparability of the two groups (see response to question #2) is problematic. Without confidence that the two groups are comparable, this analysis is prone to potential biases. The comparability of the historical data to the data based on studies 0015 and 0019 should be assessed based on age, APACHE-II scores, % of ventilated patients, primary documented pathogens, adjunctive medications used, ancillary care and management etc. as these factors can significantly impact the treatment effect and make the comparison less reliable. For example, we might expect in this case for the historical control rate to be estimated from patients with S. aureus rather than from patients with Pseudomonas aeruginosa.

b. Given the concerns with the comparability of the groups addressed in (a), some degree of discounting should be applied to any determination of an NI margin.

The following issues/limitations should be considered to assess the appropriate discounting when estimating M1:

- *Differences in historical studies and its designs*
- *Differences in baseline patient characteristics*
- *Concomitant medications used*
- *Distribution of measured and unmeasured prognostic factors that are potentially associated with mortality*
- *Prevalence of documented bacterial pathogens*
- *Mortality reporting time periods, which are aspects of clinical trials that can affect constancy.*
- *Advances in medical technology, standard of care, and management.*

c. The comparison between telavancin and vancomycin is proposed to include post-hoc selected variables assumed to predict mortality; this is problematic because it is a data-driven analysis and can bias the results. We recommend not including any covariates in the primary analysis. We also recommend that the primary analysis population be the microbiological ITT population including only patients with Gram positive and mixed Gram positive/Gram negative bacterial infections at baseline assigned to the treatment groups as they were originally randomized.

2. Do the reviewers conclude that the populations enrolled in the telavancin NP studies are similar to the populations enrolled in published studies of other treatments for NP?

Comment: There is currently insufficient information provided to determine if the patients in the current telavancin trials are similar to the patients in the historical inadequate/delayed therapy studies

4. Is the 10% NIM proposed for the analysis of non-inferiority for mortality in the telavancin studies justified by the supporting information provided?

Comment: We do not agree with the proposed calculation of M1 based on the issues identified above. In addition, we continue to have concern with an M2 margin in this population that is as high as 10%.

Scott Komo, Dr.P.H.
Mathematical Statistician, DB IV

Concur: Thamban Valappil, Ph.D.
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/s/

SCOTT S KOMO
10/26/2010

THAMBAN I VALAPPIL
10/26/2010

Statistical Review

NDA#: 22-407 / SDN 031
Name of drug: Vibativ (telavancin)
Sponsor: Theravance
Indication: Nosocomial pneumonia
Dates: 3/1/10
Statistical Reviewer: Scott Komo, DrPH
Clinical Reviewer: Janice Pohlman, MD, MPH
Project Manager: J Christopher Davi, MS

SUMMARY

This submission contains the meeting package for a March 15, 2010 meeting. The responses for selected questions are included in this review.

1. The discussion at the Workshop focused on comparing differences in mortality rates at a fixed landmark time. Since the vital status of a small proportion of subjects are unavailable for the time point of interest, the use of analytical methods, such as Kaplan Meier estimates and hazard ratios obtained from proportional hazards regression models is proposed to account for the presence of censored data. Does the Agency agree with the approach?

> *Comment: The Kaplan Meier estimates at the land mark date (e.g.,day 28) may be considered as one of the methods to address censored observations. However, this does not address the concern that censoring could be treatment related and not a random occurrence.*

2. Although the mortality endpoint does not require investigator judgment the interpretation of the results is complicated because all-cause mortality does not always measure response to the pneumonia in this seriously ill patient population. Therefore, a multivariate regression was conducted using a proportional hazards model to identify prognostic factors related to death and test whether any of these factors were also treatment-effect modifiers. Does the agency agree with this approach?

> *Comment: We view these analyses as exploratory and hypothesis generating for designing future trials.*

3. Based on the results of these analyses, Theravance believes that studies 0015 and 0019 are adequate and well controlled trials that are of adequate size to test for noninferiority of telavancin versus vancomycin using the all-cause mortality at 28-days endpoint and a 10% non-inferiority margin. Please clarify why the agency believes the studies are inadequate.

> *Comment: As stated in the Complete Response letter, both trials were designed based on a clinical response endpoint, with all-cause mortality as a secondary endpoint. Scientific literature identified to date does not permit use of clinical response as a primary endpoint, due to lack of data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. A justification for [possible] use of a 7% NI margin based on all-cause mortality was developed by the Agency based on historical literature. Since the Complete Response letter was issued, a substantial amount of missing mortality data has been recovered. However, on the surface, the patients enrolled in these trials differ from those in the historical studies that provided justification for the NI margin.*

Specifically, the patient populations enrolled in trials used for the justification had a high likelihood of diagnosis of NP based on the presence of signs such as fever, leukocytosis, and purulent respiratory secretions, along with pulmonary infiltrates on chest radiograph. These features were not present in a substantial number of patients enrolled in 0015 and 0019.

4. Theravance believes that the small differential mortality overall seen between telavancin and vancomycin appears to be attributable to patients with acute renal failure (ARF) at baseline, as described in our reply to the complete response letter. Segregating this risk into patients with and without pre-existing ARF, provides a large population of patients (without pre-existing ARF) in whom the two treatments are non-inferior based upon all-cause mortality at 28 days as an endpoint. Does the Agency have any comments regarding the methods of analysis or this finding?

Comment: The trials were designed to demonstrate non-inferiority for all subjects. However, we recognize and are concerned with the observed increase in mortality for ARF patients who received telavancin compared with those who received vancomycin. This observation warrants further exploration in future trials.

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10/26/2010

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10/26/2010

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-407 / 0000
Drug Name:	Telavancin for Injection (10 mg/kg IV q24h)
Indication(s):	Nosocomial pneumonia
Applicant:	Theravance Inc.
Date(s):	1/23/09 (letter);
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Reviewer:	Scott Komo, Dr.P.H.
Concurring Reviewers:	Thamban Valappil, Ph.D.
Medical Division:	Division of Anti-Infective and Ophthalmology Drug Products (DAIOP)
Clinical Team:	Alfred Sorbello, DO, MPH
	Janice Pohlman MD, MPH
Project Manager:	Christopher Davi, MS

Keywords: active control/non-inferiority

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The Applicant did not provide substantial evidence, based on all-cause mortality, that telavancin is effective and safe in the treatment of nosocomial pneumonia (NP) infections because a substantial proportion of the patients in both trials (Studies 0015 and 0019) had incomplete survival information for the entire mortality reporting period. Thus, a determination of the efficacy and safety of telavancin in the treatment on NP cannot be performed until additional mortality data is provided.

1.2 Brief Overview of Clinical Studies

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is the treatment of nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant strains) and *Streptococcus pneumoniae*.

The proposed dosing regimen for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days.

This submission contains two Phase 3 trials (0015 and 0019) conducted in patients with nosocomial pneumonia. These two trials were conducted using identical protocols. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours. Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively.

The predefined primary endpoint was clinical response at the Test-of-Cure (TOC) assessment (7-14 days after the End-of-Therapy). However, this review treats all-cause mortality as the primary endpoint with the rationale provided in Sections 1.3 and 5.1.

1.3 Statistical Issues and Findings

The following statistical issues were found during the review of this application – the choice of the primary endpoint, the large proportion of patients whose survival status is not known throughout the mortality reporting periods, the pooling of the trials to analyze mortality, data integrity and blinding issues, and the proportion of patients who received concomitant antimicrobials for gram-negative coverage. The most important issues that will be discussed are the choice of the primary endpoint and the large proportion of patients whose survival status is unknown throughout the reporting period. This issue is of foremost importance for both the efficacy and safety analyses.

Interpretation of the noninferiority trials using clinical response as the primary endpoint

The predefined primary endpoint for the two trials was clinical response at TOC. The endpoint chosen is a major statistical issue because the lack of historical data for this endpoint does not allow one to estimate the treatment effect of the active comparator. This estimate is an essential in determining a non-inferiority margin to be used in the interpretation of the results. Previously, the Agency presented historical data supporting a 7% noninferiority margin for the endpoint of all-cause mortality (as an alternative to clinical response) in clinical trials of NP at the 16 July 2008 meeting of the Anti-Infective Drugs Advisory Committee convened to discuss NDA 22-171 (doripenen for injection). Subsequently, a two-day workshop on NP -- co-sponsored by the Agency, the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) -- was held on 3/31/09 – 4/1/09. At this workshop, the lack of historical data on the treatment effect of antibacterials for clinical response was discussed along with an Agency presentation on the historical data for all-cause mortality in NP along with a discussion of the size of an NI margin that could be justified based on this data. Details on the justification for an NI margin in NP can be found in Sorbello et al.[1], which is presented in Appendix A-1.

Based on an Agency review of the literature and the discussion at the workshop, the clearest evidence of treatment effect was based on all-cause mortality. However, the historical literature did not provide a uniform timepoint for the assessment of mortality. The mortality reporting window should be of adequate length such that the outcome of interest reflects the attributable clinical effect of the drug rather than being confounded by the underlying comorbidities. In addition, ideally, the timing of the assessment should be prospectively defined to avoid any kind of post-hoc selection. However, at the present time there is not a clear consensus on the appropriate timing of assessment

Discussion at the workshop focused on the timepoint of 28 days after randomization/initiation of therapy. Based on Table 9, 11%-12% of the patients received 15-21 days of treatment. Therefore, because the treatment duration varies from patient-to-patient, there is also consideration that a specified timepoint after end of therapy should be used for the mortality assessment. Currently, there is not a clear consensus on what the appropriate timing of assessment of all-cause mortality should be. There are strengths and weaknesses in using either “time from randomization” or “time from end of therapy”.

At the workshop, because the clearest evidence of treatment effect was based on all-cause mortality, a recommendation was made to use all-cause mortality as the primary endpoint in NP studies. This has prompted basing the efficacy evaluation for this application on all-cause mortality rather than clinical response. Because of this, the following issue of missing mortality data is of major importance.

[1] Sorbello A, Komo S, and Valappil T. *Drug Information Journal (in press)*

Missing all-cause mortality data

A major statistical issue is the large proportion of patients whose survival status is not known through either the Study Day 28 reporting period or the EOT + 28 days reporting period (see Table 14). Specifically, for the Study Day 28 period, incomplete information occurs for 34.9% of the patients in Study 0015 and 28.5% of the patients in Study 0019. Similarly, for the EOT + 28 days period, incomplete mortality information occurs in 35%-40% of the patients for the two trials. With this large proportion of missing outcomes, interpretation of the mortality data is quite difficult because analyses that can be heavily influenced by the imputation method chosen to handle the missing data. As an example, for Study 0015, the observed mortality difference (telavancin – vancomycin) is 5.2% for the Study 28 reporting period. However, this observed mortality difference is dwarfed by the almost 35% of the patients whose survival status is incomplete for the entire reporting period. Thus, it can be seen that analyses will be very sensitive to the method chosen to account for the missing data.

The distribution of the last study day that a patient is known to be alive in patients whose survival status is not throughout the reporting period is given in Table 15. It can be seen that censoring occurs in a large proportion of patients by Study Day 21. This is concerning because the observed mortality data may not fully capture the effect or lack of effect of telavancin in treating NP because for a substantial proportion of the patients, deaths will not be counted for a week or more of the reporting period.

In August 2009, the Applicant was notified of the Agency's concern with the large proportion of patients whose survival status is incomplete. Subsequently, the Applicant stated that they would query the study sites to determine the survival status during the reporting periods for a greater number of patients.

Pooling of trials to analyze mortality

The Applicant has pooled the mortality data from the two trials as the proposed method to analyze mortality rates. They submit that pooling is reasonable because the two trials were identical in design. However, because the populations differ in terms of several important factors related to baseline renal function, the trials should not be pooled for analysis purposes. The differences in the patient populations with regard to baseline renal function is an important issue because the telavancin label for cSSSI, which was approved in September 2009, describes decreased efficacy in the treatment of cSSSI for patients with decreased renal function relative to the vancomycin. In addition, the label also mentions an increase in severe renal adverse events for patients who received telavancin relative to those who received vancomycin. In Table 16, it can be seen that the patients in Study 0015 had a statistically significantly higher rate of renal problems and diabetes which is associated with decreased renal function than patients in Study 0019. For this reason, the results of the two trials should not be pooled for analysis purposes to prevent the confounding by differences in trial populations with respect to baseline renal function.

Data Integrity and Blinding Issues

Another statistical issue is a concern regarding data integrity and blinding issues. This prompted a sponsor inspection that did not reveal any regulatory violations. However, during the inspection, it was ascertained that data was added/revised after treatment unblinding. In addition, some parts of the medical review process occurred after treatment unblnding. These determinations included decisions that would affect evaluability as well as whether patients received adequate gram-negative coverage. The adequacy of gram-negative coverage is an important issue because it is one of the factors that the Applicant is using to explain the observed increase in mortality seen for the telavancin arm relative to the vancomycin arm. A summary of the inspection and findings is provided below.

A sponsor inspection was performed from 10 September 2009 – 25 September 2009 to review the conduct of clinical studies performed in support of this application. The purpose of the inspection was to evaluate the Applicant's completion of regulatory obligations for Studies 0015 and 0019. In addition, the inspection was conducted to evaluate a complaint received by the Agency that asserted that the Applicant had improperly manipulated study data to achieve desired outcomes for Studies 0015 and 0019. A summary of the important finding will be given below

The sponsor inspection did not reveal any regulatory violations. The Applicant's documentation of dates of data transfer/data files transferred from (b) (4) the CRO responsible for data management of the two Phase 3 trials, are consistent with data transfer dates/data files/file content that were documented by (b) (4) and reviewed during the Agency inspection of the CRO and in a subsequent comparison of datasets.

Although the inspection did not reveal any regulatory violations, it did shed light on some blinding issues that will be summarized below.

1st data unlock

The following issues were identified by the Applicant and data were added/changed during this unlocking of the database:

- MIC sensitivity data for ninety-two patients (198 records) from thirty-eight sites were inadvertently left out of the for Study 0015 database. The explanation given was that (b) (4) was receiving incremental updates from (b) (4) (CRO responsible for laboratory analyses) and failed to include this data in the treatment unblinded data transfer. Prior to treatment unblinding, the Applicant had previously received treatment blinded data from (b) (4) that included this MIC sensitivity data. However, when the unblinded data was transferred, Applicant staff noticed that the MIC sensitivity data for the subset of ninety-two patients was missing. The Applicant then asked (b) (4) to include the missing data in a new data transfer.
- SAE and deaths

Applicant staff noticed after treatment unblinding that there were inconsistencies in the data that indicated that death occurred, where death was flagged in one section but SAE

and/or death report forms were not reported or included. Death could be marked in the AE, death report, Drug Discontinuation, Clinical Response at EOT, Study Completion/Follow-up/Test of Cure, and Clinical Response for Test of Cure sections.

The Applicant asked that the CRF as well as the SDTM data be updated so that deaths would be consistently captured. All of the inconsistencies found were for fourteen deaths that occurred during the safety reporting period for patients who did not have a test-of-cure (TOC) visit. The reporting period in this case was twenty-eight days after the last dose of study drug was received.

- ECG

Applicant staff discovered that ECG data for patients who were screening failures (i.e., non-randomized patients) were mistakenly included in the ECG dataset and notified (b) (4) also found some errors in protocol, site, and subject# for some patients. These errors included five patients (two in 0015 and three in 0019) who had incorrect site numbers, four patients who had an incorrect protocol# (i.e. in the Study 0019 dataset and but who were Study 0015 patients), and one patient had the wrong subject number listed. The Applicant was notified by (b) (4) of these discrepancies and the Applicant then told (b) (4) to notify the ECG vendor (b) (4) to make these corrections and delete the screening failure data. Corrections were made by the ECG vendor who sent the corrected database to (b) (4) Corrected data were included in the updated SDTM datasets from (b) (4) during the 1st data unlock.

It was stated that the main reasons to unlock the database were to add SAE and death data and also MIC sensitivity data.

2nd database unlock

The corrections/updates made during the second database unlocking involved 33 patients. The following issues were identified by Applicant who notified (b) (4) who updated the data:

- Updates to renal AE status

This data was obtained from the Applicant's renal follow-up effort undertaken in May 2008. The objective was to follow up on patients who had a renal AE whose sequela was either continuing or resolving and to provide a status update sixty days after the patients completed the study. Queries were communicated to (b) (4) who then queried the sites.

- Dosing and weight correction

The dosing database was not locked until approximately six months after SDTM database was treatment unblinded. The Applicant was still issuing queries through (b) (4) to the sites while the dosing database was open. As a result of these queries, datapoints common to the dosing database and the SDTM database needed to be updated. During this process, data entry errors were also indentified in the SDTM database.

The primary reason stated to unlock was to include the data from the renal follow-up effort.

3rd database unlock

The Applicant undertook a remonitoring effort which involved an audit of a sample of sites. It was stated that this audit was performed in response to their experience with their complicated skin and skin structure infection application (NDA 22-110). This audit was performed by (b) (4) who audited patient records primarily looking at eligibility and clinical outcome assessment data. In addition, if AEs were found that were not previously noted, these would also be identified. Three deaths and two SAEs were indentified at the sites during the remonitoring effort and Theravance was informed. Theravance notified (b) (4) to update the database to reflect the new information. (b) (4) updated the database and transferred it to Theravance.

In addition to the data changes that occurred after treatment unblinding, the inspection also revealed that some parts of the Applicant's medical review occurred after the database was treatment unblinded. A summary is provided below.

Medical Review Process

A medical review process was performed by the Applicant to make determinations on issues such as clinical evaluability, whether a patient received potentially effective antibiotics, whether a patient received adequate gram-negative effort, etc. It was ascertained that the review by the medical monitor occurred in some instances after the SDTM database was treatment unblinded. This is relevant because the medical monitor made determinations that affected patient populations as well other issues that were reflected in the Analysis files. The Analysis files would be affected by either changes in the SDTM datasets or medical review process determinations on a particular issue, e.g. potentially effective antibiotics use (see Figure 1).

The process used in the Medical Review process was that a spreadsheet was created from the SDTM files that contained the relevant datapoints necessary to make a determination on a particular issue.

The following is a list of the explanations given by the Applicant for the major medical review determinations made after treatment unblinding occurred

- PEA (Potentially effective antibiotics)

The medical monitor found forty-two patients had inadvertently been omitted from the original spreadsheet that was used to make a PEA determination. This PEA determination also affects clinical evaluability. Note it was stated that the treatment code was not included in the spreadsheet used to make the determination.

- GNECGOVM and GNEGVN (adequacy of gram-negative coverage)

These spreadsheets were used to look at the adequacy of gram-negative coverage for the purpose of exploring some of the findings in the study and performing sensitivity analyses. It should be noted that both of these spreadsheets were created approximately six months after treatment unblinding.

Concomitant antimicrobials given for gram-negative coverage

The interpretation of the efficacy analyses for gram-positive pathogens is confounded by the administration of concomitant antimicrobials to provide gram-negative coverage that also have overlapping gram-positive coverage. This adjunctive gram-negative coverage occurred in a substantial proportion of patients. The initial protocol specified that aztreonam could be used to provide gram-negative coverage but that piperacillin-tazobactam or imipenem could be used if there were concerns of aztreonam resistance. Subsequently, the protocol was revised in Amendment 1 to drop imipenem as an alternative to aztreonam.

In NP trials of agents that have only gram-positive activity, the problem of overlapping gram-positive activity of the concomitant antimicrobial agents administered to provide gram-negative coverage is a difficult issue to ignore because of the increase in resistance to aztreonam, which has only activity against gram-negative pathogens.

In the current application, the proportion of patients who received concomitant antimicrobials with overlapping gram-positive activity is substantial. In Study 0015, 24% (91/372) of the patients in the telavancin patients received piperacillin/tazobactam and 10% (38/372) received imipenem. For the vancomycin arm, 18% (69/374) received piperacillin/tazobactam and 10% (37/374) received imipenem. Similarly, in Study 0019, 22% (83/379) of the patients in the telavancin patients received piperacillin/tazobactam and 11% (42/379) received imipenem. For the vancomycin arm, 21% (81/378) received piperacillin/tazobactam and 11% (42/378) received imipenem.

As quantified in the previous paragraph, the proportion of patients who received concomitant antimicrobials with overlapping gram-positive activity is substantial and confounds the ability to determine the effect of telavancin in the submitted trials to treat gram-positive NP. This is particularly an important issue in non-inferiority trials because any such confounding effect can potentially make the treatment look similar when in fact they are not. This confounding effect should be kept in mind when interpreting the efficacy results.

2 INTRODUCTION

2.1 Overview

Telavancin is a lipoglycopeptide antibacterial agent derived from a synthetic modification of vancomycin. The proposed indication is the treatment of nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant strains) and *Streptococcus pneumoniae*.

The proposed dosing regimen for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days.

Telavancin is eliminated primarily by the kidney. The dosage is adjusted for patients with renal impairment. For patients with moderate (creatinine clearance [CrCL] 30-50 mL/min) impairment, the dosage is decreased to 7.5 mg/kg every 24 hours. In contrast, for those with severe (CrCL 10-30 mL/min) renal impairment, the dosage is decreased to 10 mg/kg every 48 hours. Finally, there are no dosage recommendations for patients with end-stage renal disease (CrCL <10 mL/min), including patients receiving hemodialysis.

Telavancin was studied previously for the treatment of complicated skin and skin structure infections (cSSSI). Three clinical trials (202b, 0017, and 0018) were conducted in patients with cSSSI at the same dosage (10 mg/kg) as the current submission. The dosage was increased from 7.5 mg/kg to 10 mg/kg during the Phase 3 trials based on the results of the results of Study 202b. Another study, 202a, was conducted at the lower the 7.5 mg/kg dosage. Telavancin was approved to treat patients with cSSSI at the 10 mg dose on 11 September 2009.

This submission contains two Phase 3 trials (0015 and 0019) conducted in patients with nosocomial pneumonia. These two trials were conducted using identical protocols. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours. Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively.

The major statistical issues to be discussed in this review are the choice of the primary endpoint and the amount of missing data that exists for the endpoint of all-cause mortality within the reporting windows.

2.2 Data Sources

The clinical study reports and datasets are located at the following location: \\Cdsesub1\evsprod\Nda022407\0000\.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The Applicant conducted two Phase 3 trials (0015 and 0019), with identical protocols, in patients with NP. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive HAP were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hours or vancomycin 1 g IV q 12 hours. Treatment duration was to be from 7 to 21 days. Because both the test and comparator drugs do not have activity against gram-negative pathogens, a substantial number of patients received empiric gram-negative coverage. Patients could receive concomitant aztreonam or metronidazole for suspected Gram-negative and anaerobic infection, respectively. In addition, piperacillin/tazobactam was also permitted for coverage of Gram-negative organisms if resistance to aztreonam was known or suspected. The Original Protocol had also allowed imipenem for Gram-negative coverage as well as aztreonam and/or metronidazole therapy; however, imipenem was removed as a treatment option in Protocol Amendment 1.

Studies 0015 and 0019 enrolled 761 (381 telavancin and 380 vancomycin) and 771 (386 telavancin and 385 vancomycin) patients respectively. Study 0015 was conducted in 22 countries with 31% of the randomized and treated patients coming from the United States, while Study 0019 was conducted in 29 countries with a much lower percentage (14%) of the randomized and treated patients coming from the United States.

Patients were randomized in a 1:1 ratio with randomization stratified on the combination of a pre-specified country grouping (see Table 1for the pre-specified country groupings), the presence or absence of diabetes, and ventilatory status of the patient.

Table 1: Country Groupings used in Stratified Randomization

Country Grouping	Study 0015	Study 0019
1	Australia	Australia
	Belgium	Canada
	Canada	France
	France	Israel
	Israel	Spain
	Italy	United States
	United Kingdom	
	United States	
2	Argentina	Argentina
	Brazil	Brazil
	Chile	Chile
	South Africa	South Africa
	Taiwan	
3	Croatia	Bulgaria
	Czech Republic	China
	Greece	Croatia
	India	Czech Republic
	Malaysia	Estonia
	Malta	Georgia
	Peru	Greece
	Poland	Korea
	Turkey	Lebanon
		Lithuania
		Mexico
		Philippines
		Poland
		Romania
		Russia
		Serbia/Montenegro
		Slovakia
		Thailand
		Ukraine

Source: Clinical Overview, Table 2

The primary objective in each trial was to compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with Gram-positive HAP with an emphasis in patients with infections due to MRSA.

A key secondary objective was to pool the data from both trials (protocols 0015 and 0019), which were of identical design, to assess the superiority of telavancin to vancomycin in patients with MRSA infections.

Baseline evaluations were performed within 24 hours prior to treatment start and included pertinent medical history; an assessment of the signs and symptoms of the infection; determination of the Glasgow Coma Score; chest x-ray or computed tomography scan (CT scan) for evaluation of radiographic lung infiltrates; oxygen status as measured by arterial blood gas is strongly encouraged, but is required for patients who are ventilated and/or have an existing arterial line; collection of respiratory specimens for Gram stain

and culture, blood culture, clinical laboratory tests, an X-ray to rule out osteomyelitis (if clinically indicated); and three 12-lead electrocardiograms (ECGs).

All patients were to have an End-of-Therapy (EOT) visit within 3 days following the last dose of study medication and a Follow-Up visit within 7 to 14 days after the EOT visit. The procedures at the EOT visit included: record signs/symptoms of pneumonia; obtain a respiratory specimen, assess clinical response; obtain chest x-ray or computed tomography scan (CT scan) for evaluation of radiographic lung infiltrates; recording of oxygen status as measured by arterial blood gas is strongly encouraged, but is required for patients who are ventilated and/or have an existing arterial line; and obtain respiratory specimen only if clinically indicated.

A Test-of-Cure (TOC) assessment (record signs/symptoms of pneumonia, obtain a respiratory specimen, assess clinical response, record all systemic antibiotics received after EOT, obtain blood and urine samples, and assess adverse events) was conducted at the Follow-Up visit for patients who were a clinical cure or had an indeterminate outcome at the EOT visit. Both the EOT and TOC evaluations included an assessment of the clinical signs and symptoms of the infection, with the assessment of the clinical response based on the comparison of a patient's signs and symptoms at the EOT or Follow-Up Visit, respectively, to those recorded at trial admission,

Inclusion criteria

1. Male and female patients ≥ 18 years old
2. Clinical signs and symptoms consistent with pneumonia acquired after at least 48 hours of continuous stay in an inpatient acute or chronic-care facility, or acquired within 7 days after being discharged from a hospitalization of ≥ 3 days duration
    - At least two of the following signs and symptoms must be present:
        - cough,
        - purulent sputum or other deep respiratory specimen,
        - auscultatory findings of pneumonia,
        - dyspnea, tachypnea, or hypoxemia,
        - identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples.

    AND
    - At least two of the following must also be present:
    - fever (> 38°C) or hypothermia (rectal/core temperature < 35°C),
    - respiratory rate > 30 breaths/min,
    - pulse rate ≥ 120 beats/min,
    - altered mental status,
    - need for mechanical ventilation,
    - elevated total peripheral WBC count > 10,000 cells/mm^3, > 15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count < 4500 cells/mm^3.
3. A chest radiograph with findings consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion) within 48 hours prior to randomization in the study

4. Availability of appropriate respiratory or sputum specimens for Gram stain and culture, and venous access for IV dosing
5. Willing to receive IV therapy for the duration of treatment
6. Informed consent can be obtained for participation in this study as defined by the local Institutional Review Board or Ethics Committee

Exclusion criteria

1. Received more than 24 hours of potentially effective systemic (IV/IM or PO) antibiotic therapy for Gram-positive pneumonia immediately prior to randomization, (unless documented to have not responded to at least 3 days of treatment or if the isolated pathogen for the current pneumonia was resistant in vitro to previous treatment). For patients with renal impairment who have received one or more doses of vancomycin during the last week prior to the enrollment, please contact the Study Physician Helpline to determine eligibility.
2. Respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture
3. Known infection with MSSA or S. pneumoniae and patient will require more than 24 hours of concomitant study medication therapy with an antibiotic for Gram-negative coverage that has activity versus MSSA or S. pneumoniae (e.g., piperacillin-tazobactam)
4. Known or suspected pulmonary disease that precludes evaluation of therapeutic response (e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs); cystic fibrosis or active tuberculosis
5. Known or suspected *Legionella pneumophila* pneumonia
6. Known or suspected infection with an organism that is not susceptible to medications permitted by the protocol.
7. Documented or suspected meningitis, endocarditis, or osteomyelitis
8. Refractory shock defined as supine systolic blood pressure < 90 mm Hg for > 2 hours with evidence of hypoperfusion or requirement for high-dose sympathomimetic agents (dopamine ≥ 10 μg/kg/min or norepinephrine ≥ 0.1 μg/kg/min)
9. Baseline QTc > 500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K+ or Mg++ blood levels that cannot be corrected
10. Severely neutropenic (absolute neutrophil count < 500/mm³) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or have HIV with CD4 count < 100/mm³ during the last 6 months
11. Requirement for concomitant administration of intravenous Sporanox® (itraconazole), Vfend® (voriconazole), Geodon® (ziprasidone), or any other medication containing a cyclodextrin solubilizer
12. a) Female patients of childbearing potential if they are pregnant, nursing, or unable to use a highly effective method of birth control during the study and for at least one complete menstrual cycle following the last dose of study medication. A negative serum pregnancy result must be documented prior to treatment. A highly effective method of birth control is defined as one that results in a low failure rate (i.e., < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence, or a vasectomized partner.

b) Male patients must agree to use medically acceptable birth control for a least three months following last dose of study medication. A vasectomy or a condom used with a spermicide is a medically acceptable birth control method for males.

13. Prior enrollment in a clinical trial of telavancin
14. Known hypersensitivity to, or intolerance of, study medications or their formulation excipients
15. Treatment with another investigational medication within 30 days of study entry
16. Considered unlikely to survive at least 7 days due to underlying illness
17. Considered unlikely to comply with the study procedures or to return for scheduled post-treatment evaluations
18. Any other condition that in the opinion of an investigator, would confound or interfere with evaluation of safety or efficacy of the investigational medication, or prevent compliance with the study protocol

Endpoints

Primary Efficacy

The primary efficacy endpoint is clinical response at TOC. Patients who were failures at End-of-therapy were not to have a Test-of-cure evaluation. Consequently, for purpose of analysis, a clinical response of "failure" at the End-of-therapy assessment will be extrapolated to the Test-of-cure evaluation, even if a value is recorded on the CRF at Follow-up/Test-of-cure.

Any patient who dies on or after Study Day 3 and before the Test-of-cure evaluation—or if no Follow-up/Test-of-cure evaluation was done, within 28 days (inclusive) after last study medication—where the death is attributable to the HAP episode under study, will be imputed to be a "failure" with respect to Clinical Response at TOC, regardless of any value recorded on the CRF for Clinical Response at TOC.

Secondary Efficacy Endpoints

- By pathogen microbiological response at TOC

By-pathogen microbiological response at the Follow-up visit is defined for each unique baseline respiratory pathogen. The endpoint is evaluated using culture results, if available; otherwise, Clinical Response is presumed to be indicative of microbiological response and is used as a surrogate.

- By patient microbiological response
- All-cause mortality

Deaths will be identified from the Death Report CRF. Deaths will be identified through the Follow-up/Test-of-cure evaluation. If no Follow-up visit was made, deaths that occur within 28 days after last study medication (that is, through Post-treatment Study Day 28P, inclusive) will be considered

- Mortality attributable to primary infection
- Duration of study medication treatment
- Time to resolution of fever, i.e. > 38° F
- Length of stay in ICU
- Number of days on mechanical ventilation, for patients on ventilation at randomization

Safety endpoints

- Adverse events
- QT and QTc intervals
- Laboratory results: Hematology, serum chemistry, and urinalysis

Sample Size

At the time of protocol development, the study's planned enrollment of 312 patients per arm was expected to provide 109 clinically evaluable patients per arm, with the assumption that at least 35% of enrolled patients would be clinically evaluable. If the population clinical cure rates for telavancin and vancomycin are both 60%, then a one-sided, 0.025-level test of the non-inferiority of telavancin relative to vancomycin, and employing a non-inferiority Δ-criterion of 20%, has 86% power.

Analysis Populations

1. All-Treated: The "All-Treated" (AT) analysis population was to be comprised of patients who received any amount of study medication. Patients were to be analyzed according to the treatment group assigned by randomization;
2. Modified All-Treated: The "Modified All-Treated" (MAT) analysis population was to be comprised of patients in the All-Treated population who baseline respiratory pathogen identified;
3. Clinically Evaluable: The "Clinically Evaluable" (CE) analysis population was to be comprised of patients in the All-Treated population who received the study medication assigned by the randomization schedule and who meets all of the following criteria:
    - The patient met the following protocol inclusion criteria (IC), or else was approved for enrollment by the study hotline monitor:
        - IC #2, which requires certain signs and symptoms consistent with pneumonia
        - IC #3, which requires a chest radiograph consistent with a diagnosis of pneumonia
        - IC #4, which requires the availability of appropriate specimens for Gram stain and culture, and venous access for dosing.
    - The patient did not violate the following protocol exclusion criteria (EC), or else was approved for enrollment by the study hotline monitor:
        - EC #1, which excludes patients who have received more than a specified amount of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization.
        - EC #2, which excludes patients with respiratory tract specimens or sputum with only Gram-negative bacteria
        - EC #3, which excludes patients with MSSA or S. pneumoniae who also require more than a specified amount of concomitant antibiotic therapy for Gram-negative coverage that has activity versus MSSA or *S. pneumonia*
        - EC#4, which excludes patients with known or suspected pulmonary disease that precludes evaluation of therapeutic response, cystic fibrosis, or active tuberculosis

    - EC #5, which excludes patients with known or suspected *Legionella pneumophila* pneumonia
    - EC #6, which excludes patients who are known or suspected to be infected with an organism that is not susceptible to medications permitted by the protocol.
    - EC #7, which excludes patients with documented or suspected meningitis, endocarditis, or osteomyelitis
- The patient's identified analysis pathogen(s) were not solely Gram-negative pathogens. That is, either the patient had a Gram-positive analysis pathogen, or no analysis pathogen was identified.
- The patient did not have pneumonia due to *Stenotrophomonas maltophilia* or *Burkholderia cepacia* at Baseline.
- The patient did not have a persistent S. aureus bacteremia, defined as two or more *S. aureus*-positive blood cultures on different days between Study Day 1 and TOC, inclusive.
- The patient did not receive more than two days of vancomycin or teicoplanin between Study Day -4 and Study Day 1, inclusive. The rationale for excluding patients who have received prior treatment with vancomycin is to exclude prior treatment failures to vancomycin. Only intravenous vancomycin will be considered as a potential basis for exclusion from the CE population; oral administration will not be a basis for exclusion.
- The patient was treated with the study medication assigned by the randomization.
- The patient received at least 80% of intended doses of active study medication.
- The patient did not receive potentially effective concomitant systemic antibiotic therapy for more than 2 calendar days any time before the TOC assessment. The day of the TOC assessment is not counted for this criterion.
- The patient was a "failure" at End-of-therapy, or else was either a "cure" or a "failure" at Test-of-cure.
- If the patient was not a "failure" at End-of-therapy, then the Test-of-cure assessment was made between Study Day 6P and Study Day 28P inclusive.
- If the patient was a "cure," the patient received at least 5 days of active study medication.
- If the patient was a "failure," the patient received active study medication daily through Study Day 3.

Additionally, for patients who died on or after Study Day 3, where the death is attributable to the HAP episode under study, the receipt of PEAT will not exclude them from the CE population

4. Microbiologically Evaluable: The "Microbiologically Evaluable" (ME) analysis population was to be comprised of patients in the CE population who also have a Gram-positive baseline respiratory pathogen

The primary analysis was to test both non-inferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the non-inferiority analysis, both the AT and CE analysis populations were considered co-primary. For the superiority analysis, the AT population served as the primary population.

Reviewer's Comment:
For efficacy analyses, the analysis populations should exclude patients who had only gram-negative pathogens cultured at baseline. This approach is followed because neither the test article nor the active comparator have activity against gram-negative pathogens so the inclusion of patients who have gram-negative pathogens recovered at baseline would measure the effect of the adjunctive therapy and potentially bias the results toward noninferiority.

The primary efficacy analysis was to initially test for the clinical non-inferiority of telavancin relative to vancomycin using a difference in the rate of clinical response at TOC and employing a non-inferiority margin of 20%. The testing was to be performed by using a 2-sided 95% confidence interval for the difference in clinical response rates based on the normal approximation to the binomial distribution. If any cell size is less than 10, as might occur during a subgroup analysis, the confidence interval will be calculated using the adjustment presented by Agresti and Caffo to adjust for the sparse cell size. If noninferiority was established, then statistical superiority would be examined using the confidence interval approach to determine whether the lower bound of 2-sided 95% confidence interval was greater than zero.

The disposition of patients is shown in Table 2. For both studies, the disposition of patients was similar between treatment arms.

Table 2: Disposition of Patients for Studies 0015 and 0019

	Study 0015		Study 0019	
	Telavancin (N=381) N (%)	Vancomycin (N=380) N (%)	Telavancin (N=386) N (%)	Vancomycin (N=385) N (%)
Randomized	381 (100%)	380 (100%)	386 (100%)	385 (100%)
Received Study Drug	372 (98%)	374 (98%)	377 (98%)	380 (99%)
Randomized by Not Treated	9 (2%)	6 (2%)	9 (2%)	5 (1%)
Completed Course Of Study Therapy	206 (55%)	230 (61%)	228 (60%)	224 (59%)
Resolution of Signs and Symptoms in ≤ 21 days	204 (55%)	229 (61%)	224 (59%)	216 (57%)
Infection not resolved but patient received maximum allowable 21 days of treatment	2 (<1%)	1 (<1%)	4 (1%)	8 (2%)
Premature Discontinuation of Study Medication	166 (45%)	144 (39%)	149 (40%)	156 (41%)
Unsatisfactory Therapeutic Response, Did Not Receive Maximum Allowable 21 Days of Treatment	28 (8%)	36 (10%)	25	(7%)
Death	38 (10%)	29 (8%)	33 (9%)	31 (8%)
Two Consecutive ECGs with QTc > 500 msec	8 (2%)	1 (<1%)	5 (1%)	2 (<1%)
Adverse Event	22 (6%)	11 (3%)	16 (4%)	15 (4%)
Patient Withdrew Consent	11 (3%)	12 (3%)	15 (4%)	15 (4%)
Major Protocol Deviation	4 (1%)	0	2 (<1%)	4 (1%)
Infection due to Gram-negative Organisms only	11 (3%)	9 (2%)	5 (1%)	2 (<1%)
Infection due to *Stenotrophomonas Maltophllia* or *Burkholderia Cepacia*	0	4 (1%)	1 (<1%)	1 (<1%)
Persistent S. aureus Bacteremia	0	0	0	2 (<1%)
Gram-positive Coverage No Longer Clinically Indicated	27 (7%)	18 (5%)	42 (11%)	45 (12%)
Documented Meningitis, Endocarditis, or Osteomyelitis	0	0	1 (<1%)	2 (<1%)
Required Non-study Antibiotics	6 (2%)	5 (1%)	2 (<1%)	6 (2%)
Other	11 (3%)	19 (5%)	2 (<1%)	7 (2%)

Source: Summary of Clinical Efficacy, Table 10
2 patients in Study 0019 were randomized to the vancomycin group by received telavancin instead.

The number of patients in each treatment group was evenly balanced in the AT, CE, MAT, and ME population, see Table 3. As mentioned earlier, for efficacy analyses, patients who had gram-negative pathogens isolated only at baseline should be excluded because their inclusion has the potential to bias the analyses towards demonstrating noninferiority.

Table 3: Analysis Populations

	Study 0015		Study 0019	
Population	Telavancin	Vancomycin	Telavancin	Vancomycin
AT	372 (100%)	374 (100%)	377 (100%)	380 (100%)
Only gram-negative pathogens isolated at baseline	70 (19%)	67 (18%)	79 (21%)	76 (20%)
Modified AT (MAT)	257 (69%)	247 (66%)	303 (80%)	282 (74%)
Respiratory Pathogens	249 (97%)	245 (99%)	297 (98%)	279 (99%)
Blood Pathogens Only	8 (3%)	2 (<1%)	6 (2%)	3 (1%)
CE	141 (38%)	172 (46%)	171 (45%)	170 (45%)
ME	108 (29%)	113 (30%)	135 (36%)	124 (33%)
Respiratory Pathogens	105 (97%)	113 (100%)	134 (99%)	123 (99%)
Blood Pathogens Only	3 (3%)	0	1 (<1%)	1 (<1%)
ME as % of CE Population	77%	66%	79%	73%

Source: Modified from Summary of Clinical Efficacy, Table 18

The demographics of the AT population are summarized in Table 4. For each trial, the two treatment groups appeared similar with respect to the many baseline demographic characteristics presented in the table. However, on average, there were fewer patients from US sites in Study 0019 (14%) than for Study 0015 (31%). In addition, patients in Study 0015 had an increased rate of renal impairment, renal problems, and diabetes then patients in Study 0019.

Table 4: Baseline Demographics (AT Population)

	Study 0015		Study 0019	
	TLV (N=372)	VANC (N=374)	TLV (N=377)	VANC (N=380)
US vs. Non-US				
US	117 (31%)	113 (30%)	60 (16%)	46 (12%)
Non-US	255 (69%)	261 (70%)	317 (84%)	334 (88%)
Age				
Mean ± SD	63 ± 19.2	64 ± 17.3	61 ± 17.8	62 ± 18.0
Min, Max	18, 99	19, 97	18, 100	18, 97
Age Distribution				
<65 years	170 (46%)	162 (43%)	182 (48%)	184 (48%)
≥65 years	202 (54%)	212 (57%)	195 (52%)	196 (52%)
Age Distribution				
<75 years	241 (65%)	250 (67%)	278 (74%)	271 (71%)
≥75 years	131 (35%)	124 (33%)	99 (26%)	109 (29%)
Sex				
Male	235 (63%)	213 (57%)	252 (67%)	256 (67%)
Female	137 (37%)	161 (43%)	125 (33%)	124 (33%)
Race				
Asian	91 (24%)	87 (23%)	81 (21%)	91 (24%)
Black, of African heritage	10 (3%)	14 (4%)	15 (4%)	6 (2%)
White	267 (72%)	272 (73%)	248 (66%)	254 (67%)
Other including Mixed Race	4 (1%)	1 (<1%)	33 (9%)	29 (8%)
Type of Pneumonia				

VAP	103 (28%)	100 (27%)	113 (30%)	111 (29%)
Late VAP (≥4 days on ventilation at diagnosis	91 (24%)	81 (22%)	98 (26%)	90 (24%)
HAP	269 (72%)	274 (73%)	264 (70%)	269 (71%)
APACHE II (complete scores)				
Mean ± SD	16 ± 6.2	17 ± 5.8	16 ± 5.7	17 ± 6.2
0 - 13 Points	80 (37%)	72 (35%)	60 (33%)	63 (32%)
14 - 19 Points	75 (35%)	78 (38%)	70 (38%)	74 (37%)
≥20 Points	59 (28%)	56 (27%)	52 (29%)	63 (32%)
N	214	206	182	200
Medical History				
Diabetes	118 (32%)	114 (30%)	85 (23%)	77 (20%)
Congestive Heart Failure	71 (19%)	78 (21%)	59 (16%)	63 (17%)
COPD	86 (23%)	90 (24%)	87 (23%)	88 (23%)
Chronic Renal Failure	32 (9%)	35 (9%)	11 (3%)	17 (4%)
Shock	14 (4%)	23 (6%)	15 (4%)	18 (5%)
ARDS	24 (6%)	20 (5%)	9 (2%)	10 (3%)
Acute Lung Injury (but not ARDS)	33 (9%)	20 (5%)	18 (5%)	13 (3%)
ICU				
ICU at Baseline	224 (60%)	216 (58%)	207 (55%)	224 (59%)
Body Mass Index (kg/m^2)				
Underweight < 18.5 (kg/m^2)	28 (8%)	29 (8%)	41 (11%)	37 (10%)
Normal Wt 18.5 - < 25 (kg/m^2)	150 (40%)	163 (44%)	172 (46%)	189 (50%)
Overweight 25 - < 30 (kg/m^2)	108 (29%)	99 (26%)	119 (32%)	107 (28%)
Obese 30 - < 40 (kg/m^2)	63 (17%)	64 (17%)	39 (10%)	42 (11%)
Morbidly Obese ≥40 (kg/m^2)	20 (5%)	16 (4%)	6 (2%)	5 (1%)
Missing	3 (<1%)	3 (<1%)	0	0
Baseline Serum Creatinine Clear Clearance (central lab)				
>80 mL/min	138 (37%)	146 (39%)	179 (47%)	176 (46%)
>50-80 mL/min	86 (23%)	85 (23%)	92 (24%)	88 (23%)
30-50 mL/min	80 (22%)	80 (21%)	61 (16%)	67 (18%)
<30 mL/min	57 (15%)	50 (13%)	37 (10%)	38 (10%)
Missing	11 (3%)	13 (3%)	8 (2%)	11 (3%)
Diabetes status at baseline				
Nondiabetic	272 (73%)	274 (73%)	308 (82%)	315 (83%)
Diabetic	100 (27%)	100 (27%)	69 (18%)	65 (17%)
Hemodialysis				
Patient on hemodialysis	11 (3%)	9 (2%)	3 (<1%)	5 (1%)

Source: ISE, Table 5-11; CSR, Supporting Tables 31, 33, and 34

Other baseline microbiological characteristics in the MAT population are provided in Table 5. The two treatment arms are similar for the baseline pathogens. It should be noted that only a relative small number of patients had *Streptococcus pneumoniae* recovered (telavancin: 29; vancomycin: 30). Additionally, only a few patients had *Enterococcus faecalis* or *Enterococcus faecium* recovered.

Table 5: Baseline Gram-Positive Respiratory Pathogens (Micro AT Population)

	Study 0015		Study 0019	
Population	Telavancin (n=257)	Vancomycin (n=247)	Telavancin (n=303)	Vancomycin (n=282)
Staphylococcus aureus	168 (65.4%)	170 (68.8%)	199 (65.7%)	178 (63.1%)
MRSA	111 (43.2%)	113 (45.7%)	117 (38.6%)	117 (41.5%)
MSSA	61 (23.7%)	57 (23.1%)	83 (27.4%)	63 (22.3%)
Streptococcus pneumoniae	15 (5.8%)	7 (2.8%)	14 (4.6%)	23 (8.2%)
Enterococcus faecalis	3 (1.2%)	6 (2.4%)	10 (3.3%)	13 (4.6%)
Enterococcus faecium	1 (0.4%)	0 (0.0%)	3 (1.0%)	1 (0.4%)

Source: SCE, Appendix, Table 6
Note: More than one pathogen may have been present in any patient

The results for the study defined primary endpoint, clinical response at TOC, is presented in Table 6. However, there is no historical data to justify a non-inferiority margin for clinical response endpoint and the details are discussed in Section 5.1.

Table 6: Clinical Response at TOC

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
All-Treated				
Cure	214 (57.5%)	221 (59.1%)	227 (60.2%)	228 (60.0%)
Failure	46 (12.4%)	68 (18.2%)	53 (14.1%)	52 (13.7%)
Indeterminate	56 (15.1%)	41 (11.0%)	39 (10.3%)	38 (10.0%)
Missing	56 (15.1%)	44 (11.8%)	58 (15.4%)	62 (16.3%)
- Total -	372 (100.0%)	374 (100.0%)	377 (100.0%)	380 (100.0%)
Difference (95% CI)	-1.6% (-8.6% , 5.5%)		0.2% (-6.8% , 7.2%)	
Clinically Evaluable				
Cure	118 (83.7%)	138 (80.2%)	139 (81.3%)	138 (81.2%)
Failure	23 (16.3%)	34 (19.8%)	32 (18.7%)	32 (18.8%)
- Total -	141 (100.0%)	172 (100.0%)	171 (100.0%)	170 (100.0%)
Difference (95% CI)	3.5% (-5.1% , 12.0%)		0.1% (-8.2% , 8.4%)	

In Section 5.1 of this review, an alternative primary endpoint of all-cause mortality is discussed. Because of the lack of consensus as to the proper length of the mortality reporting period, results based on two reporting periods are presented in this review(Study initiation to Study 28 and to EOT + 28 days). It can be seen that for both of the reporting periods, a large proportion of the patients has incomplete survival information for the entire mortality reporting period. This high proportion of patients with missing data makes interpretation of the data extremely difficult resulting in analyses that can be heavily influenced by the imputation method chosen to handle the missing data.

The large proportion of the patients with incomplete survival information occurred because the safety reporting period for these trials was either through the TOC assessment or if the TOC assessment did not occur, then twenty-eight days after the last dose of study drug was received.

The efficacy analyses presented in Table 7 and Table 8 exclude patients who had only gram-negative pathogens cultured at baseline. This approach is taken because neither the test article nor the active comparator have activity against gram-negative pathogens so including patients who have gram-negative pathogens recovered at baseline would likely only measure the effect of the adjunctive therapy and potentially bias the results toward noninferiority.

Table 7: Deaths between Start of Study Drug and Study Day 28 (AT Population excluding patients who have only gram-negative pathogens cultured at baseline)

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Deaths Between Start of Study Drug and Study Day 28	78 (25.8)	64 (20.8)	66 (22.2)	64 (21.1)
Alive	127 (42.1)	132 (43.0)	147 (49.3)	150 (49.3)
Missing outcome[1]	97 (32.1)	111 (36.2)	85 (28.5)	90 (29.6)
-Total-	302 (100%)	307 (100%)	298 (100%)	304 (100%)

[1] Incomplete survival information for the mortality reporting period

Patients are categorized as randomized. Two patients randomized to the vancomycin group received telavancin —by Study Day 28, 1 subject had died at or prior to this day and the other subject was alive

Table 8: Deaths between Start of Study Drug and EOT + 28 days (AT Population excluding patients who have only gram-negative pathogens cultured at baseline)

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Deaths Between Start of Study Drug and EOT + 28 Days	88 (29.1)	72 (23.5)	72 (24.2)	74 (24.3)
Alive	101 (33.4)	102 (33.2)	120 (40.3)	124 (40.8)
Missing outcome[1]	113 (37.4)	133 (43.3)	106 (35.6)	106 (34.9)
-Total-	302 (100)	307 (100)	298 (100)	304 (100)

[1] Incomplete survival information for the mortality reporting period

Patients are categorized as randomized. Two patients randomized to the vancomycin group received telavancin – by EOT + 28 days, 1 subject had died at or prior to this day and the other subject was alive

The dosing in the study was designed to be for 7-21 days in length for both studies. As can be seen in Table 9, most patients (42%-44%) received 7-10 days of treatment.

Table 9: Days of Study Medication (AT population)

	0015		0019		Pooled	
	Telavancin	Vancomycin	Telavancin	Vancomycin	Telavancin	Vancomycin
<3 Days	23 (6%)	15 (4%)	17 (5%)	17 (4%)	40 (5%)	32 (4%)
3-6 Days	77 (21%)	62 (17%)	52 (14%)	53 (14%)	129 (17%)	115 (15%)
7-10 Days	152 (41%)	172 (46%)	163 (43%)	160 (42%)	315 (42%)	332 (44%)
11-14 Days	79 (21%)	85 (23%)	95 (25%)	97 (26%)	174 (23%)	182 (24%)
15-21 Days	39 (10%)	38 (10%)	48 (13%)	47 (12%)	87 (12%)	85 (11%)
>21 Days	2 (<1%)	2 (<1%)	2 (<1%)	6 (2%)	4 (<1%)	8 (1%)
- Total -	372 (100%)	374 (100%)	377 (100%)	380 (100%)	749 (100%)	754 (100%)

Source: ISE, Table 5-20

3.2 Evaluation of Safety

Because it is not clear which reporting period most accurately captures the potential safety risk of telavancin relative to vancomycin, two reporting periods are presented (study initiation through Study Day 28 and EOT + 28 days) in Table 10 and Table 11.

Table 10: Deaths between Start of Study Drug and Study Day 28 (AT Population)

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Deaths Between Start of Study Drug and Study Day 28	92 (24.7%)	73 (19.5%)	80 (21.1%)	88 (23.3%)
On Therapy	22 (5.9%)	22 (5.9%)	26 (6.9%)	20 (5.3%)
After End of Study Drug	70 (18.8%)	51 (13.6%)	54 (14.2%)	68 (18.0%)
Alive	154 (41.4%)	167 (44.7%)	186 (49.1%)	187 (49.5%)
Missing outcome[1]	126 (33.9%)	134 (35.8%)	113 (29.8%)	103 (27.2%)
-Total-	372 (100%)	374 (100%)	379 (100%)	378 (100%)

Source: Applicant 8/12/09 response to information request, Table 1
[1] Incomplete survival information for the mortality reporting period
Patients are categorized as treated

Table 11: Deaths between Start of Study Drug and EOT + 28 days (AT Population)

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Deaths Between Start of Study Drug and EOT + 28 Days	102 (27.4%)	82 (21.9%)	88 (23.2%)	99 (26.2%)
On Therapy	22 (5.9%)	22 (5.9%)	26 (6.9%)	20 (5.3%)
After End of Study Drug	80 (21.5%)	60 (16.0%)	62 (16.4%)	79 (20.9%)
After TOC Visit	22 (5.9%)	19 (5.1%)	18 (4.7%)	21 (5.6%)
Alive	125 (33.6%)	133 (35.6%)	152 (40.1%)	153 (40.5%)
Missing outcome[1]	145 (39.0%)	159 (42.5%)	139 (36.7%)	126 (33.3%)
-Total-	372 (100%)	374 (100%)	379 (100%)	378 (100%)

Source: Applicant 8/12/09 response to information request, Table 2
[1] Incomplete survival information for the mortality reporting period
Patients are categorized as treated

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Subgroup analyses of mortality through Study Day 28 by gender, race, and age in the AT population are presented in Table 12. It should be noted that a large proportion of patients had incomplete survival information for the mortality reporting period that makes it difficult to meaningfully interpret the results.

Table 12: Day 28 Mortality by Subgroup (AT)

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
Age				
<65 Years	170	162	182	184
Deaths Between Start of Study Drug and Study Day 28	31 (18.2)	21 (13.0)	22 (12.1)	26 (14.1)
Alive	78 (45.9)	80 (49.4)	108 (59.3)	100 (54.4)
Missing outcome[1]	61 (35.9)	61 (37.6)	52 (28.6)	58 (31.5)
≥65 Years	202	212	195	196
Deaths Between Start of Study Drug and Study Day 28	61 (30.2)	52 (24.5)	57 (29.2)	63 (32.1)
Alive	76 (37.6)	87 (41.0)	77 (39.5)	88 (44.9)
Missing outcome[1]	65 (32.2)	73 (34.4)	61 (31.3)	45 (23.0)
Sex				
Female	137	161	125	124
Deaths Between Start of Study Drug and Study Day 28	32 (23.4)	35 (21.7)	30 (24.0)	32 (25.8)
Alive	63 (46.0)	65 (40.4)	60 (48.0)	62 (50.0)
Missing outcome[1]	42 (30.7)	61 (37.9)	35 (28.0)	30 (24.2)
Male	235	213	252	256
Deaths Between Start of Study Drug and Study Day 28	60 (25.5)	38 (17.8)	49 (19.4)	57 (22.3)
Alive	91 (38.7)	102(47.9)	125 (49.6)	126 (49.2)
Missing outcome[1]	84 (35.7)	73 (34.3)	78 (40.0)	73 (28.5)
Race				
Asian	91	87	81	91
Deaths Between Start of Study Drug and Study Day 28	19 (20.9)	14 (16.1)	17 (21.0)	19 (20.9)
Alive	53 (58.2)	63 (72.4)	40 (49.4)	55 (60.4)
Missing outcome[1]	19 (20.9)	10 (11.5)	24 (29.6)	17 (18.7)
Black	10	14	15	6
Deaths Between Start of Study Drug and Study Day 28	3 (30.0)	2 (14.3)	3 (20.0)	1 (16.7)
Alive	4 (40.0)	8 (57.1)	7 (46.7)	1 (16.7)
Missing outcome[1]	3 (30.0)	4 (28.6)	5 (33.3)	4 (66.7)
White	267	272	248	254
Deaths Between Start of Study Drug and Study Day 28	70 (26.2)	56 (20.6)	53 (21.4)	62 (24.4)
Alive	95 (35.6)	96 (35.3)	124 (50.0)	121 (66.1)
Missing outcome[1]	102 (38.2)	120 (44.1)	71 (28.6)	71 (27.8)
Other	4	1	33	29
Deaths Between Start of Study Drug and Study Day 28		1	6 (18.2)	7 (24.1)
Alive	2 (50.0)		14 (42.4)	11 (37.9)
Missing outcome[1]	2 (50.0)		13 (39.4)	11 (37.9)

[1] Incomplete survival information for the mortality reporting period

4.2 Other Special/Subgroup Populations

A subgroup analysis of mortality through Study Day 28 by baseline renal function is presented in Table 13. As seen earlier, it should be noted that a large proportion of patients had incomplete survival information for the mortality reporting period that makes interpretation of the results difficult.

Table 13: Day 28 Mortality by Baseline Creatinine Clearance (AT)

	0015		0019	
	Telavancin	Vancomycin	Telavancin	Vancomycin
>80 mL/min	138	146	179	176
Deaths Between Start of Study Drug and Study Day 28	17 (12.3)	21 (14.4)	18 (10.1)	30 (17.0)
Alive	65 (47.1)	69 (47.3)	105 (58.7)	90 (51.1)
Censored	56 (40.6)	56 (38.4)	56 (31.3)	56 (31.8)
>50 – 80 mL/min	86	85	92	88
Deaths Between Start of Study Drug and Study Day 28	23 (26.7)	12 (14.1)	22 (23.9)	24 (27.3)
Alive	34 (39.5)	38 (44.7)	47 (51.1)	44 (50.0)
Censored	29 (33.7)	35 (41.2)	23 (25.0)	20 (22.7)
30 – 50 mL/min	80	80	61	67
Deaths Between Start of Study Drug and Study Day 28	25 (31.2)	20 (25.0)	15 (24.6)	16 (23.9)
Alive	26 (32.5)	37 (46.2)	26 (42.6)	31 (46.3)
Censored	29 (36.2)	23 (28.8)	20 (32.8)	20 (29.8)
<30 mL/min	57	50	37	38
Deaths Between Start of Study Drug and Study Day 28	24 (42.1)	19 (38.0)	21 (56.8)	16 (42.1)
Alive	27 (47.4)	17 (34.0)	6 (16.2)	17 (44.7)
Censored	6 (10.5)	14 (28.0)	10 (27.0)	5 (13.2)

Creatinine clearance based on central lab results

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The following statistical issues were found during the review of this application – the choice of the primary endpoint, the large proportion of patients whose survival status is not known throughout the mortality reporting periods, the pooling of the trials to analyze mortality, data integrity and blinding issues, and the proportion of patients who received concomitant antimicrobials for gram-negative coverage. The most important issues that will be discussed are the choice of the primary endpoint and the large proportion of patients whose survival status is unknown throughout the reporting period. This issue is of foremost importance for both the efficacy and safety analyses.

Interpretation of the noninferiority trials using clinical response as the primary endpoint

The predefined primary endpoint for the two trials was clinical response at TOC. The endpoint chosen is a major statistical issue because the lack of historical data for this endpoint does not allow one to estimate the treatment effect of the active comparator. This estimate is an essential in determining a non-inferiority margin to be used in the interpretation of the results. Previously, the Agency presented historical data supporting a 7% noninferiority margin for the endpoint of all-cause mortality (as an alternative to

clinical response) in clinical trials of NP at the 16 July 2008 meeting of the Anti-Infective Drugs Advisory Committee convened to discuss NDA 22-171 (doripenen for injection). Subsequently, a two-day workshop on NP -- co-sponsored by the Agency, the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) -- was held on 3/31/09 – 4/1/09. At this workshop, the lack of historical data on the treatment effect of antibacterials for clinical response was discussed along with an Agency presentation on the historical data for all-cause mortality in NP along with a discussion of the size of an NI margin that could be justified based on this data. Details on the justification for an NI margin in NP can be found in Sorbello et al.[2], which is presented in Appendix A-1.

Based on an Agency review of the literature and the discussion at the workshop, the clearest evidence of treatment effect was based on all-cause mortality. However, the historical literature did not provide a uniform timepoint for the assessment of mortality. The mortality reporting window should be of adequate length such that the outcome of interest reflects the attributable clinical effect of the drug rather than being confounded by the underlying comorbidities. In addition, ideally, the timing of the assessment should be prospectively defined to avoid any kind of post-hoc selection. However, at the present time there is not a clear consensus on the appropriate timing of assessment

Discussion at the workshop focused on the timepoint of 28 days after randomization/initiation of therapy. Based on Table 9, 11%-12% of the patients received 15-21 days of treatment. Therefore, because the treatment duration varies from patient-to-patient, there is also consideration that a specified timepoint after end of therapy should be used for the mortality assessment. Currently, there is not a clear consensus on what the appropriate timing of assessment of all-cause mortality should be. There are strengths and weaknesses in using either “time from randomization” or “time from end of therapy”.

At the workshop, because the clearest evidence of treatment effect was based on all-cause mortality, a recommendation was made to use all-cause mortality as the primary endpoint in NP studies. This has prompted basing the efficacy evaluation for this application on all-cause mortality rather than clinical response. Because of this, the following issue of missing mortality data is of major importance.

Missing all-cause mortality data

A major statistical issue is the large proportion of patients whose survival status is not known through either the Study Day 28 reporting period or the EOT + 28 days reporting period (see Table 14). Specifically, for the Study Day 28 period, incomplete information occurs for 34.9% of the patients in Study 0015 and 28.5% of the patients in Study 0019. Similarly, for the EOT + 28 days period, incomplete mortality information occurs in 35%-40% of the patients for the two trials. With this large proportion of missing outcomes, interpretation of the mortality data is quite difficult because analyses that can be heavily influenced by the imputation method chosen to handle the missing data. As an

[2] Sorbello A, Komo S, and Valappil T. *Drug Information Journal (in press)*

example, for Study 0015, the observed mortality difference (telavancin – vancomycin) is 5.2% for the Study 28 reporting period. However, this observed mortality difference is dwarfed by the almost 35% of the patients whose survival status is incomplete for the entire reporting period. Thus, it can be seen that analyses will be very sensitive to the method chosen to account for the missing data.

The distribution of the last study day that a patient is known to be alive in patients whose survival status is not throughout the reporting period is given in Table 15. It can be seen that censoring occurs in a large proportion of patients by Study Day 21. This is concerning because the observed mortality data may not fully capture the effect or lack of effect of telavancin in treating NP because for a substantial proportion of the patients, deaths will not be counted for a week or more of the reporting period.

In August 2009, the Applicant was notified of the Agency's concern with the large proportion of patients whose survival status is incomplete. Subsequently, the Applicant stated that they would query the study sites to determine the survival status during the reporting periods for a greater number of patients.

Table 14: Number of AT patients whose mortality information is incomplete

Period	0015			0019		
	Telavancin (n=372)	Vancomycin (n=374)	Total (n=746)	Telavancin (n=379)	Vancomycin (n=378)	Total (n=757)
Study Day 28	126 (33.9%)	134 (35.8%)	260 (34.9%)	113 (29.8%)	103 (27.2%)	216 (28.5%)
EOT + 28 days	145 (39.0%)	159 (42.5%)	304 (40.8%)	139 (36.7%)	126 (33.3%)	265 (35.0%)

Source: Applicant 8/12/09 response to information request, Table 2
Patients are categorized as treated

Table 15: Distribution of the Last Study Day Known to be Alive in Patients whose mortality information is incomplete

	Study 0015		Study 0019	
Study Day	Telavancin	Vancomyin	Telavancin	Vancomyin
Day 1-7	2	4	4	2
Day 8-14	32	26	18	18
Day 15-21	55	75	62	48
Day 22-28	37	29	29	35
Day 29-35	14	19	17	20
Day 36-42	5	5	8	3
Day 43-49	0	1	1	0

Reporting period is EOT + 28 days

Pooling of trials to analyze mortality

The Applicant has pooled the mortality data from the two trials as the proposed method to analyze mortality rates. They submit that pooling is reasonable because the two trials were identical in design. However, because the populations differ in terms of several important factors related to baseline renal function, the trials should not be pooled for analysis purposes. The differences in the patient populations with regard to baseline renal function is an important issue because the telavancin label for cSSSI, which was approved in September 2009, describes decreased efficacy in the treatment of cSSSI for

patients with decreased renal function relative to the vancomycin. In addition, the label also mentions an increase in severe renal adverse events for patients who received telavancin relative to those who received vancomycin. In Table 16, it can be seen that the patients in Study 0015 had a statistically significantly higher rate of renal problems and diabetes which is associated with decreased renal function than patients in Study 0019. For this reason, the results of the two trials should not be pooled for analysis purposes to prevent the confounding by differences in trial populations with respect to baseline renal function.

Table 16: Baseline characteristics by Trial (AT Population)

	Study 0015 (N=746)		Study 0019 (N=757)		p-value[2]
	N	%	n	%	
History of diabetes	232	31.1%	162	21.4%	<0.0001
Chronic renal failure	67	9.0%	28	3.7%	<0.0001
Baseline creatinine clearance < 50 ml/min[1]	267	35.8%	203	26.8%	0.0002
Diabetic at baseline	200	26.8%	134	17.7%	<0.0001
On hemodialysis at baseline[3]	20	2.7%	8	1.1%	0.0325

[1] Based on central laboratory results
[2] Based on a continuity corrected Chi-square test
[3] p-value based on a Fisher's exact test

Data Integrity and Blinding Issues

Another statistical issue is a concern regarding data integrity and blinding issues. This prompted a sponsor inspection that did not reveal any regulatory violations. However, during the inspection, it was ascertained that data was added/revised after treatment unblinding. In addition, some parts of the medical review process occurred after treatment unblnding. These determinations included decisions that would affect evaluability as well as whether patients received adequate gram-negative coverage. The adequacy of gram-negative coverage is an important issue because it is one of the factors that the Applicant is using to explain the observed increase in mortality seen for the telavancin arm relative to the vancomycin arm. A summary of the inspection and findings is provided below.

A sponsor inspection was performed from 10 September 2009 – 25 September 2009 to review the conduct of clinical studies performed in support of this application. The purpose of the inspection was to evaluate the Applicant's completion of regulatory obligations for Studies 0015 and 0019. In addition, the inspection was conducted to evaluate a complaint received by the Agency that asserted that the Applicant had improperly manipulated study data to achieve desired outcomes for Studies 0015 and 0019. A summary of the important finding will be given below

The sponsor inspection did not reveal any regulatory violations. The Applicant's documentation of dates of data transfer/data files transferred from (b) (4) ((b) (4) the CRO responsible for data management of the two Phase 3 trials, are consistent with data transfer dates/data files/file content that were documented by (b) (4) and reviewed during the Agency inspection of the CRO and in a subsequent comparison of datasets.

Although the inspection did not reveal any regulatory violations, it did shed light on some blinding issues that will be summarized below.

1st data unlock

The following issues were identified by the Applicant and data were added/changed during this unlocking of the database:

- MIC sensitivity data for ninety-two patients (198 records) from thirty-eight sites were inadvertently left out of the for Study 0015 database. The explanation given was that (b) (4) was receiving incremental updates from (b) (4) (CRO responsible for laboratory analyses) and failed to include this data in the treatment unblinded data transfer. Prior to treatment unblinding, the Applicant had previously received treatment blinded data from (b) (4) that included this MIC sensitivity data. However, when the unblinded data was transferred, Applicant staff noticed that the MIC sensitivity data for the subset of ninety-two patients was missing. The Applicant then asked (b) (4) to include the missing data in a new data transfer.
- SAE and deaths

Applicant staff noticed after treatment unblinding that there were inconsistencies in the data that indicated that death occurred, where death was flagged in one section but SAE and/or death report forms were not reported or included. Death could be marked in the AE, death report, Drug Discontinuation, Clinical Response at EOT, Study Completion/Follow-up/Test of Cure, and Clinical Response for Test of Cure sections.

The Applicant asked that the CRF as well as the SDTM data be updated so that deaths would be consistently captured. All of the inconsistencies found were for fourteen deaths that occurred during the safety reporting period for patients who did not have a test-of-cure (TOC) visit. The reporting period in this case was twenty-eight days after the last dose of study drug was received.

- ECG

Applicant staff discovered that ECG data for patients who were screening failures (i.e., non-randomized patients) were mistakenly included in the ECG dataset and notified (b) (4) also found some errors in protocol, site, and subject# for some patients. These errors included five patients (two in 0015 and three in 0019) who had incorrect site numbers, four patients who had an incorrect protocol# (i.e. in the Study 0019 dataset and but who were Study 0015 patients), and one patient had the wrong subject number listed. The Applicant was notified by (b) (4) of these discrepancies and the Applicant then told (b) (4) to notify the ECG vendor ((b) (4) to make these corrections and delete the screening failure data. Corrections were made by the ECG vendor who sent the corrected database to (b) (4) Corrected data were included in the updated SDTM datasets from (b) (4) during the 1st data unlock.

It was stated that the main reasons to unlock the database were to add SAE and death data and also MIC sensitivity data.

2nd database unlock

The corrections/updates made during the second database unlocking involved 33 patients. The following issues were identified by Applicant who notified (b) (4) who updated the data:

- Updates to renal AE status

This data was obtained from the Applicant's renal follow-up effort undertaken in May 2008. The objective was to follow up on patients who had a renal AE whose sequela was either continuing or resolving and to provide a status update sixty days after the patients completed the study. Queries were communicated to (b) (4) who then queried the sites.

- Dosing and weight correction

The dosing database was not locked until approximately six months after SDTM database was treatment unblinded. The Applicant was still issuing queries through (b) (4) to the sites while the dosing database was open. As a result of these queries, datapoints common to the dosing database and the SDTM database needed to be updated. During this process, data entry errors were also indentified in the SDTM database.

The primary reason stated to unlock was to include the data from the renal follow-up effort.

3rd database unlock

The Applicant undertook a remonitoring effort which involved an audit of a sample of sites. It was stated that this audit was performed in response to their experience with their complicated skin and skin structure infection application (NDA 22-110). This audit was performed by (b) (4) who audited patient records primarily looking at eligibility and clinical outcome assessment data. In addition, if AEs were found that were not previously noted, these would also be identified. Three deaths and two SAEs were indentified at the sites during the remonitoring effort and Theravance was informed. Theravance notified (b) (4) to update the database to reflect the new information. (b) (4) updated the database and transferred it to Theravance.

In addition to the data changes that occurred after treatment unblinding, the inspection also revealed that some parts of the Applicant's medical review occurred after the database was treatment unblinded. A summary is provided below.

Medical Review Process

A medical review process was performed by the Applicant to make determinations on issues such as clinical evaluability, whether a patient received potentially effective antibiotics, whether a patient received adequate gram-negative effort, etc. It was ascertained that the review by the medical monitor occurred in some instances after the SDTM database was treatment unblinded. This is relevant because the medical monitor made determinations that affected patient populations as well other issues that were reflected in the Analysis files. The Analysis files would be affected by either changes in the SDTM datasets or medical review process determinations on a particular issue, e.g. potentially effective antibiotics use (see Figure 1).

The process used in the Medical Review process was that a spreadsheet was created from the SDTM files that contained the relevant datapoints necessary to make a determination on a particular issue.

The following is a list of the explanations given by the Applicant for the major medical review determinations made after treatment unblinding occurred

- PEA (Potentially effective antibiotics)

The medical monitor found forty-two patients had inadvertently been omitted from the original spreadsheet that was used to make a PEA determination. This PEA determination also affects clinical evaluability. Note it was stated that the treatment code was not included in the spreadsheet used to make the determination.

- GNECGOVM and GNEGVN (adequacy of gram-negative coverage)

These spreadsheets were used to look at the adequacy of gram-negative coverage for the purpose of exploring some of the findings in the study and performing sensitivity analyses. It should be noted that both of these spreadsheets were created approximately six months after treatment unblinding.

Concomitant antimicrobials given for gram-negative coverage

The interpretation of the efficacy analyses for gram-positive pathogens is confounded by the administration of concomitant antimicrobials to provide gram-negative coverage that also have overlapping gram-positive coverage. This adjunctive gram-negative coverage occurred in a substantial proportion of patients. The initial protocol specified that aztreonam could be used to provide gram-negative coverage but that piperacillin-tazobactam or imipenem could be used if there were concerns of aztreonam resistance. Subsequently, the protocol was revised in Amendment 1 to drop imipenem as an alternative to aztreonam.

In NP trials of agents that have only gram-positive activity, the problem of overlapping gram-positive activity of the concomitant antimicrobial agents administered to provide gram-negative coverage is a difficult issue to ignore because of the increase in resistance to aztreonam, which has only activity against gram-negative pathogens.

In the current application, the proportion of patients who received concomitant antimicrobials with overlapping gram-positive activity is substantial. In Study 0015, 24% (91/372) of the patients in the telavancin patients received piperacillin/tazobactam and 10% (38/372) received imipenem. For the vancomycin arm, 18% (69/374) received piperacillin/tazobactam and 10% (37/374) received imipenem. Similarly, in Study 0019, 22% (83/379) of the patients in the telavancin patients received piperacillin/tazobactam and 11% (42/379) received imipenem. For the vancomycin arm, 21% (81/378) received piperacillin/tazobactam and 11% (42/378) received imipenem.

As quantified in the previous paragraph, the proportion of patients who received concomitant antimicrobials with overlapping gram-positive activity is substantial and confounds the ability to determine the effect of telavancin in the submitted trials to treat gram-positive NP. This is particularly an important issue in non-inferiority trials because any such confounding effect can potentially make the treatment look similar when in fact they are not. This confounding effect should be kept in mind when interpreting the efficacy results.

5.2 Conclusions and Recommendations

The Applicant did not provide substantial evidence based on all-cause mortality that telavancin is effective and safe in the treatment of NP infections because a substantial proportion of the patients in both trials (Studies 0015 and 0019) had incomplete survival information for the entire mortality reporting period. Thus, a determination of the efficacy and safety of telavancin in the treatment on NP cannot be performed until additional mortality data is provided.

A APPENDICES

A1 Noninferiority Margin for Clinical Trials of Antibacterial Drugs for Nosocomial Pneumonia

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