BRIEFING PACKAGE

Division of Anti-Infective Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research, FDA

NDA 22-407

VIBATIV® (TELAVANCIN for Injection)

APPLICANT: THERAVANCE, Inc

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

NOVEMBER 29, 2012

PROPOSED INDICATION:

TREATMENT OF PATIENTS WITH NOSOCOMIAL PNEUMONIA (ALSO REFERRED TO AS HOSPITAL-ACQUIRED PNEUMONIA (HAP)), INCLUDING VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought this issue to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

TABLE OF CONTENTS

INTRODUCTION

Vibativ® (telavancin for injection) was approved for use in the United States on September 11, 2009 for the treatment of complicated skin and skin structure infections (cSSSI) (NDA 22-110). Approval was supported by two Phase 3 clinical trials of patients with cSSSIs, in which telavancin demonstrated non-inferiority to vancomycin. In pursuit of registering an additional treatment indication for nosocomial pneumonia (NP), two Phase 3 trials (0015 and 0019) enrolled patients who were randomized to receive either telavancin or vancomycin. The NP trials were conducted by the applicant between early 2005 and mid-2007. The prespecified primary efficacy analysis for each of the NP trials was a test of noninferiority for clinical response at the test of cure assessment 7-14 days after the last dose of study drug.

Beginning in 2008, public discussions were held concerning an approach to justification of a non-inferiority margin for NP trials based on 28-day all-cause mortality as the primary endpoint. The Agency did not find it possible to justify a margin for the endpoint of clinical response based on a review of previously conducted NP trials or the historical literature. The Agency issued Draft Guidance, entitled *"Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment"*, on November 29, 2010 recommending 28-day all-cause mortality as the primary endpoint for non-inferiority trials in NP[1]. Concerns were raised in the public docket regarding the Draft Guidance, particularly trial feasibility and comorbid conditions contributing to mortality rather than failure to treat the infection. Issues surrounding development of antibacterial drugs for NP were further discussed at an AIDAC meeting on November 4, 2011.[2]

On January 23, 2009, the Applicant submitted NDA 22-407 seeking approval of telavancin for the indication of NP to the FDA. Upon review, the Agency requested additional mortality data. The Applicant resubmitted their application in June 2010, which included the additional mortality data and additional post-hoc analyses of mortality. While the pre-specified primary endpoint of clinical response 7-14 days after the last dose of study drug was met in both trials, indicating that telavancin was non-inferior to vancomycin on the basis of clinical response in the treatment of NP due to gram-positive pathogens, the Agency stated that both trials did not provide sufficient evidence of non-inferiority compared to vancomycin using a 10% margin for a mortality endpoint in the population of patients with nosocomial pneumonia caused by Gram-positive bacteria. Subsequently, the applicant submitted a Formal Dispute Resolution Request and an Appeal.

While the Dispute Resolution Request and Appeal were denied, Dr. John Jenkins, Director of the Office of New Drugs at the FDA, urged the applicant to resubmit the application, and recommended that an AIDAC meeting be held to discuss the application. Dr. Jenkins noted that the application raises a number of scientific issues. These include:

1. the appropriateness of analyzing mortality as the primary efficacy endpoint to support approval when the trials were not designed for this purpose,

2. the appropriate population for the mortality analysis (e.g., the all-treated population, patients with a Gram-positive pathogen),

3. the appropriateness of combining the two trials for the mortality analysis given the observed differences in some baseline characteristics of patients between the two trials and the heterogeneous result of the analysis of all-cause mortality between the two trials,

4. whether to include or exclude patients with baseline renal failure in the analysis considering the warning in the current telavancin labeling regarding an increased risk of nephrotoxicity and decreased efficacy in patients with moderate to severe baseline renal impairment treated with telavancin for cSSSI, and

5. how to interpret the "lean" toward increased mortality seen with telavancin in some of the mortality analyses (e.g., the all-treated analysis of Study 015).

1. BACKGROUND

1.1. TELAVANCIN PRODUCT INFORMATION

Telavancin is a semisynthetic derivative of vancomycin and a first-in-class lipoglycopeptide antibacterial drug. In vitro, telavancin has been shown to be bactericidal against clinically important Gram-positive bacteria, including *Streptococcus pneumoniae* and *Staphylococcus aureus,* including methicillin-resistant isolates (MRSA). The bactericidal activity appears to result from a dual mechanism that includes inhibition of bacterial cell wall synthesis and disruption of the functional integrity of the bacterial plasma membrane.

In clinical trials, patients with nosocomial pneumonia received 10 mg/kg of telavancin administered over a 60 minute period by intravenous infusion once every 24 hours for 7 to 21 days. Telavancin is eliminated primarily by the kidney. In patients with creatinine clearance (CrCL) <50 mL/min, a dosage adjustment is recommended. Of note, intermittent hemodialysis has not been shown to remove clinically significant quantities of telavancin from plasma. Telavancin is approximately 90% protein bound. Telavancin has been shown to be well-distributed to lung epithelial lining fluid (ELF) and to pulmonary alveolar macrophages. In vitro experiments have demonstrated that the antibacterial activity of telavancin is not affected by the presence of pulmonary surfactant.

1.2. TELEVANCIN CLINICAL DEVELOPMENT AND REGULATORY HISTORY

Telavancin was approved for use in the United States on September 11, 2009 for the treatment of cSSSI (NDA 22-110). In two Phase 3 clinical trials of patients with cSSSIs suspected to be caused by Gram-positive bacterial pathogens, telavancin demonstrated noninferiority to vancomycin. Renal toxicity and potential for QTc prolongation were the most significant safety issues identified. Increases in serum creatinine to 1.5 times baseline occurred more frequently among telavancin-treated patients with normal baseline serum creatinine (15%) compared with vancomycin-treated patients with normal baseline serum creatinine (7%). Also, decreased efficacy with moderate/severe baseline renal impairment was observed. In a subgroup analysis of the pooled cSSSI studies, clinical cure rates in telavancin-treated patients were lower in patients

with baseline CrCL ≤50 mL/min compared to those with CrCL >50 mL/min. The WARNINGS/PRECAUTIONS section (5.4) of the Prescribing Information informs prescribers that efficacy may be reduced in patients with moderate/severe baseline renal impairment (baseline CrCL ≤50 mL/min).[3]

Due to this observation of reduced efficacy in patients with baseline renal impairment, one of the postmarketing commitments (PMC) at the time of the approval for the cSSSI indication was to conduct a prospective study to determine if there may be some effect of renal function on the biological activity of telavancin. In addition, the Applicant was required to prospectively study microbiologic susceptibility to telavancin over the five year period after introduction to the market. A risk evaluation and mitigation strategy (REMS) was also implemented due to the risk of fetal toxicity and the Applicant was required to establish a pregnancy registry to collect data on fetal outcomes in women exposed to telavancin during pregnancy.

In pursuit of the indication for the treatment of NP, the Applicant conducted two Phase 3 clinical trials (0015 and 0019) of non-inferiority design. These trials compared the safety and efficacy of telavancin and vancomycin in the treatment of adult patients with both hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). The design of these trials, which were intended to enrich the population with patients who had NP due to Gram-positive pathogens, was originally based on the 1998 FDA *Guidance for Industry: Nosocomial Pneumonia—Developing Antimicrobial Drugs for Treatment* and *Developing Antimicrobial Drugs—General Considerations for Clinical Trials,* now revised and replaced by the November 29, 2010 Draft Guidance discussed above.

Prior to closure of the clinical database, the final Statistical Analysis Plan for Studies 0015 and 0019 was submitted to the FDA in November 2007. On July 16, 2008, at a meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) to discuss doripenem,[4] the FDA presented an approach to justification of a non-inferiority margin for the indication of NP (including ventilator-associated pneumonia) based on 28-day all-cause mortality as the primary endpoint as the Agency had not been able to justify a margin for the endpoint of clinical response based on the historical literature. The two telavancin trials (Studies 0015 and 0019), however, were designed based on a 20% non-inferiority margin for a clinical response efficacy endpoint.

On January 23, 2009, the Applicant submitted NDA 22-407 for the treatment of NP to the FDA. Upon review, the Division conducted a post-hoc analysis of 28-day all-cause mortality and also found that the study populations differed substantially between the two trials with respect to the frequencies of various baseline characteristics and comorbid conditions that could have potentially affected the risk for mortality. In the course of the review, the Division concluded that it would be problematic to pool the data from the two trials. In addition, there were missing mortality outcomes for a number of patients. Since there were inadequate data to reach a conclusion regarding the efficacy of the drug, the Division requested that the Applicant submit additional mortality data. Additionally, the Division noted that criteria utilized for inclusion in the trials were not consistent with recommendations of the 1998 FDA Draft Guidance for Industry: "Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment" nor the recommendations in the ATS/IDSA Guidelines for the Management of Hospital-Acquired Pneumonia[5].

Consequently, the Division did not approve the application for the treatment of NP and made a number of recommendations to the applicant concerning further analyses of the ATTAIN trials:

1) Obtain and analyze all available mortality data.

2) Provide a rationale for pooling across the two clinical trials, specifically regarding consistency of the treatment difference for telavancin relative to vancomycin across the trials (given the difference in distribution of baseline prognostic factors for mortality between the two trials and the proportion of subjects whose mortality status is censored).

3) Determine if patients enrolled in the trials met the ATS/IDSA criteria for nosocomial pneumonia − "chest x-ray plus two clinical features" (CXR+2F) – and conduct a sensitivity analysis.

The second cycle resubmission, submitted June 30, 2010, incorporated the missing mortality data and the additional analyses of mortality. Included were analyses for two populations: the primary analysis population (the full, As-Randomized [AT, or As-Treated] population), and a supportive analysis population (CXR+2F). In addition, microbiological subsets of interest were also evaluated in the mortality analysis. These included the original modified all-treated (MAT) subset (patients with any baseline pathogen), the subset with any Gram-positive baseline pathogen (including patients with both Gram-positive and Gram-negative baseline pathogens), and the subset with only Gram-positive baseline pathogens.

On December 21, 2010, the Division concluded that it could not approve the NDA based on the data submitted. In the Division's determination, despite the recovery of a substantial amount of missing mortality data, Study 0015 failed to demonstrate noninferiority of telavancin compared to vancomycin when assessing 28-day all-cause mortality using a 10% NI margin in the population of patients with a Gram-positive pathogen. As with the first-cycle submission, considering that subjects in Study 0015 were more likely than subjects in Study 0019 to have certain potential risk factors for mortality (e.g. diabetes mellitus and renal impairment); therefore, the Division did not believe that it would be appropriate to pool patients across the two trials. The Division also recommended that in further analyses, renal function status should be specifically defined by standardized measures, such as creatinine clearance.

The Applicant submitted a Formal Dispute Resolution Request to the Office of Antimicrobial Products (OAP) on August 24, 2011. The request was denied by Edward Cox, MD, MPH, Director, OAP. On October 14, 2011, the Applicant subsequently submitted an Appeal to the Office of New Drugs (OND) and maintained that Studies 0015 and 0019 demonstrated that telavancin is noninferior to vancomycin based on the prespecified endpoint, clinical cure, and thereby met the statutory standard for approval for the new indication (treatment of NP). Additionally, the Applicant argued that since the Agency had not finalized its Draft Guidance to Industry regarding appropriate endpoints and statistical analysis plan, it is inappropriate to impose a requirement to demonstrate efficacy based on a different endpoint, 28-day all-cause mortality, when the Phase 3 trials were agreed to by the Agency before the trials were conducted. Although the Director of OND, John Jenkins, MD, denied this appeal, his recommendation to the Applicant was to resubmit the application for further review, with guidance from the Division for additional analyses, and discussion at an AIDAC meeting (see Response to Formal Dispute

Resolution Appeal letter at Appendix 7.2). After meeting with OND, OAP, and the Division, the Applicant agreed to proceed with a resubmission with public discussion at a meeting of the AIDAC, and subsequently submitted a complete response to the NDA on July 11, 2012.

In September 2011, following the Committee for Human Medicinal Products (CHMP) favorable opinion in May 2011, the European Commission granted marketing authorization for Vibativ (telavancin for injection) for the treatment of adults with NP, including VAP, known or suspected to be caused by MRSA when other alternatives are not suitable.[6]

2. NOSOCOMIAL PNEUMONIA DRAFT FDA GUIDANCE

At present, linezolid, levofloxacin, ciprofloxacin, and piperacillin/tazobactam are approved by the FDA for the treatment of NP. Vancomycin is commonly used for serious Gram-positive infections, but gradual increases in minimum inhibitory concentration (MIC) values for MRSA have been documented in many regions of the United States.[7]

In pursuit of new strategies to determine an optimal clinical endpoint and develop new clinical trial designs, the FDA has initiated several collaborative efforts to address clinical trial design and the development of antibacterial drugs NP. At a workshop co-sponsored by the FDA, Infectious Diseases Society of America (IDSA), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and Society of Critical Care Medicine (SCCM) on March 31 and April 1, 2009,[8] the goal of the workshop was to develop trial designs that could not only produce robust evidence for efficacy and safety in the treatment of NP, but also could be conducted feasibly and efficiently. Although consensus was reached on the clinical syndromes and analysis populations for enrollment, there remained controversy regarding several areas of trial design. Among the major issues discussed, the all-cause mortality endpoint raised a number of concerns, such as the appropriateness of treatment effect extrapolated from historical studies and the frequency of non-respiratory events contributing to mortality. The workshop also discussed non-mortality endpoints, such as days in the intensive care unit, days on the ventilator, P_aO_2/FiO_2 ratio; however, critics of this approach emphasized that there could be a lack of consistency in these evaluations due to the uncertainty of consistent treatment effect upon these variables.

The Agency issued its Draft Guidance, *"Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment",* on November 29, 2010.[9] The Guidance included recommendations for a study population enriched by patients meeting clinical, radiographic and microbiologic criteria specific for NP and an estimated mortality rate of approximately 20%. The 2010 Draft Guidance recommended 28-day all-cause mortality as the primary efficacy endpoint, utilizing an active control in a non-inferiority (NI) trial. Establishing an M_1 of 20%, with a justification for an NI margin of 10%, the estimated sample size per arm would be approximately 481 per arm. The microbiologic intent-to-treat (micro-ITT) population was recommended as the primary analysis population, assuming an evaluable proportion of about 70%. Historical data were limited, however, for the justification of a margin based on clinical signs and symptoms.

The issues surrounding development of antibacterials for NP were also discussed at an AIDAC meeting on November 4, 2011.[10] Comments submitted to the docket in response to the issuance of the Draft Guidance were discussed. There were several areas of criticism: In general, it was felt that the Guidance was not practical. Concern was reiterated regarding the use of mortality as the primary efficacy endpoint, specifically that advances in ICU care, which have reduced mortality to less than 20%, could also reduce the observable treatment effect of the study drug. There were concerns raised that the recommendation for the micro-ITT analysis would render the requisite trial population too large to be feasible. Additionally there were also concerns regarding the uncertainty of the timing of 28-day all-cause mortality and that this endpoint may fail to capture earlier differences in treatment effect that are subsequently washed out by mortality associated with comorbid conditions. The advantages and limitations of some alternative statistical approaches were discussed, such as less discounting to arrive at the M_1 or treatment effect. Providing that a margin of 12.5% could be supportable, this would reduce the estimated sample size per arm to approximately 320. A proposal for an NI margin of 1.7 using an odds ratio metric was also discussed. The Committee found the odds ratio to be an innovative idea, as it addresses the issue of variability in mortality rates.

As the Agency continues to evaluate the comments from the public and AIDAC in an effort to finalize the Guidance, there are still several issues that are surrounded by a degree of uncertainty, such as acceptable levels of missingness or censored observations, the ideal primary analysis set, and the utility of additional exploratory analyses such as Kaplan-Meier survival analysis and regression methods using a specified hazard ratio (given the availability of historical evidence to support the ratio and the issues raised with the use of post-hoc selection of covariates).

3. MICROBIOLOGY

3.1. MECHANISM OF ACTION

Studies presented by the Applicant in NDA 22-110 and NDA 22-407 generally support the claim for two distinct mechanisms of action for telavancin against Gram-positive bacteria. Like members of the glycopeptide class, telavancin appears to inhibit peptidoglycan synthesis. Studies support the contention that telavancin also acts to depolarize the microbial cell membrane through association with Lipid II, possibly adding to the antimicrobial effect of the drug.

3.2. IN VITRO ANTIBACTERIAL ACTIVITY

In the NDA 22-110 submission, the Applicant provided summary data from two large prospective studies and 17 other investigations of the in vitro activity of telavancin against a variety of Gram-positive pathogens. NDA 22-407 included summary data from five additional surveillance studies (approximately 16,000 Gram-positive isolates). Against *S. aureus* isolates (including those identified as MRSA), the MIC_{90} values ranged from 0.25 mcg/mL to 0.5 mcg/mL. Against *S. pneumoniae* isolates, the overall MIC_{90} was approximately 0.03 mcg/mL.

In the clinical trials conducted to evaluate telavancin for the treatment of NP (Studies 0015 and 0019), there were 647 isolates of *S. aureus* collected (global, modified all-treated [MAT] population) from respiratory specimens, including 315 described as MRSA. Against all *S. aureus* isolates (including MRSA), the MIC_{90} was 0.5 mcg/mL. The highest MIC noted for any *S. aureus* isolate was 1 mcg/mL. In the two pivotal trials, there were 52 isolates of *S. pneumoniae* collected from respiratory specimens (global, MAT population). The MIC_{90} for these isolates was 0.03 mcg/mL (with only two isolates recovered with MIC values at 0.06 mcg/mL, the highest value noted in the studies). The activities of telavancin and vancomycin against these (and other) isolates are summarized in Table 1.

Microbial eradication rates in the microbiologically evaluable (ME) population were comparable in the telavancin-treated subjects and vancomycin subjects (Table 2). The majority of subjects had a single Gram-positive respiratory pathogen isolated (164 in the telavancin arm, 165 in the vancomycin arm), and in this group, microbial eradication was higher in the telavancin treated subjects (82.9% for the telavancin-treated subjects and 75.8% for the vancomycin-treated subjects, in the pooled data, ME population). This difference was also observed in the individual studies.

Table 1: Susceptibility of Gram-Positive Pathogens Isolated from Baseline Respiratory in Studies 0015 and 0019 to Telavancin and Vancomycin – MAT Population (global)

	Minimum Inhibitory Concentration (µg/mL)							
	Telavancin				Vancomycin			
	N	MIC_{50}	MIC_{90}	Range	N	MIC_{50}	MIC_{90}	Range
Organisms From Telavancin-treated Patients								
STAPHYLOCOCCUS AUREUS	335	0.25	0.5	0.12 - 1	335	1	1	≤ 0.25 - 2
- MRSA	203	0.5	0.5	0.12 - 1	203	1	1	≤ 0.25 - 2
- MSSA	132	0.25	0.5	0.12 - 1	132	1	1	≤ 0.25 - 2
ENTEROCOCCUS FAECALIS	13	0.5	1	0.25 - 2	13	1	2	≤ 0.5 - 2
ENTEROCOCCUS FAECIUM	4	0.25	-	0.12 - 0.25	4	0.5	-	≤ 0.5 - ≤ 0.5
STREPTOCOCCUS PNEUMONIAE	24	0.015	0.03	0.008 - 0.03	24	0.25	0.5	0.12 - 0.5
Organisms from Vancomycin-treated Patients								
STAPHYLOCOCCUS AUREUS	312	0.25	0.5	0.06 - 1	312	1	1	≤ 0.25 - 2
- MRSA	204	0.5	0.5	0.06 - 1	204	1	1	≤ 0.25 - 2
- MSSA	108	0.25	0.5	0.12 - 0.5	108	1	1	≤ 0.25 - 2
ENTEROCOCCUS FAECALIS	19	1	1	0.25 - 1	19	1	1	≤ 0.5 - 2
ENTEROCOCCUS FAECIUM	1	8	-	8 - 8	1	256	-	256 - 256
STREPTOCOCCUS PNEUMONIAE	27	0.015	0.03	0.008 - 0.06	27	0.25	0.5	0.25 - 0.5

Source: NDA 22-407, Microbiology Report, v1.0, Section 5.3.5.4.1.10.3, Table 24

Table 2: **By-pathogen Microbiological Eradication Rates at Test-of-cure – ME Population, Studies 0015 and 0019; Gram-positive Pathogens at Baseline**

	0015		0019		Total	
	Telavancin 10 mg/kg (N=108)	Vancomycin (N=113)	Telavancin 10 mg/kg (N=135)	Vancomycin (N=124)	Telavancin 10 mg/kg (N=243)	Vancomycin (N=237)
Gram-positive Pathogens at Baseline						
STAPHYLOCOCCUS AUREUS	79 / 98 (80.6%)	81 / 109 (74.3%)	91 / 121 (75.2%)	80 / 105 (76.2%)	170 / 219 (77.6%)	161 / 214 (75.2%)
- MRSA	56 / 70 (80.0%)	63 / 84 (75.0%)	47 / 69 (68.1%)	52 / 70 (74.3%)	103 / 139 (74.1%)	115 / 154 (74.7%)
- MSSA	26 / 32 (81.3%)	18 / 25 (72.0%)	44 / 52 (84.6%)	29 / 37 (78.4%)	70 / 84 (83.3%)	47 / 62 (75.8%)
STREPTOCOCCUS PNEUMONIAE	9 / 10 (90.0%)	3 / 4 (75.0%)	10 / 10 (100.0%)	15 / 17 (88.2%)	19 / 20 (95.0%)	18 / 21 (85.7%)
ENTEROCOCCUS FAECALIS	1 / 1 (100.0%)	2 / 3 (66.7%)	4 / 7 (57.1%)	8 / 8 (100.0%)	5 / 8 (62.5%)	10 / 11 (90.9%)
ENTEROCOCCUS FAECIUM	0 / 1 (0.0%)		2 / 2 (100.0%)		2 / 3 (66.7%)	

Source: NDA 22-407, Microbiology Report, v1.0, Section 5.3.5.4.1.10.3, Table 26

Data from more recent surveillance studies support the in vitro activity of telavancin noted in earlier studies and in clinical trials. In a study published in 2010, Pfaller and colleagues reported the results of in vitro antimicrobial testing (MIC method) against a large collection of Gram-positive isolates.11 The results are summarized in the following table (Table 3).

Table 3: Antimicrobial activity of telavancin and comparator antimicrobial agents against 2279 isolates of Gram-positive cocci from patients with nosocomial pneumonia, 2007-08

Organism	Antimicrobial	MIC (mcg/mL)		
		Range	50%	90%
Staphylococcus aureus (1756)				
	telavancin	0.3-0.5	0.12	0.25
	vancomycin	≤ 0.12-2	1	1
	daptomycin	≤ 0.06-1	0.25	0.5
	linezolid	0.25-8	1	2
S. aureus (oxacillin-susceptible) (966)				
	telavancin	0.03-0.5	0.12	0.25
	vancomycin	≤ 0.12-2	1	1
	daptomycin	≤ 0.06-1	0.25	0.5
	linezolid	0.5-4	2	2
S. aureus (oxacillin-resistant) (790)				
	telavancin	0.03-0.5	0.12	0.25
	vancomycin	0.25-2	1	1
	daptomycin	0.12-1	0.25	0.5
	linezolid	0.25-8	1	2
Streptococcus pneumoniae (314)				
	telavancin	≤ 0.015-0.06	≤ 0.015	0.03
	penicillin[a]	≤ 0.015-16	0.03	4
	penicillin[b]	≤ 0.015-16	0.03	4
	vancomycin	≤ 0.12-0.5	0.5	0.5
	linezolid	0.25-2	1	1
S. pneumoniae, penicillin-susceptible (166)				
	telavancin	≤ 0.015-0.06	≤ 0.015	0.03
	penicillin[a]	≤ 0.015-0.06	≤ 0.015	0.03
	penicillin[b]	≤ 0.015-0.06	≤ 0.015	0.03
	vancomycin	≤ 0.12-0.5	0.25	0.5
	linezolid	0.25-2	1	1
S. pneumoniae, penicillin-intermediate (40)				
	telavancin	≤ 0.015-0.03	≤ 0.015	0.03
	penicillin[a]	≤ 0.12-1	0.25	1
	penicillin[b]	≤ 0.12-1	0.25	1
	vancomycin	0.25-0.5	0.25	0.5
	linezolid	0.25-2	1	1
S. pneumoniae, penicillin-resistant (108)				
	telavancin	≤ 0.015-0.06	≤ 0.015	0.03
	penicillin[a]	2-16	2	4
	penicillin[b]	2-16	2	4
	vancomycin	≤ 0.12-0.5	0.5	0.5
	linezolid	0.25-2	1	1

[a]Criteria as published by CLSI for "penicillin parenteral (non-meningitis)"
[b]Criteria as published by CLSI for "penicillin (oral penicillin V)"
Source: Reference 11

3.3. RESISTANCE

The Applicant provided sufficient data to demonstrate a low potential for development of resistance to bacterial species considered in the proposed indications. Data presented in NDA 22-407 suggested that telavancin is an inducer of the VanA operon, but does not induce activity of the VanB operon. Population analysis profiles did not detect heteroresistance to telavancin in isolates of *S. aureus*. No resistance to telavancin was noted in isolates collected in clinical trials. Antimicrobial resistance in isolates of *S. aureus* or *S. pneumoniae* has not been detected in the large surveillance studies that have been reviewed by the Agency since the NDA submission.

4. EVALUATION OF EFFICACY

4.1. OVERVIEW OF STUDIES 0015 AND 0019

Based on the 1998 FDA guidance document, Studies 0015 and 0019 were each originally designed as active-controlled, non-inferiority trials. The primary efficacy endpoint was clinical response, determined by the investigator, at the test of cure (TOC) evaluation. The non-inferiority margin (telavancin – vancomycin) was prospectively set at 20%. In addition, the data from the two trials were prospectively intended to be combined to assess the superiority of telavancin to vancomycin in patients with MRSA infections (in the all-treated population).

Following the initial review of the application, the Applicant prepared a post-hoc plan for the analysis of all-cause mortality, relying on FDA recommendations with respect to the choice of analysis population(s), selection of appropriate time points, accounting for censored data, and choice of the appropriate metric for comparing treatments. The Applicant was able to query the clinical research sites to retrieve available survival data through Study Day 49 for each patient.

Various sensitivity analyses were also applied to the primary and secondary endpoints to evaluate consistency of results and support the conclusions to be drawn. These sensitivity analyses included the assessment of the impact of concomitant potentially effective antibacterial therapy, exclusion of patients whose baseline respiratory samples did not meet specified reliability criteria, exclusion of patients who did not have confirmatory radiologic evidence of pneumonia, and exclusion of patients who did not receive adequate Gram-negative coverage.

4.1.1. Study Objectives

The prespecified 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 on patients with infections due to MRSA". A key secondary objective was "to pool the data from both trials to assess the superiority of telavancin to vancomycin in patients with MRSA infections."[12]

The post-hoc primary objective was "to demonstrate the non-inferiority of telavancin to vancomycin in the treatment of HAP, with respect to all-cause mortality, for subjects with nosocomial pneumonia by ATS/IDSA criteria".[12]

Post-hoc secondary efficacy objectives included:

- Demonstrate the noninferiority of telavancin to vancomycin in the treatment of HAP, with respect to clinical response at TOC.
- Evaluate telavancin all-cause mortality rates compared to vancomycin all-cause mortality rates in defined subgroups.

4.1.2. Study Design

The two trials (0015 and 0019) had identical protocols; both were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram-positive isolates 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 for suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. Patients could receive concomitant aztreonam and/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.

The study entry criteria were selected to enroll patients who had clinical and radiographic evidence of NP. Since the trials were not designed to evaluate all-cause mortality at a specified timepoint, they did not control for factors that may have resulted in unrelated, inevitable death, such as decisions to limit medical care (e.g., "Do Not Resuscitate" [DNR] or "Comfort Care Only"), baseline differences in acuity of illness, or the presence of comorbidities. The only exclusion criteria that limited the severity of illness were related to probability of imminent death, such as refractory shock, profound neutropenia, or likelihood of ventricular arrhythmia due to QT prolongation.

4.1.3. Major Inclusion Criteria

To be eligible for inclusion in these studies, patients were required to meet all of the following criteria:

- Males and females ≥18 years of age
- 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/mm3, > 15% immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count < 4500 cells/mm^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
- Availability of appropriate respiratory or sputum specimens for Gram stain and culture, and venous access for IV dosing

4.1.4. Major Exclusion Criteria

Patients were to be excluded from these studies if they met any of the following criteria:

- Received more than 24 hours of potentially effective systemic (IV/IM or PO) antibacterial 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, investigators were to contact the Study Physician Helpline to determine eligibility.
- Respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture
- 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)
- 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
- Known or suspected *Legionella pneumophila* pneumonia
- Known or suspected infection with an organism that is not susceptible to medications permitted by the protocol.
- Documented or suspected meningitis, endocarditis, or osteomyelitis
- 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)
- Baseline QTc > 500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K^+ or Mg^{++} blood levels that cannot be corrected
- Severely neutropenic (absolute neutrophil count < 500/mm^3) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or have HIV with CD4 count < 100/mm^3 during the last 6 months
- Requirement for concomitant administration of intravenous Sporanox® (itraconazole), Vfend® (voriconazole), Geodon® (ziprasidone), or any other medication containing a cyclodextrin solubilizer

4.1.5. Study Procedures

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 (GCS); chest x-ray (CXR) or computed tomography scan (CT scan) for evaluation of radiographic lung infiltrates; oxygen status as measured by arterial blood gas was strongly encouraged, but required for patients who were ventilated and/or had 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). The components of the Acute Physiology and Chronic Health Evaluation (APACHE II) were also collected.

4.1.5.1. Antibacterial Drug Dosage Regimens

The vancomycin regimen was to be monitored, and dosage adjusted on the basis of weight and/or renal function, following the institutional policy at each investigative site, by personnel who were not blinded to study treatment. In a similar manner, the dosage of telavancin was to be adjusted in patients with moderate to severe renal insufficiency as follows:

Table 4: Dosage Adjustments for Telavancin in Patients with Renal Insufficiency

Creatinine Clearance (mL/min)*	Telavancin Dosage
30-50	7.5 mg/kg q 24hr
<30	10 mg/kg q 48hr
Hemodialysis	10 mg/kg q 48hr (supplemental telavancin not required following dialysis)

* Use the Cockcroft-Gault equation to estimate creatinine clearance:

$$\text{CrCL (mL/min)} = \frac{(140 - \text{age}) \times \text{ideal body weight (IBW)}}{\text{Serum creatinine} \times 72}$$

For females, multiply the result by 0.85.
Use actual body weight if <IBW
IBW (male) = 50kg + 0.9 kg/cm over 152 cm height
IBW (female) = 45.5kg + 0.9 kg/cm over 152 cm height

Source: NDA 22-407, ISE v2.0, section 4.2.1

4.1.5.2. Concomitant Antibacterial Therapy and Adequacy of Gram-Negative Coverage

As previously noted, concomitant Gram-negative coverage was left to investigators' discretion. Aztreonam was to be used for empiric and specific Gram-negative coverage whenever possible, but piperacillin-tazobactam was permitted if resistance to aztreonam was suspected or documented. Given that piperacillin-tazobactam has activity against many Gram-positive pathogens (except MRSA), patients infected with organisms other than MRSA and requiring more than a brief duration (24 to 48 hours) of piperacillin-tazobactam (or other Gram-negative agents) were not to be enrolled. Empiric coverage with these agents was to be discontinued as soon as feasible if organisms other than MRSA were recovered. Medical monitors blinded to treatment assignment identified those patients who had received potentially effective antibacterial therapy (PEA) on the basis of *in vitro* susceptibility data for the baseline

pathogens, or known susceptibility/resistance patterns for the organisms and antibacterial drugs being reviewed, if specific *in vitro* data were not available. Sensitivity analyses were conducted to assess the impact on clinical response and mortality of excluding patients who received more than a brief duration (i.e., >2 calendar days) of antibacterial drugs potentially effective against their Gram-positive baseline pathogen(s) and also with the exclusion of patients who did not receive adequate Gram-negative coverage.

4.1.5.3. Clinical Response

Upon a patient's termination of study medication (i.e., at the end-of-therapy [EOT] Visit), the investigator was to assess the patient's clinical response at EOT as cure, failure, or indeterminate as defined below:

- Failure:

At least one of the following:

  - Persistence or progression of signs and symptoms of pneumonia that still require antibiotic therapy
  - Termination of study medication due to "lack of efficacy" and initiation within 2 calendar days of therapy with a potentially effective anti-staphylococcal medication
  - Death on or after Day 3 attributable to primary infection (as judged by the investigator)

- Cure: Signs and symptoms of pneumonia improved to the point that no further antibacterial drugs for pneumonia were required, and baseline radiographic findings improved or did not progress
- Indeterminate: Inability to determine outcome (for example, Gram-positive antibacterial coverage no longer required but Gram-negative antibacterial coverage continuing at EOT)

All patients were to have an 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 was strongly encouraged, but was required for patients who were ventilated and/or had 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.

4.1.5.4. Statistical Methods

Four analysis groups were prospectively defined for efficacy-related summaries. These four groups were not mutually exclusive; a subject could belong to more than one group. In all four populations, subjects were analyzed according to the treatment to which they were randomized:

- All-treated (AT): All subjects who received any amount of study medication.
- Modified All-treated (MAT): Subjects in the AT Population who also had a baseline pathogen identified, defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, endotracheal aspirate, blind bronchial suction, bronchoalveolar lavage, mini–bronchoalveolar lavage, or protected specimen brush.
- Clinically Evaluable (CE): Subjects in the AT Population whose adherence to protocol made it reasonable to infer that his/her clinical outcome reflected the effect of study medication.
- Microbiologically Evaluable (ME): Subjects in the CE Population who also had a Gram-positive baseline respiratory pathogen, as defined above for the MAT Population.

The pre-specified analyses were to test both noninferiority and superiority of telavancin to vancomycin with respect to clinical response at the Test of Cure assessment. For the original noninferiority analysis, both the AT and CE analysis populations were considered co-primary. For the superiority analysis, the AT population served as the primary population. Secondary efficacy variables included by-subject and by-pathogen microbiological response at TOC, clinical response at end of treatment (EOT), by-subject and by-pathogen microbiological response at EOT, and all-cause mortality.

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

4.2. DIAGNOSIS OF PNEUMONIA

4.2.1. Clinical Features

The inclusion criteria selected for Studies 0015 and 0019 were initially proposed to be consistent with available FDA guidance (Draft Guidance for Industry, "Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment," published in 1998). In 2005, after the initiation of the telavancin NP studies, the ATS/IDSA Guidelines for the diagnosis and management of NP was published.[5] The ATS/IDSA criteria include 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). The Agency and the Applicant discussed conducting a re-analyses in order to achieve a more accurate combination of clinical findings for

starting empiric antibacterial therapy. Applying these criteria to the patients enrolled in Studies 0015 and 0019 results in a population (AT-ATS/IDSA) that accounts for 85.8% of the enrolled patients (AT).

4.2.2. Baseline Chest Radiography

To avoid delay in initiating treatment in Studies 0015 and 0019, given the urgency to commence antibacterial therapy early in this critically ill population, the chest radiographs were to be interpreted by the investigator or a site radiologist. The study protocols required a chest radiograph (or CT scan) with findings consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion) within 48 hours before randomization in the study. The protocols did not require that the chest radiographs (or CT scans) be read by an independent radiologist. FDA medical reviewers requested that the chest radiograph reports be included in the case report form (CRF) for submission to the NDA. Radiology reports (site radiologist interpretations) or, if not available, the other source documents for radiological findings were collected from the study sites. Although the chest radiograph data had been routinely monitored during the conduct of the study, a decision was made to verify the concordance between these CRF data and the radiology reports or other source documents. The radiology reports or other source documents and CRF data were submitted to an independent radiology core laboratory for a treatment-blinded review. The radiology report or other source document was assessed and then compared with data from the chest radiograph CRF (Pulmonary Radiography Log) for each patient. Each radiology report or other source document was assessed as either consistent with the CRF data, not consistent with the CRF data, or providing insufficient information to make possible a determination. A sensitivity analysis was performed, which included only patients with adjudicated data for the diagnosis of pneumonia, to determine the consistency in diagnosis of pneumonia between the CRF and the site radiologist reports. The CRF data were used to define the ATS/IDSA population.

4.2.3. Respiratory Specimens

A baseline pathogen was defined as an organism known to cause pneumonia identified from the baseline respiratory cultures from sputum, endotracheal aspirate (ETA), blind bronchial suctioning (BBS), bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB). A sputum or endotracheal suction sample was considered adequate if it had >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per field at 100× magnification (low-power, 10× objective). If baseline respiratory cultures did not identify a respiratory pathogen (or if baseline respiratory cultures were not available), then an organism known to cause pneumonia that was identified from baseline blood cultures was considered a baseline pathogen. Reliability criteria shown in Tables 5 and 6 below are adapted from Tables 4 and 5, section 2.5.4.2.1, in the Applicant's Clinical Overview.

Table 5: Reliability Criteria for Respiratory Samples

Collection Method*	Reliability Criteria
Sputum	Sputum Method 1: White blood cell (WBC) count >25/LPF and squamous epithelial cells (SEC) <10/LPF Sputum Method 2: Squamous epithelial cells (SEC) <10/LPF
Endotracheal aspirate (ETA)	Squamous epithelial cells (SEC) <10/LPF
Invasive Procedure**	All invasive procedures deemed reliable, by definition

*The reliability of collection methods is ordered with least reliable method (sputum) first.
**Blind bronchial suctioning (BBS), bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB) LPF, low-power field
Source: NDA 22-407, ISE v2.0, section 5.1.4.1

Table 6: Respiratory Sample Reliability Levels

Respiratory Sample Reliability	Reliability Criteria
Level I	Reliable sputum Method 1 or Method 2, plus Reliable ETA, plus All invasive procedures
Level II	Reliable ETA, plus All invasive procedures
Level III	All invasive procedures

Source: NDA 22-407, ISE v2.0, section 5.1.4.1

4.3. COMPARISON BETWEEN STUDIES 0015 AND 0019: DEMOGRAPHICS, BASELINE CHARACTERISTICS AND APPROPRIATENESS OF POOLING

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, the presence or absence of diabetes, and ventilatory status of the patient.

The disposition of patients is shown in Table 7. In Study 0015, there was a trend that more telavancin patients (175/381, or 45.9%) compared to vancomycin patients (150/380, or 39.5%) prematurely discontinued study medication (difference = 6.5%; 95% CI = [-0.5%, 13.5%], p-value = 0.07). Of note, 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 was 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 7: 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 but 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: NDA 22-407, 2.7.3, Summary of Clinical Efficacy, v1.0, Tables 14 and 15 (original application)
* Two patients in Study 0019 were randomized to the vancomycin group by received telavancin instead.

In this briefing document, results presented are based on FDA-defined populations, shown in Table 8. These include the all-treated (AT) population, microbiological all-treated (MAT) population where at least one Gram-positive pathogen was isolated at baseline, and the MAT population where MRSA was isolated at baseline. The MAT including those with a Gram-positive pathogen isolated at baseline was chosen because the test and comparator drugs only have activity against Gram-positive pathogens.

Table 8: Analysis Populations

	Study 0015		Study 0019	
Population	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)
MAT – at least 1 gram+ pathogen	187 (50)	180 (48)	224 (59)	206 (54)
MRSA	115 (31)	114 (30)	118 (31)	117 (31)
CE	141 (38)	172 (46)	171 (45)	170 (45)

Source: NDA 22-407, 2.7.3, Summary of Clinical Efficacy, v3.0, Table 44
MAT based on both respiratory and blood specimens but predominately respiratory

Table 9 shows the baseline demographic information for patients randomized and treated in Study 0015 and Study 0019. In each study the treatment groups were balanced with respect to

most of the demographic factors. However, there were fewer patients from US sites in Study 0019 (14%) than for Study 0015 (31%). In addition, patients in Study 0015 had increased rates of renal impairment, renal failure, congestive heart failure and diabetes than patients in Study 0019.

Table 9: 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

Table 9 continued on following page

Table 9 (continued): Baseline Demographics (AT Population)

	Study 0015		Study 0019	
	TLV (N=372)	VANC (N=374)	TLV (N=377)	VANC (N=380)
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)
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				
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)
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: NDA 22-407, ISE, Table 5-11; CSR, Supporting Tables 31, 33, and 34 (original application), SCE Table 45 (current submission)

The distribution of the baseline Gram-positive respiratory pathogens in the MAT population is provided in Table 10.

Table 10: Baseline Gram-Positive Respiratory Pathogens (Micro AT Population)

Population	Study 0015		Study 0019	
	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: NDA 22-407, SCE, Table 53 (current submission)

The dosing for comparator and study drug was designed for 7-21 days in duration for both trials. As can be seen in Table 11, most patients (42%-44%) received 7-10 days of treatment.

Table 11: Days of Study Medication (AT population)

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

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

4.4. PRE-SPECIFIED PRIMARY ANALYSIS: CLINICAL CURE

The prespecified primary analysis was to evaluate noninferiority based on the difference between the telavancin and vancomycin groups for the investigator's assessment of clinical response rates at the TOC visit using an NI margin of 20%. If noninferiority was demonstrated, then the superiority of telavancin to vancomycin for clinical response at the TOC assessment would be evaluated. For the noninferiority analysis, both the AT and CE analysis populations were

considered co-primary. For the superiority analysis, the AT population served as the primary population. Clinical cure assessments are summarized in the following table (Table 12).

Table 12: Clinical Cure at Test of Cure – CE & AT-ATS/IDSA Analysis Sets, Studies 0015 and 0019

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% (-6.8, 7.2)
All-Treated — ATS/IDSA	182/309 (58.9)	184/316 (58.2)	0.7 (-7.1, 8.4)	194/325 (59.7)	202/339 (59.6)	0.1 (-7.4, 7.6)
MAT – Gram$^+$	108/187 (57.8)	106/180 (58.9)	-1.1 (-11.2, 8.9)	131/224 (58.5)	124/206 (60.2)	-1.8 (-11.0, 7.6)
MRSA	68/115 (59.1)	66/114 (57.9)	1.2 (-11.5, 14.0)	59/118 (50.0)	63/117 (53.8)	-3.8 (-16.6, 8.9)
CE	118/141 (83.7)	138/172 (80.2)	3.5 (-5.1 , 12.0)	139/171 (81.3)	138/170 (81.2)	0.1 (-8.2 , 8.4)

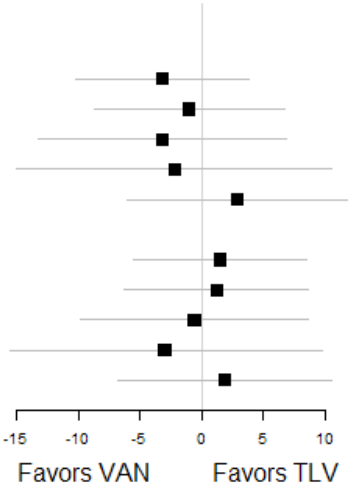
Source: NDA 22-407, Summary of Clinical Efficacy, v3.0, Table 57

The interpretation of the results based on clinical response as given in Table 12 is limited as we have not been able to justify a noninferiority margin for the endpoint of clinical response based on the historical literature. In addition, there are concerns regarding potential inconsistencies with clinical response, where cure is defined as signs and symptoms of pneumonia improved to the point that no further antibacterial therapy for pneumonia were required, and baseline radiographic findings improved or did not progress. The main concern relates to how well-defined and reliable this endpoint is in evaluating patient benefit due to the large number of patients who were considered clinical cures at the TOC assessment but subsequently died by Day 28.

Assay sensitivity is critical to support the conclusions of an adequate and well-controlled trial. Due to concern regarding potential inconsistencies and how well-defined and reliable the clinical response endpoint is in evaluating patient benefit, the Agency identified patients who were considered clinical cures at the TOC assessment but subsequently died by Day 28. There were 16 such patients in Study 0015 and 17 in Study 0019. Although these TOC assessments of "failure" by the investigator were meant to be assigned if subsequent death was attributable to primary infection (see Section 7.1.1 for details on each of these patients), many of the deaths in the assigned as "cure" group occurred in close temporal proximity to the TOC assessment (Mean: Study 0015 = 3.7 days [3.1]; Study 0019 = 4.9 days [3.7]) and many of the deaths could not be ruled out as infection-related. Deaths within the 28-day window were considered clinical failures for the following analyses (summarized in Figure 1).

Figure 1: Clinical Response at TOC with Deaths Considered Failures

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



Source: FDA Reviewer, 95% CI calculated based on Agresti-Caffo method
MAT based on both respiratory and blood cultures but predominately respiratory

4.5. POST-HOC AND SECONDARY ANALYSES:

4.5.1. 28-Day All-Cause Mortality

In the original NDA, there were incomplete survival data 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 queried clinical research sites to collect available data and updated survival status. In the current resubmission, the percentage of patients with incomplete survival data for the 28-day period substantially decreased (Study 0015: 6%; Study 0019: 5%).

The distribution of the last day that patients were known to be alive for patients whose 28-day survival status is unknown is shown in the following table (Table 13).

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

Source: FDA Reviewer

Updated vital status data is shown in Table 14. Patients with missing data at Day 28 were designated as censored observations.

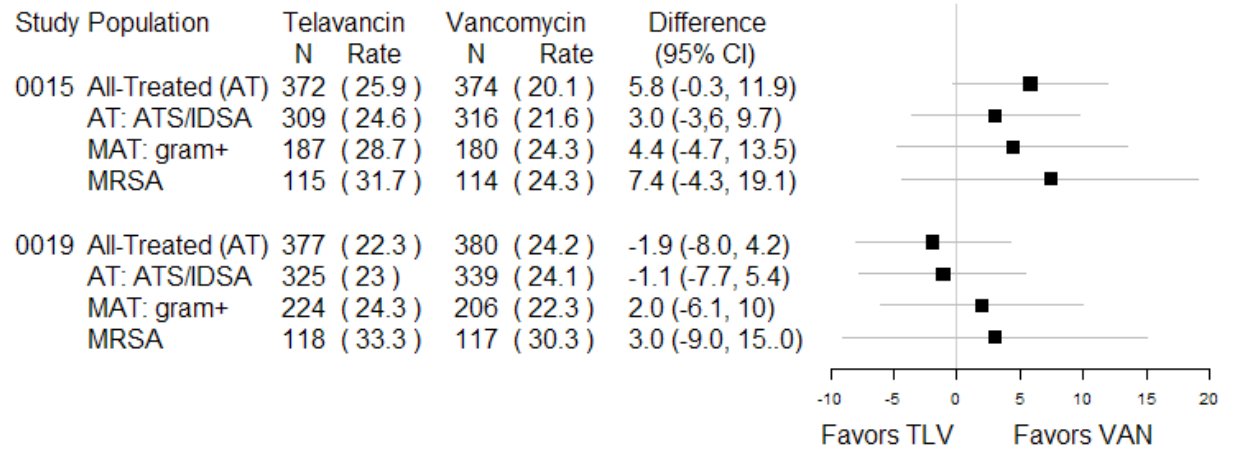
Table 14: Vital Status at Day 28 by Study – AT Population

	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%)

Source: Adapted from NDA 22-407, ISE addendum v1.0, 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 2. The results for the AT population for Study 0015 are concerning because, 1) telavancin mortality rate is almost significantly higher (p=0.06) than vancomycin (treatment difference: 5.8%; 95% CI: (-0.3%, 11.9%) in Study 0015; and 2) the upper bound for Study 0015 is higher than a NI margin of 10%.

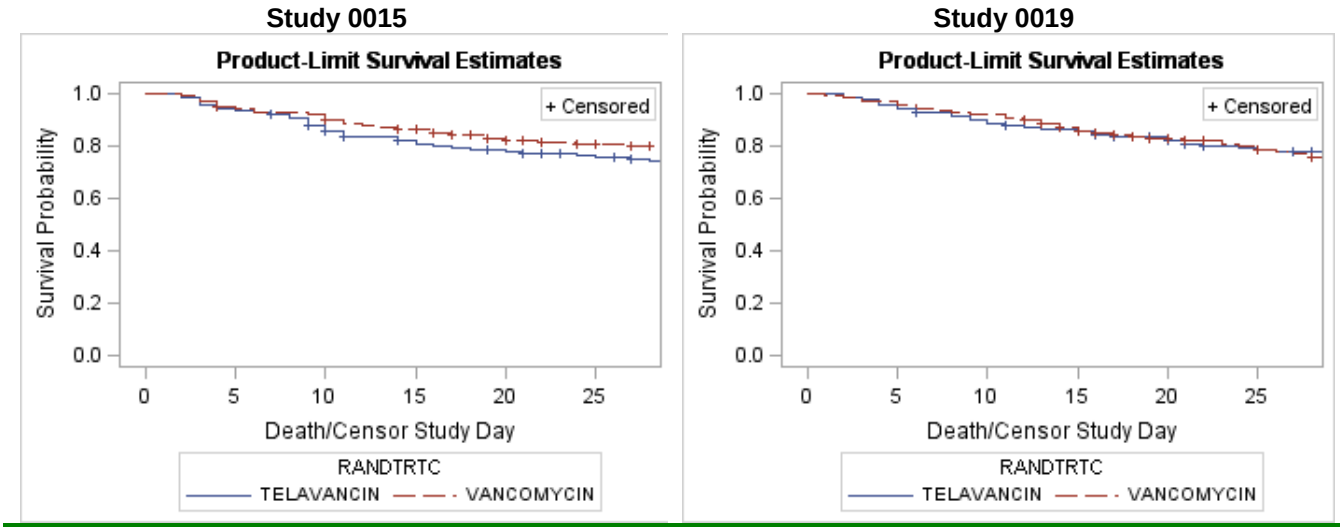
Figure 2: 28-day All-Cause Mortality (Based on K-M estimates)



Source: FDA Reviewer

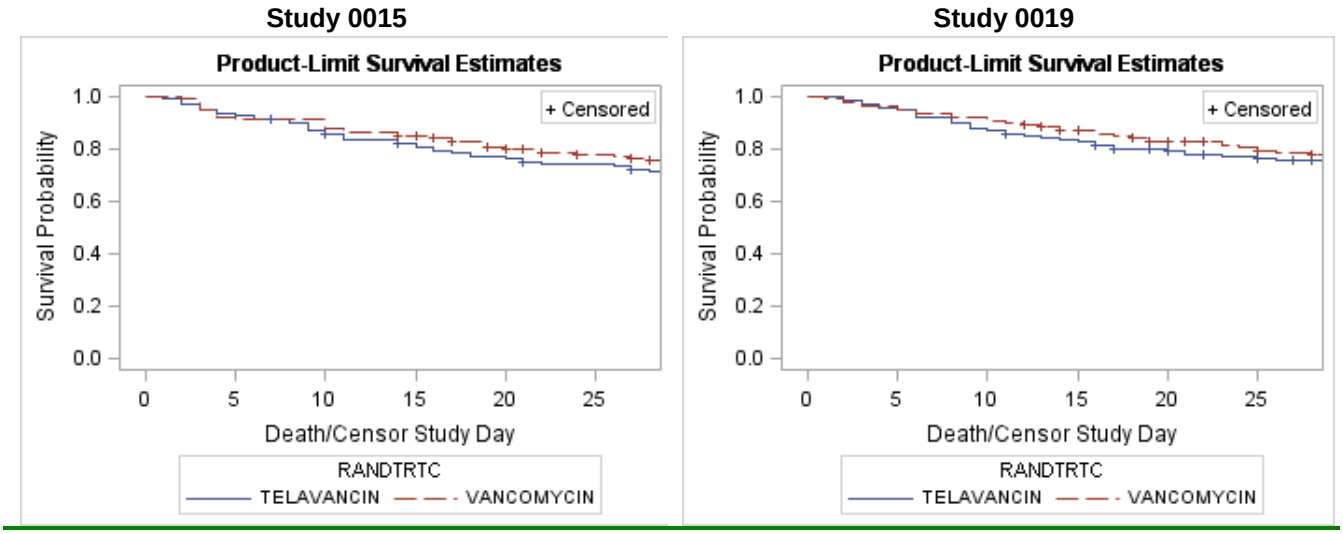
Figure 3 and Figure 4 provide the Kaplan-Meier survival curves and are shown below for the AT and the MAT patients who had a Gram-positive pathogen isolated at baseline. In Study 0015, the survival curve for telavancin is almost significantly lower (Chi-square=3.49, df=1, p=0.06) than the survival curve for vancomycin using a log-rank test. The survival curves appear to diverge after approximately a week on study drug. This holds for both the AT and MAT with baseline Gram-positive pathogen populations. In contrast for Study 0019, there was no significant difference between the two survival curves (AT: Chi-square=0.19, df=1, p=0.66; MAT: Chi-square=0.35, df=1, p=0.55).

Figure 3: Kaplan-Meier Survival Curves (AT Population) – Studies 0015 and 0019



Source: FDA Reviewer

Figure 4: Kaplan-Meier Survival (MAT w/ baseline Gram+ pathogen) – Studies 0015 & 0019



Source: FDA Reviewer

The Division decided that the appropriate primary efficacy population is the MAT with baseline Gram-positive pathogen population because telavancin and the comparator drug only have activity against the Gram-positive pathogens isolated at baseline. As shown in Figure 2, 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%**). The upper bound of the 95% CI for mortality difference in Study 0015 is higher than a NI margin of 10%.

Even though the trials used identical protocols, the Division has concerns about pooling the two trials to assess mortality because of the differential treatment effects shown in Figure 2. These

differential effects are possibly a reflection of 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, immunocompromise, 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.

4.5.2. Role and Effect of Prior and/or Concomitant Therapy

The interpretation of the efficacy analyses for Gram-positive pathogens is confounded by the administration of concomitant antibacterials 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 antibacterial agents administered to provide Gram-negative coverage is a difficult issue. Aztreonam is preferred as it has activity against Gram-negative pathogens with no overlapping Gram-positive activity. Due to possible resistance to Aztreonam, some clinical investigators prefer to use alternative agents for Gram-negative coverage which has overlapping Gram-positive activity.

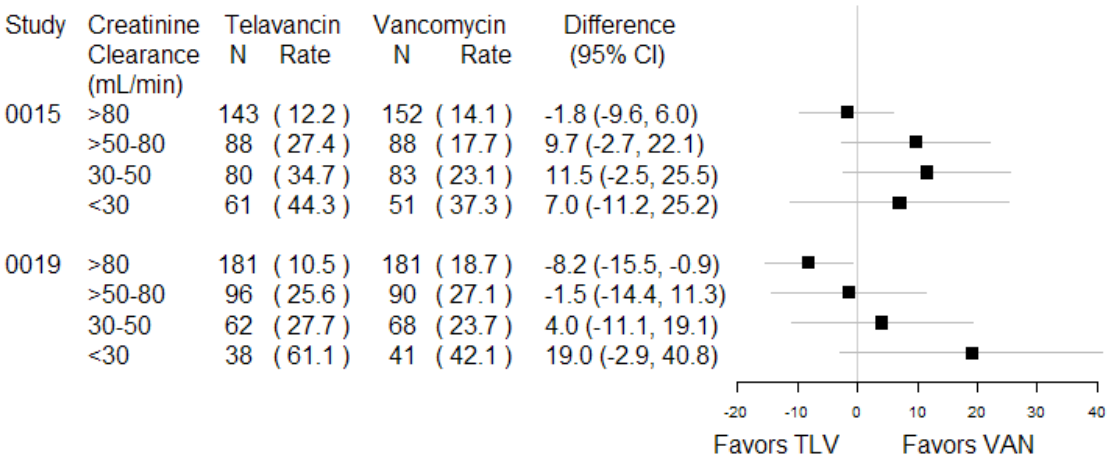
In the current application, the proportion of patients who received concomitant antibacterials with overlapping Gram-positive activity was substantial. In Study 0015, 24% (91/372) of the patients in the telavancin arm received piperacillin/tazobactam and 10% (38/372) received imipenem. For the vancomycin 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 arm 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.

This high proportion of patients who received concomitant antibacterials with overlapping Gram-positive activity may substantially confound the ability to determine the effect of telavancin in the submitted trials to treat Gram-positive NP. This is an important issue in noninferiority trials because any such confounding effect can make the treatment look similar when in fact they are not. This confounding effect should be kept in mind when interpreting the efficacy results.

4.5.3. Effect of Baseline Renal Function on Clinical Response and Mortality

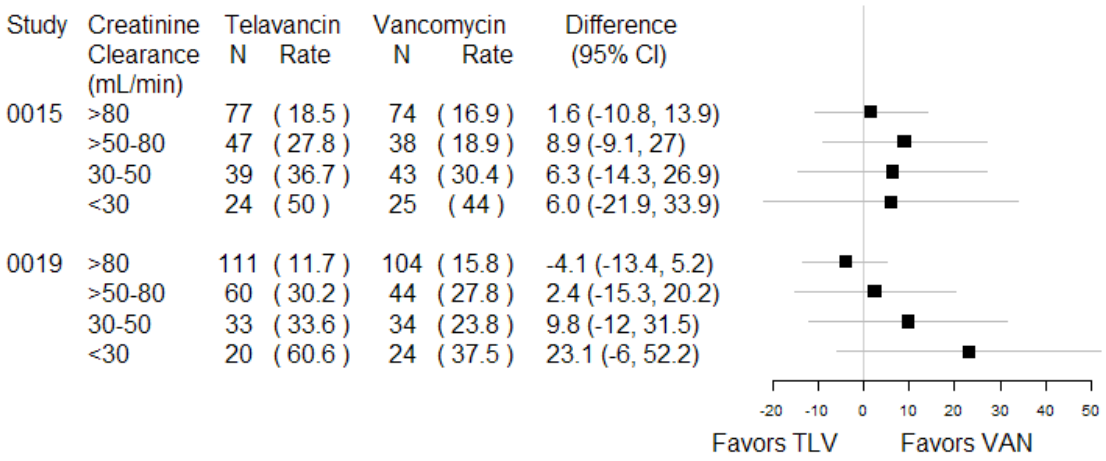
In the telavancin cSSSI trials, there were concerns of reduced efficacy for patients with baseline renal impairment. These concerns resulted in a Warning in the Prescribing Information that informs prescribers that efficacy may be reduced in patients with moderate/severe baseline renal impairment (baseline CrCL ≤50 mL/min). Because of these findings, analyses were performed to evaluate whether baseline renal impairment was an effect modifier for mortality in the NP trials. Stratified analyses of 28-day all-cause mortality by baseline renal impairment for the AT and MAT populations are shown in Figure 5 and Figure 6. In the AT population, it can be seen for Study 0019 that there is a trend of increased mortality of telavancin relative to vancomycin as baseline renal impairment increases. However, this relationship is less clear in the AT population for Study 0015 where the increased mortality of telavancin relative to vancomycin appears to occur for patients with CrCL <80 mL/min. The results are similar for the MAT patients who had a Gram-positive pathogen isolated at baseline.

Figure 5: 28-Day All-Cause Mortality (based on K-M estimates) by Baseline Creatinine Clearance (AT Population)



Source: FDA Reviewer

Figure 6: 28-Day All-Cause Mortality (based on K-M estimates) by Baseline Creatinine Clearance (MAT Patients with a Baseline Gram-positive Pathogen Isolated)



Source: FDA Reviewer

Other baseline factors that could affect renal function and are potential effect modifiers were also investigated by looking at the stratified analyses and using Cochran's Q statistic to assess the homogeneity of the mortality difference across strata. The analyses found baseline creatinine clearance, congestive heart failure, and receipt of nephrotoxic medications at baseline as possible effect modifiers. The results are given in the following table (Table 15):

Table 15: Potential Effect Modifiers for 28-day All-cause Mortality (AT Population)

	Study 0015			Study 0019		
Renal function	**Chi-Square**	**df**	**p-value**	**Chi-Square**	**df**	**p-value**
Baseline creatinine clearance	4.16	3	0.25	6.66	3	0.08
Hx of diabetes	0.13	1	0.72	0.09	1	0.76
Age (<65, ≥65)	0.04	1	0.84	0.31	1	0.58
Congestive heart failure	3.05	1	0.08	0.05	1	0.82
Receipt of baseline nephrotoxic meds	3.50	1	0.06	3.07	1	0.08

Source: FDA Reviewer, Based on Cochran's Q statistic

Analyses of 28-day all-cause mortality stratified by risk factor are shown in the following table (Table 16).

Table 16: 28-day All-Cause Mortality by Baseline Renal Risk Factor (AT Population)

	Study 0015					Study 0019				
	Telavancin		Vancomycin		Difference	Telavancin		Vancomycin		Difference
	N	Mort Rate	N	Mort Rate	TLV - VAN (95% CI)	N	Mort Rate	N	Mort Rate	TLV - VAN (95% CI)
History of diabetes										
Yes	118	34.3	114	26.8	7.4 (-4.5, 19.4)	85	23.9	77	27.7	-3.8 (-17.5, 9.8)
No	254	22	260	17.2	4.9 (-2, 11.8)	292	21.8	303	23.2	-1.5 (-8.2, 5.3)
Age										
≥65 years	202	31.9	212	25.3	6.6 (-2.1, 15.3)	195	31.8	196	32	-0.2 (-9.5, 9.1)
<65 years	170	18.7	162	13.3	5.4 (-2.6, 13.4)	182	12.1	184	15.7	-3.5 (-10.7, 3.6)
Congestive heart failure										
Yes	100	41.3	115	26	15.4 (2.7, 28)	95	32.1	90	32.7	-0.7 (-14.3, 12.9)
No	272	20.1	259	17.6	2.6 (-4.1, 9.3)	282	19	290	21.5	-2.5 (-9.1, 4.2)
Baseline nephrotoxic medications										
Yes	165	33.9	174	21.5	12.4 (2.9, 22)	182	23.2	182	19.5	3.7 (-4.8, 12.2)
No	207	19.5	200	18.8	0.7 (-7, 8.4)	195	21.3	198	28.4	-7.1 (-15.7, 1.5)

Source: FDA Reviewer

5. CLINICAL SAFETY

The summary of clinical safety in this section describes findings from the original NDA submission and includes post-marketing experience following the approval of telavancin for cSSSI in September 2009; however, manufacturing issues arising in November 2011 have limited drug product availability and have thus limited spontaneous safety reporting since then. The safety data in Studies 0015 and 0019 were obtained from the population as-treated, including all patients who received at least one dose of the designated study medication. Given the major safety signals identified with telavancin for the cSSSI treatment indication, this overview will focus on nephrotoxicity (particularly in patients with risk factors for renal dysfunction) and QTc prolongation.

Because telavancin is eliminated primarily by the kidney, a dosage adjustment is required and summarized in the following table (Table 17) in the US Package Insert (USPI) for VIBATIV (telavancin) for injection.

Table 17: Dosage Adjustment in Patients with Renal Impairment

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

As calculated using the Cockcroft-Gault formula

As noted in the CLINICAL TRIALS section and highlighted in the WARNINGS AND PRECAUTIONS section, clinical cure rates in patients treated with telavancin for cSSSI were lower in patients with baseline CrCL ≤50 mL/min compared to those with CrCL >50 mL/min. A similar decrease was not observed in the vancomycin treated patients. As discussed in Section 1.2 of this Briefing Document, the Applicant was required, with the approval for the cSSSI indication, to conduct a prospective study that would help determine if there may be some effect of renal function on the biological activity of telavancin.

Additionally, while employing a risk evaluation and mitigation strategy (REMS) for developmental toxicity, the Applicant was also required to initiate a pregnancy registry. Currently, due to the observation of developmental outcomes in three animal species (reduced fetal weight, and in some animals, digit and limb malformations), there are concerns about potential adverse outcomes in humans. Although there has not yet been any data obtained from this registry, the USPI warns that women of childbearing potential should have a serum pregnancy test prior to administration of telavancin and should avoid use during pregnancy unless the potential benefit to the patient outweighs the risk to the fetus.

5.1. RENAL FUNCTION

5.1.1. Mortality and Baseline Renal Impairment/Risk Factors

In the original NDA (22-407) submission, although there were a substantial percentage of censored events for mortality in both Studies 0015 and 0019, there were concerns regarding this data from a safety perspective during the first cycle review. The results from Study 0015 suggested a substantially higher risk for death in the telavancin group compared to the vancomycin group. This same observation for Study 0019 did not suggest a similar conclusion. Demographic and baseline data (described in Section 4.3) indicate that there were significantly higher proportion of patients in Study 0015 than 0019 with renal insufficiency and diabetes (Table 18). Despite identical trial designs, these baseline characteristics and co-morbid conditions are independent predictors of mortality (see Section 4.5.3). Patients with these risk factors may be at higher risk of mortality with telavancin.

Table 18: Baseline characteristics by Trial (AT Population, treatment arms combined)

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

Source: FDA Reviewer

Due to this observation of higher mortality rates (in the NP trials) and lower cure rates (in NP and cSSSI trials) associated with baseline risk factors for renal impairment, the Applicant has proposed labeling (to be highlighted in the WARNINGS AND PRECAUTIONS section of the USPI) stating that patients with pre-existing severe renal impairment (CrCL <30 mL/min) should only be given telavancin for treatment of NP if the perceived benefit outweighs the risks. However, as seen with the cSSSI trials and included in the current USPI, the observation of decreased clinical cure rates suggests that renal toxicity could modify treatment effect in patients with baseline moderate/severe renal insufficiency (CrCL ≤50 mL/min). Referring to Figure 5 in Section 4.5.3, mortality rates in patients treated with telavancin trended higher than in vancomycin-treated patients with increasing degree of renal impairment (for patients with baseline CrCL <80 mL/min in Study 0015 and CrCL <50 ml/min in Study 0019). This observation suggests that there could also be a significant safety risk in patient populations with

pre-existing renal impairment that is delineated by a CrCL cutoff higher than the 30 ml/min cutoff proposed by the Applicant.

Also of note, the telavancin (for injection) drug product contains hydroxypropyl-beta-cyclodextrin (HPBC), which is a solubilizer and, as indicated in the current USPI, can accumulate in patients with renal dysfunction. While beta-cyclodextrin is known to be nephrotoxic, hydroxypropyl-beta-cyclodextrin is an alternative that has been shown to have a more benign toxicologic profile.[13]

5.1.2. Renal Treatment Emergent Adverse Events

Not unexpectedly, compared to the cSSSI trials, the patients enrolled in Studies 0015 and 0019, tended to be older (54% of patients ≥65 years; 31% of patients ≥75 years), with many comorbid conditions. The severity of illness in the NP patient population is further reflected in the proportion of patients at baseline with APACHE II scores ≥20 points: 22% in the telavancin group and 25% in the vancomycin group. More than half of all patients were in the ICU at baseline, and approximately 9% of all patients were using vasopressor/inotropic medications. In the context of a patient population that has a higher incidence of severe comorbidities, this section will discuss an analysis of treatment emergent adverse events (TEAE), both serious and those leading to study discontinuation. Analyses will compare telavancin-treated patients to vancomycin-treated patients in the All-Treated (AT) safety population, i.e. all subjects who received any amount of study medication.

All serious renal TEAE, listed by preferred term, for both trials are shown in the following table (Table 19). In Study 0015, there was a particularly marked imbalance within the Renal System Organ Class (SOC): The number of telavancin-treated subjects who had a serious renal TEAE was significantly higher than those treated with vancomycin. Most of these patients were identified as having "acute renal failure" by the investigator: Eleven patients in the treated with telavancin, compared to three who were treated with vancomycin.

Table 19: Serious Renal TEAE by Preferred Term – AT Safety Population

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

*Statistically significant, Source: FDA Reviewer

Specific TEAE, listed by preferred term and assessed as related to the study drug by the investigator, are listed in the following tables (Table 20 and Table 21), for Studies 0015 and 0019, respectively. Renal-related TEAE are highlighted. The finding of more subjects in the

telavancin-treated arm having ARF compared to the vancomycin-treated arm was not seen in Study 0019.

Table 20: All Serious TEAE that were assessed as being related, Study 0015 – AT Safety Population

AE Preferred term	Telavancin N=372 n (%)	Vancomycin N=374 n (%)
Renal failure acute	**8 (2.15%)**	**2 (0.53%)**
Blood creatinine increased	**3 (0.81%)**	**0 (0.00%)**
Renal insufficiency	**3 (0.81%)**	**3 (0.80%)**
Myocardial ischemia	1 (0.27%)	0 (0.00%)
Polyneuropathy	1 (0.27%)	0 (0.00%)
Clostridium colitis	1 (0.27%)	0 (0.00%)
Cardio-respiratory arrest	1 (0.27%)	0 (0.00%)
Anuria	**1 (0.27%)**	**0 (0.00%)**
Ventricular tachycardia	1 (0.27%)	0 (0.00%)
Atrial fibrillation	0 (0.00%)	2 (0.53%)

Source: FDA Reviewer

Table 21: All Serious TEAE that were assessed as being related, Study 0019 – AT Safety Population

AE Preferred term	Telavancin N=379 n (%)	Vancomycin N=378 n (%)
Cardiac arrest	1 (0.26%)	0 (0.00%)
Gastrointestinal hemorrhage	1 (0.26%)	0 (0.00%)
Ischemic stroke	1 (0.26%)	0 (0.00%)
Renal failure acute	**1 (0.26%)**	**5 (1.32%)**
Atrial fibrillation	1 (0.26%)	0 (0.00%)
Cerebrovascular accident	0 (0.00%)	1 (0.26%)
Convulsion	0 (0.00%)	1 (0.26%)
Hepatocellular damage	0 (0.00%)	1 (0.26%)
Renal impairment	**0 (0.00%)**	**1 (0.26%)**
Thrombocytopenia	0 (0.00%)	2 (0.53%)

Source: FDA Reviewer

The most frequent TEAE stratified by SOC that resulted in discontinuation of study medication in Study 0015 included Investigations and Renal/Urinary Disorders. As shown in the following table (Table 22), the number of these discontinuations was significantly higher in Study 0015.

Table 22: All TEAE that resulted in Discontinuation of Study Medication – AT Safety Population

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

*statistically significant difference, Source: FDA Reviewer

Among patients with normal baseline creatinine (≤1.2 mg/dL), the incidences of all renal TEAE were comparable across the two studies. However, among patients with abnormal baseline creatinine (>1.2 mg/dL), more telavancin-treated patients experienced renal TEAE compared to vancomycin-treated patients. These TEAE, stratified by baseline creatinine for each trial, are shown in the following table (Table 23). Differences between treatment groups were not statistically significant.

Table 23: Patients who experienced a renal TEAE stratified by Baseline Creatinine – AT Safety Population

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

Source: FDA Reviewer

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

Table 24: All Renal-related TEAE (Serious and Non-serious) – AT Safety Population

Preferred term	**0015**		**0019**		**Total**
	TLV N=372	**VAN N=374**	**TLV N=379**	**VAN N=378**	**N=1532**
Blood creatinine increased	11 (2.96%)	6 (1.60%)	7 (1.85%)	6 (1.59%)	30 (1.96%)
Renal failure acute	18 (4.84%)	10 (2.67%)	16 (4.22%)	18 (4.76%)	62 (4.05%)
Renal failure chronic	2 (0.54%)	1 (0.27%)	2 (0.53%)	0 (0.00%)	5 (0.33%)
Renal impairment	2 (0.54%)	3 (0.80%)	6 (1.58%)	4 (1.06%)	15 (0.98%)
Renal insufficiency	5 (1.34%)	8 (2.14%)	7 (1.85%)	3 (0.79%)	23 (1.50%)
Renal tubular acidosis	1 (0.27%)	1 (0.27%)	0 (0.00%)	0 (0.00%)	2 (0.13%)

Source: FDA Reviewer

Data regarding concomitant antibacterial medication use in patients who developed renal-related TEAEs is provided in the following table (Table 25).

Table 25: Administration in Patients Who Experienced Renal-Related TEAE - AT Safety Population

	0015		**0019**	
	TLV N=372	**VAN N=374**	**TLV N=379**	**VAN N=378**
Renal-related TEAEs	39 (10.5%)*	29 (7.8%)	38 (10.2%)**	31 (8.3%)**
Concomitant antibacterial drugs	17 (4.6%)	7 (1.9%)	0	0
Concomitant aminoglycoside	4 (1.1%)	1 (0.3%)	0	0
No concomitant antibacterial drugs	22 (5.9%)	22 (5.9%)	38 (10.2%)	31 (8.3%)

n=subject count; * one patient (0015-38020-4269) with multiple renal TEAEs was counted twice; ** one telavancin- treated (0019-05000-6414) and two vancomycin-treated (0019-01019-6621 and 0019-20014-6423) patients with multiple renal TEAEs were counted twice.
Source: FDA Reviewer

Measures of central tendency in most chemistry laboratory values were comparable across the two trials. However, there was a consistent pattern with respect to renal function, in which there were mean increases in serum creatinine and decreases in creatinine clearance in the telavancin groups compared to the vancomycin groups of both trials. These analyses are shown in Table 26.

Also of note, increases in serum creatinine to 1.5 times baseline occurred more frequently among telavancin-treated patients (16%) compared with vancomycin-treated patients (10%).

Table 26: Mean Changes from Baseline – AT Safety Population

	Study 0015		Study 0019	
	Telavancin	**Vancomycin**	**Telavancin**	**Vancomycin**
Parameter (units)	n Mean Δ (SD)	n Mean Δ (SD)	n Mean Δ (SD)	n Mean Δ (SD)
Creatinine (μmol/L)	346 **13.28** (74.91)	356 **-6.45** (91.50)	354 **8.48** (52.88)	358 **-0.58** (67.98)
Creatinine clearance (ml/min)	337 **-1.71** (32.51)	346 **4.02** (36.93)	347 **-4.65** (38.43)	352 **6.33** (43.00)

Source: FDA Reviewer

As previously mentioned, the patients enrolled in Studies 0015 and 0019 tended to be older compared to subjects enrolled in the cSSSI trials. Since risk for certain comorbidities, such as renal injury, increase with age, this was reflected as patients are stratified by age: Forty-four of 399 (11.0%) telavancin-treated patients ≥65 years of age had adverse events indicative of renal impairment compared to 30 of 352 patients (8%) <65 years of age.

Given the difference in the baseline characteristics between Studies 0015 and 0019 (higher incidence of co-morbid conditions in Study 0015 that are independent predictors of mortality), and also considering the increased risk of renal events between treatment groups in Study 0015, this also suggests that patients with these risk factors may be at higher risk of renal toxicity with telavancin compared to vancomycin. When accounting for the difference in the overall patient population, who in the setting of NP tend to be at higher risk of death with more baseline comorbid conditions, these analyses of renal adverse events provide additional evidence of potential nephrotoxicity and are consistent with the warnings in the current USPI as labeled for the treatment of cSSSI.

5.2. CARDIAC ADVERSE EVENTS AND EFFECTS ON THE QTC INTERVAL

As part of NDA 22-110 for cSSSI, the Applicant performed a thorough QT/QTc study, which demonstrated that telavancin prolonged the QTc interval >10 msec. In the current USPI, the risk has been highlighted by cautioning use in patients who are also taking drugs known to prolong the QT interval. In keeping with the findings of the QT study, patients with congenital long QT syndrome; two consecutive baseline QTc >500 msec; uncompensated heart failure; and severe left ventricular hypertrophy were excluded from participation in the ATTAIN trials. However, because of the disease being treated, the patient population in the NP trials tended to be more severely ill, and many of the NP patients had other pre-existing cardiac conditions at baseline and/or abnormal baseline ECG findings.

There were few QTc outliers (QTcF increase from baseline >60 msec and/or maximum QTcF value >500 msec) in the treatment groups, but there were no apparent clinical consequences as a result of these observations. None of the patients meeting extreme ECG criteria experienced arrhythmias attributable to prolonged QTcF interval, and no patients treated with either study

medication experienced torsades de pointes. Interactions with other risk factors for drug-induced torsade de pointes (e.g., hypokalemia, diuretic use; congestive heart failure, presence of other QT prolonging drugs) were examined and did not appear to be associated with an increased risk for significant outlying degrees of QTcF prolongation. More patients in the vancomycin group (19%) than in the telavancin group (17%) experienced cardiac AEs, including patients with outlying QTc values (17% telavancin, 35% vancomycin). Serious cardiac TEAE for each study group are summarized in Table 27.

Table 27: Serious Cardiac Treatment Emergent Adverse Events by SOC – AT Safety Population

	Telavancin	Vancomycin
Study 0015	18 (4.84%)	21 (5.61%)
Study 0019	12 (3.17%)	20 (5.29%)

Source: FDA Reviewer

Discontinuations due to QTc prolongation occurred more often in the telavancin group: There were eight telavancin-treated and one vancomycin-treated patients in Study 0015 and five telavancin-treated and two vancomycin-treated patients in Study 0019 who were discontinued from study medication due to having two consecutive ECGs with QTc >500 msec.

6. POINTS FOR ADVISORY COMMITTEE DISCUSSION

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

1. Do the results provide substantial evidence of the safety and effectiveness of telavancin for treatment of nosocomial pneumonia?

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

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

If so, what are these recommendations?

7. APPENDICES

7.1. APPENDIX 1: ADDITIONAL SENSITIVITY ANALYSES

7.1.1. Clinical cure and 28-Day All-Cause Mortality

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

Study Medication	Subject ID	TOC Study Day	Death Study Day	Days between Cure and	Cause of Death as cited by Investigator
Vancomycin	0015-01014-4132	20	22	2	Cardiac arrest
Telavancin	0015-02011-4566	13	15	2	Severe cerebral damage due to seizures
Telavancin	0015-02024-4216	15	18	3	Respiratory failure
Vancomycin	0015-06016-4399	18	21	3	Unknown
Vancomycin	0015-07001-4486	23	24	1	Septic shock from urinary tract infection
Telavancin	0015-07002-4069	23	27	4	Congestive heart failure
Vancomycin	0015-09004-4640	15	28	13	Unknown
Telavancin	0015-12016-4649	27	27	0	Multiple organ failure
Vancomycin	0015-18001-4652	19	21	2	(Respiratory failure?)
Telavancin	0015-33016-4457	22	25	3	Unknown
Telavancin	0015-38024-4787	18	22	4	Unknown
Telavancin	0015-38148-4114	15	21	6	Clinical deterioration
Telavancin	0015-38270-4747	17	21	4	Unknown
Telavancin	0015-38271-4112	27	28	1	Unknown
Telavancin	0015-38271-4124	11	15	4	Cardiopulmonary arrest
Telavancin	0015-38348-4709	19	26	7	Unknown
Telavancin	0019-01019-6032	16	20	4	Cardiac failure
Vancomycin	0019-01019-6339	18	23	5	Shock
Vancomycin	0019-01019-6341	21	28	7	Septic shock
Telavancin	0019-01021-6340	21	26	5	Septic shock due to *Candida albicans*
Vancomycin	0019-01022-6059	15	26	11	Hypoglycemia/pneumonia aspiration
Vancomycin	0019-01022-6624	12	13	1	Meningitis/subarachnoid hemorrhage
Vancomycin	0019-05003-6069	14	14	0	Urinary sepsis by *Enterobacter cloacae*
Vancomycin	0019-05003-6626	17	27	10	Acute ventilatory failure
Vancomycin	0019-06005-6693	23	28	5	Unknown
Telavancin	0019-12009-6203	19	21	2	Sudden death
Vancomycin	0019-18004-6717	14	26	12	Brain metastasis
Telavancin	0019-18012-6382	22	23	1	Unknown

Source: FDA Reviewer

7.2. APPENDIX 2: RESPONSE TO FORMAL DISPUTE RESOLUTION APPEAL

[See attached]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 022407

DISPUTE APPEAL – DENIED

Theravance, Inc.
Attention: Rebecca Coleman, Pharm. D.
Vice President, Regulatory Affairs and Quality
901 Gateway Boulevard
South San Francisco, CA 94080

Dear Dr. Coleman:

Please refer to your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for VIBATIV (telavancin) for injection, 250 mg and 750 mg, for the treatment of nosocomial pneumonia (NP).

We also refer to your December 6, 2011, request for formal dispute resolution, received on December 7, 2011, to the Office of New Drugs. The request for dispute resolution concerns the deficiencies described in the November 23, 2009, and December 21, 2010, complete response (CR) letters from the Division of Anti-infective Products (DAIP), explaining that the sNDA does not provide substantial evidence of safety and efficacy of telavancin in the treatment of NP. Your request for formal dispute resolution followed your August 24, 2011, appeal to the Office of Antimicrobial Products (OAP) and the subsequent denial of that appeal on October 14, 2011, by Edward Cox, M.D., M.P.H., Director, OAP. We also refer to the meeting held between FDA and Theravance on January 20, 2012, where the issues raised in your request for formal dispute resolution were discussed.

In your dispute resolution submission, you take the position that the data submitted in the sNDA demonstrate that telavancin is non-inferior (NI) to vancomycin on the pre-specified primary endpoint of cure rate in the treatment of NP and meet the statutory standard for approval of this new indication. You also state your view that it is inappropriate for the Agency to impose a requirement that you demonstrate efficacy based on a different primary endpoint, all-cause mortality, when your phase 3 trials were agreed to by the Agency before the trials were conducted. Further, you note that the Agency has not finalized its guidance to sponsors regarding its current thinking on appropriate endpoints and statistical analysis plans for clinical trials for evaluating drugs for the treatment of NP and has not initiated procedures to withdraw approval for antibacterial drugs with a NP indication that were approved based on a clinical cure endpoint. Despite your objections to the Agency's requirement that you demonstrate efficacy based on a mortality endpoint, you also claim that the data submitted in the sNDA meet the Agency's proposed NI margin of 10% for mortality. You request that I find that the available data are adequate to support approval and that the deficiencies cited in the two CR letters do not warrant the conduct of additional clinical trials prior to approval.

I have carefully reviewed the materials you submitted in support of your appeal, the reviews, meeting minutes, and decision memoranda prepared by FDA staff, the CR letters, and Dr. Cox's appeal denied letter. I have also consulted with staff in OAP, the Office of Biostatistics (OB), the Office of Regulatory Policy, Lisa LaVange, Ph.D., Director, OB, and Robert Temple, M.D., Deputy Center Director for Clinical Science.

I have completed my review of your request for formal dispute resolution and deny your appeal. Although I am denying your appeal, I recommend that you resubmit the application for further review by the Agency and presentation to an Anti-Infective Drugs Advisory Committee (AIDAC) meeting.

As you are aware, the Agency's current thinking on the appropriate use and interpretation of NI trials for the approval of antibacterial drugs, and for other drug classes, has evolved significantly over the past decade. The evolution in the Agency's approach to NI trials has been driven by a more complete understanding of the scientific issues that underlie the design, analysis, and interpretation of these trials. The Agency has engaged with various stakeholders throughout this process, and has sought input and communicated its evolving thinking through numerous public meetings and workshops, advisory committee meetings, and publication of draft and final guidance on the broad issue of NI trials, the use of NI trials in anti-infective drugs in general, and for specific anti-infective diseases.

The Agency's current thinking on the use of NI trials is based on the need to clearly establish the beneficial effect of the active comparator that will serve as the reference product in the trials to establish the efficacy and safety of the new, or test, drug. Information on the beneficial effect of the active control that can be assumed to be present in the NI trials is ideally derived from adequate and well-controlled trials comparing the reference drug to placebo or no treatment, and is commonly referred to as M1. Once M1 is established, the NI margin for a trial comparing a test drug to the reference drug can be established. This NI margin, in effect, represents a clinical judgment of how much of the beneficial effect of the reference drug could be "lost" by the test drug and still be considered to demonstrate efficacy of the test drug. The NI margin is some fraction of M1 and is commonly referred to as M2.

In many diseases, it is relatively simple to determine M1 and to develop an acceptable NI margin. Unfortunately, for a variety of reasons stated in Dr. Cox's October 14, 2011, letter, which I will not repeat here, reliable identification of M1 and development of an acceptable NI margin for antibacterial drugs have proven to be quite challenging. For some anti-infective indications, the Agency has determined that M1 cannot be reliably determined and an interpretable NI margin cannot be established. In such cases (e.g., acute bacterial sinusitis), the Agency has advised sponsors of the need to conduct superiority trials to support approval of a new drug. In other cases the Agency has been able to identify data that support a science-based determination of M1 and has used these data to develop a recommended NI margin.

In the case of NP (also known as hospital-acquired bacterial pneumonia [HABP], with a subset known as ventilator-associated bacterial pneumonia [VABP]), the Agency has been unable to find sufficient data to determine a reliable estimate of M1 for the endpoint of clinical cure, and therefore has been unable to recommend an evidence-based and interpretable NI margin. The Agency has identified data that we believe would support a reliable estimate of M1 for the endpoint of all-cause mortality. It was on the basis of this new understanding of the available scientific data that the Agency published for comment a draft guidance on development of drugs for the treatment of HABP/VABP in November 2010. In that draft guidance, the Agency recommends use of all-cause mortality as the primary endpoint and a NI margin of 10%.

The Agency's current inability to establish a science-based NI margin for clinical cure in NP does not mean that the Agency does not recognize the importance of clinical cure as one of the primary goals of antibacterial drug therapy in patients with NP and as an important endpoint to evaluate in clinical trials. The Agency also recognizes the limitations of using all-cause mortality as the primary endpoint for NP trials, which include the fact that some fraction of the deaths in the trial may not be related to the patient's pneumonia. Unfortunately, based on the available data, the Agency's current thinking is that a science-based and interpretable NI margin for clinical cure in NP cannot be determined. As you note, the Agency has not finalized the draft HABP/VABP guidance. At present, the Agency continues to evaluate comments from the public and from the AIDAC meeting held in November 2011 to discuss the draft guidance. Some of the issues you have raised in your dispute resolution submission are also being considered as the Agency works to finalize guidance for this indication.

The challenge the Agency faces anytime it makes a change in policy on the scientific or clinical requirements for approval is how to apply the new policy to applications from sponsors whose development programs were complete, or nearly complete, at the time of the policy change, as well as the impact of the policy change on drugs that were approved based on the old policy. You raise this dilemma as an issue of fairness in your dispute. The development program of telavancin in NP was agreed to with the Agency and the clinical trials were ongoing during the time the Agency was reconsidering its approach to the use of NI trials in approval of antibacterial drugs. The Agency's draft guidance on HABP/VABP was published after the phase 3 clinical trials for telavancin in NP were completed and after the sNDA was submitted. The Agency's evolving thinking in this area was considered during the review of your sNDA and referenced in the CR letters, which I view as appropriate. You view the application of this change in Agency policy as unfair and request that the Agency "grandfather" telavancin and approve it based on the previous approach of relying on clinical cure as the primary endpoint for approval of drugs for the treatment of NP.

The Agency's policy is that it must apply the most current thinking and science as it makes decisions on individual applications. To do otherwise would prevent the Agency from incorporating new science into its decision making and perpetuate past practices, which in some cases may have proven to be flawed or outdated. The Agency has also generally not revisited all past decisions once our policy on a given issue changes. The Agency may, however, revisit past decisions if it has concerns that the approved drug may be ineffective or unsafe for its intended use. You argue that since the Agency has not initiated procedures to withdraw approval of the NP indication for previously-approved antibacterial drugs that were approved based on a clinical cure endpoint; it should review the telavancin NDA in accordance with the approval standard applied to these antibacterial drugs. This argument is inconsistent with the need for the Agency to apply the most current science to its review of, and decisions on, new applications. A system that required the Agency to revisit every prior decision as science evolves and standards change would make the regulatory process impossibly cumbersome and burdensome on both the Agency and sponsors of approved applications. I also note that during our January 20, 2012, meeting representatives of Theravance and your counsel acknowledged that withdrawal of the NP indication from previously-approved antibacterial drugs was not your desired outcome.

The clinical development program for telavancin in NP has generated a large amount of data, which I believe must be carefully re-evaluated to support a decision on whether the new indication should be approved. These data may also help the Agency inform its thinking on the appropriate design, endpoints, and analysis for trials to support approval of antibacterial drugs in NP.

As you point out in your dispute resolution submission, telavancin met the pre-specified primary endpoint in both Study 0015 and 0019; i.e., it met the pre-specified NI margin for clinical cure. The trials were not designed or powered to assess all-cause mortality as a primary endpoint, and it is not surprising that the analysis of the all-treated population failed to meet the Agency's recommended 10% NI margin for this endpoint in Study 0015. You have argued that by pooling the two trials (which had identical protocols) and applying particular statistical methodologies to analyze the data, the pooled results meet the 10% NI margin. Thus, you argue that the available data support approval even when using the Agency's stated preference for all-cause mortality as the primary endpoint. There are, however, a number of complex scientific issues that must be addressed in evaluating the available data. These include:

1. the appropriateness of analyzing mortality as the primary efficacy endpoint to support approval when the trials were not designed for this purpose,
2. the appropriate population for the mortality analysis (e.g., the all-treated population, patients with a Gram-positive pathogen),
3. the appropriateness of combining the two trials for the mortality analysis given the observed differences in some baseline characteristics of patients between the two trials and the heterogeneous result of the analysis of all-cause mortality between the two trials,
4. whether to include or exclude patients with baseline renal failure in the analysis considering the warning in the current telavancin labeling regarding an increased risk of nephrotoxicity

and decreased efficacy in patients with moderate to severe baseline renal impairment treated with telavancin for complicated skin and skin structure infections, and

5. how to interpret the "lean" toward increased mortality seen with telavancin in some of the mortality analyses (e.g., the all-treated analysis of Study 015).

While the Agency has stated its preference for all-cause mortality as the primary endpoint, I believe it is important that the Agency make use of all the available data to help it reach its decision on whether the benefits of telavancin outweigh its risks in the treatment of NP. Before making a new decision on whether the available data support approval, I believe it would be beneficial for you to resubmit the application for further Agency review and reconsideration of these complex issues. Your resubmission should include all new analyses that you believe are informative to the interpretation of the data, as well as responses to the deficiencies stated in the last CR letter. I also believe that this application should be presented for discussion at a public meeting of the AIDAC, so that the Agency can obtain expert advice on the complex scientific issues as well as input on whether the available data support a conclusion that the benefits of telavancin for NP outweigh its risks in some patient population. I recommend that you request a meeting with DAIP to discuss the plans for your resubmission.

In our meeting on January 20, 2012, you stated your willingness to participate in an AIDAC discussion of this sNDA; however, you expressed concerns that the presentations and questions to the committee not be a "stacked deck." As I interpret your concerns, you want to ensure that the data will be presented to the committee in a fair manner. In particular, you were concerned that the Agency briefing documents and presentations not state that the only acceptable endpoint for approval is all-cause mortality with a NI margin of 10%, as recommended in the draft HABP/VABP guidance. While the Committee members are aware of the draft HABP/VABP guidance, the Agency background materials and presentations for the meeting can make clear that the guidance is not final, and that we are seeking their advice on the "totality of the data" from the current application, noting that the development program was completed before the draft guidance was issued. So, I believe we can have a "fair hearing" before the AIDAC, and I will work with the staff in OAP and OB to ensure that goal. I will also make every effort to attend the committee meeting, and ask that Drs. LaVange and Temple attend as well if their schedules allow.

In summary, I believe it is important for the Agency to reconsider this application in light of the challenging scientific issues that have been raised regarding interpretation of the available data. I believe it is important that our re-evaluation include input from the public and AIDAC and that we carefully consider their input before making a new decision on whether telavancin can be approved for the treatment of NP based on the currently available data. I hope that you will agree to resubmit the application and to work with OAP in planning for an AIDAC meeting during the new review cycle.

Questions regarding next steps as described in this letter should be directed to J. Christopher Davi, M.S., Senior Regulatory Project Manager, at (301) 796-0702.

If you wish to appeal this decision to the next level, your appeal should be directed to Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Dispute Resolution Project Manager, Amy Bertha. Any questions concerning your appeal should be addressed to Ms. Bertha at (301) 796-1647.

Sincerely,

{See appended electronic signature page}

John Jenkins, M.D.
Director
Office of New Drugs

Center for Drug Evaluation and Research

cc:
Hyman, Phelps & McNamara, P.C.
Attention: Josephine M. Torrente
Regulatory Counsel
700 Thirteenth Street, NW Suite 1200
Washington, D.C. 20005-5929

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN K JENKINS
02/17/2012

8. REFERENCES

[1] 2010 Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf. Last accessed October 15, 2012.

[2] November 4, 2011 meeting of the Anti-Infective Drugs Advisory Committee. Meeting materials available at: http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm
Last accessed October 29,2012.

[3] VIBATIV (telavancin hydrochloride) injection United States Package Insert. Available at: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=5e7c066c-0950-47ce-899d-76881d80c492. Last accessed October 15, 2012.

[4] July 16, 2008 Meeting of the Anti-Infective Drugs Advisory Committee. Final meeting minutes available at: http://www.fda.gov/ohrms/dockets/ac/08/minutes/2008-4364m1-Final.pdf
Last accessed October 29, 2012.

[5] American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005 Feb 15;171(4):388-416.

[6] CHMP summary of positive opinion for Vibativ. May 20, 2011, and VIBATIV® European Marketing Authorization 14 September 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Summary_of_opinion_-_Initial_authorisation/human/001240/WC500106519.pdf. Last accessed October 15, 2012.

[7] Sakoulas G, Moellering RC Jr. Increasing antibiotic resistance among methicillin-resistant *Staphylococcus aureus* strains. *Clin Infect Dis*. 2008;46 Suppl 5:S360-7.

[8] Clinical Trial Design for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia; Public Workshop. Transcripts available at http://www.fda.gov/Drugs/NewsEvents/ucm169877.htm
Last accessed October 29, 2012.

[9] 2010 Guidance for Industry Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf. Last accessed October 15, 2012.

[10] November 4, 2011 Meeting of the Anti-Infective Drugs Advisory Committee. Meeting materials available at http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm242307.htm
Last accessed October 29, 2012.

[11] Pfaller MA, Mendes RE, *et al*. Telavancin activity against Gram-positive bacteria isolated from respiratory tract specimens of patients with nosocomial pneumonia. *J Antimicrob Chemother*. 2010; 65: 2396-404.

[12] NDA 22-407, Summary of Clinical Efficacy, v3.0, Section 2.7.3.2.2

[13] Gould S, Scott RC. 2-Hydroxypropyl-beta-cyclodextrin (HP-beta-CD): a toxicology review. *Food Chem Toxicol*. 2005;43(10):1451-9.