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RESEARCH**

APPLICATION NUMBER:

022407Orig1s000

MEDICAL REVIEW(S)

Deputy Division Director Decisional Memo

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|--------------------------------|--|
| Date | (electronic stamp) |
| From | Katherine Laessig, MD |
| Subject | Deputy Division Director Decisional Memo |
| NDA # | 22-407 |
| Applicant Name | Theravance, Incorporated |
| Date of Submission | March 13, 2013 |
| PDUFA Goal Date | September 13, 2013 |
| Established (USAN) Name | telavancin, tradename Vibativ® |
| Dosage Forms / Strength | Single dose vials of 250 or 750 mg sterile lyophilized telavancin powder for intravenous injection |
| Proposed Indication(s) | Treatment of nosocomial pneumonia in adults |
| Recommended Action: | Approval |

| | |
|------------------------------------|--------------------------------------|
| Material Reviewed/Consulted | |
| Action Package, including: | Names of discipline reviewers |
| CMC Review | Mark Seggel |
| CDTL Review | Benjamin Lorenz |

CDTL=Cross-Discipline Team Leader

1.0 Background

This is the fourth review cycle for this application. Please see my memo dated February 22, 2013, for a complete discussion of the regulatory history of this NDA. Briefly, the applicant had demonstrated sufficient evidence of the safety and efficacy of telavancin during the last cycle for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) in adults caused by *Staphylococcus aureus* when alternative treatments are not suitable. However, their listed manufacturing site, (b) (4) had a withhold status based on the Office of Compliance assessment due to significant cGMP issues. Therefore, the applicant received a complete response letter after the third cycle for the following deficiency:

The application is not approvable however, because it does not meet the standards for approval under Section 505 of the Federal Food Drug & Cosmetic Act (FD&C Act). Specifically, as provided in 505(d), the Agency will refuse to approve the application if “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity” of the product.

Your NDA indicates that (b) (4) will manufacture telavancin at (b) (4) facility in (b) (4). FDA has determined that (b) (4) has violated the FD&C Act by manufacturing, processing, packing, labeling, holding, and distributing drug products in violation of current good manufacturing practices (“cGMPs”) at its (b) (4) site. On (b) (4), the Department of Justice, on the Agency’s

behalf, filed a Consent Decree of Permanent Injunction against (b) (4) in the United States District Court for the (b) (4) that precludes (b) (4) from, among other things, manufacturing, processing, packing, labeling, holding, or distributing drugs until a remediation plan has been implemented and numerous conditions are met.

FDA is unable to approve an application in the absence of an appropriate manufacturing facility and process. Before NDA 22-407 can be approved, it will be necessary for you to have an acceptable manufacturing facility.

The applicant has submitted this class II resubmission to address the aforementioned deficiencies. There is no new pharmacology/toxicology, clinical pharmacology, or statistical information contained in this resubmission. The following will summarize the new CMC and safety information contained in the submission by review discipline. For further detail, please refer to the CMC review and the CDTL memo.

2.0 Product Quality

The CMC reviewer, Mark Seggel, recommends this application for approval. He notes that the applicant, Theravance, identified and qualified a new drug product manufacturer, Hospira McPherson, located in McPherson, Kansas. (b) (4) has been withdrawn as a drug product manufacturing facility. All facilities involved in the manufacturing, packaging, and control of telavancin, including Hospira McPherson, have acceptable cGMP status. The Office of Compliance issued an Overall Recommendation of Acceptable for NDA 22-407 on May 6, 2013.

Minor labeling changes to the vial label and carton have been made to reflect changes in product ownership and NDC. In addition, minor changes to the Preparation and Administration have been recommended by DMEPA to minimize foaming that may occur during reconstitution. Dr. Seggel finds these changes acceptable.

3.0 Safety Update

The applicant submitted no new safety findings from their review of the available postmarketing data since the previous submission. However, in the Agency's recent 915 New Molecular Entity Post-market Safety Summary, new safety concerns were identified. Specifically, cases of hypersensitivity and anaphylaxis were noted. Appropriate changes to the Highlights, Contraindications, Warnings and Precautions, and Postmarketing Experience sections of the product labeling have been made to inform prescribers about this adverse reaction. With these changes, the medical officer (acting as CDTL) Dr. Benjamin Lorenz, recommends approval of this application.

4.0 Other Regulatory Issues

Since this is a new indication, PREA is triggered. However, studies of pediatric patients ages 0 to 17 years for this indication are deferred until June 30, 2019, as the product is ready for approval for use in adults and the pediatric studies have not been completed. The applicant has agreed to the following deferred pediatric studies:

1995-001: Conduct a single dose pharmacokinetic (PK) trial in patients ≥ 1 to 17 years old

Final Protocol Submission: 12/13
Trial Completion: 9/14
Final Report Submission: 3/15

1995-002: Conduct a single dose pharmacokinetic (PK) trial in neonates/infants 0 to <1 year old

Final Protocol Submission: 12/14
Trial Completion: 9/15
Final Report Submission: 3/16

1995-003: Conduct a Phase 3, randomized, comparator-controlled trial of telavancin in children from birth to 17 years old with gram positive infections.

Final Protocol Submission: 12/15
Trial Completion: 12/18
Final Report Submission: 6/19

The REMS for VIBATIV (telavancin) for injection was originally approved under NDA 22-110 on September 11, 2009, and a REMS modification was approved on July 27, 2011. Upon action, NDA 22-407 will be administratively closed and NDA 22-110 will be the primary application for VIBATIV (telavancin) for injection. Therefore, the proposed REMS submitted to NDA 22-407 constitutes a proposed modification to the approved REMS under NDA 22-110. Since this NDA 22-407 will be administratively closed, as NDA 22-110 is the primary NDA for this drug, all future REMS correspondences and submissions will be submitted to NDA 22-110.

The proposed modifications to the REMS consist of:

- Addition of a new goal to inform healthcare professionals about the increased risk of mortality associated with VIBATIV in patients with pre-existing creatinine clearance of ≤ 50 mL/min being treated for HABP/VABP.
- A revised Medication Guide that includes information about the risk of increased mortality seen in patients with HABP/VABP who had pre-existing creatinine clearance ≤ 50 mL/min.
- A revised Dear Healthcare Provider (DHCP) letter that includes information about the increased risk of mortality seen in patients with HABP/VABP who had pre-existing creatinine clearance ≤ 50 mL/min, the risk of nephrotoxicity, and risk of fetal developmental toxicity.
- The DHCP letter must be issued 60 days, 6 months, 1 and 2 years, following the date of the approval of this REMS modification.

The proposed REMS was submitted on June 18, 2013 and is acceptable. The modified REMS consists of a Medication Guide, a communication plan, and a timetable for submission of assessments of the REMS.

The timetable for submission of assessments has been modified to be 18 months, 3 years, and 7 years from the date of the approval of this REMS modification. The revised REMS assessment plan should include, but is not limited to, the following:

- a. Surveys assessing healthcare professionals' and patients' understanding of the potential risk of fetal developmental toxicity if women are exposed to VIBATIV (telavancin) while pregnant.
- b. Surveys assessing healthcare professionals' understanding of:
 1. the increased risk of mortality in VIBATIV (telavancin)-treated patients with pre-existing creatinine clearance of ≤ 50 mL/min being treated for hospital acquired bacterial pneumonia (HABP)/ ventilator-associated bacterial pneumonia (VABP).
 2. the need to monitor renal function (serum creatinine and creatinine clearance) prior to initiating therapy with VIBATIV (telavancin), during therapy (every 48 to 72 hours or more frequently if clinically indicated), and at the end of therapy.
 3. the need to perform a serum pregnancy test prior to initiating therapy with VIBATIV (telavancin) in Females of Reproductive Potential (FRP).
 4. the need to counsel FRP, including those being treated in the outpatient setting, about pregnancy prevention and use of effective contraception during VIBATIV (telavancin) use.
- c. A summary and analysis of maternal and fetal outcomes for all reported pregnancies (from any data source) including:
 1. a cumulative number of all fetal exposures and outcomes reported for all reported pregnancies and;
 2. a root cause analysis to investigate the pregnancies reported with VIBATIV (telavancin) use in the U.S.
- d. A report on periodic assessments of the distribution and dispensing of the Medication Guide in accordance with CFR 208.24. (This may be achieved through the patient survey).
- e. A report on failures to adhere to the Medication Guide distribution and dispensing requirements, and corrective actions taken to address noncompliance.

5.0 Regulatory Action

Since (b) (4) has been withdrawn as a manufacturing facility for telavancin and the new drug product manufacturer, Hospira McPherson, has been found acceptable, I concur with the

recommendation of the CDTL and Product Quality reviewers that the product quality manufacturing deficiencies have been resolved, and that this application can be approved.

Katherine A. Laessig, M.D.

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

/s/

KATHERINE A LAESSIG
06/21/2013

Deputy Division Director Decisional Memo

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|--------------------------------|--|
| Date | (electronic stamp) |
| From | Katherine Laessig, MD |
| Subject | Deputy Division Director Decisional Memo |
| NDA # | 22-407 |
| Applicant Name | Theravance, Incorporated |
| Date of Submission | July 12, 2012 |
| PDUFA Goal Date | January 11, 2013 |
| Established (USAN) Name | telavancin, tradename Vibativ® |
| Dosage Forms / Strength | Single dose vials of 250 or 750 mg sterile lyophilized telavancin powder for intravenous injection |
| Proposed Indication(s) | Treatment of nosocomial pneumonia in adults |
| Recommended Action: | Complete Response |

| Material Reviewed/Consulted Action Package, including: | Names of discipline reviewers |
|--|--------------------------------------|
| CMC Review | Mark Seggel |
| CDTL Review | Benjamin Lorenz |
| Statistical Review | Scott Komo |
| Microbiology Review | Kerry Snow |
| Clinical Pharmacology Review | Ryan Owen |
| Labeling Reviews | Shawna Hutchins Adora Ndu |

CDTL=Cross-Discipline Team Leader

1.0 Background

Telavancin (TLV) is an injectable, lipoglycopeptide antibacterial agent, produced by chemical modification of vancomycin. Its mechanism of action is via inhibition of bacterial wall synthesis by interfering with peptidoglycan synthesis and cross-linking. TLV also causes disruption of the functional integrity of the cell membrane by depolarizing the membrane. It has activity against Gram-positive bacteria including *Staphylococcus aureus* and *Streptococcus pneumoniae*, that may cause nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP). TLV was approved for the treatment of complicated skin and skin structure infections (cSSSI) caused by designated, TLV-susceptible, Gram-positive organisms including methicillin-resistant *S. aureus* on September 11, 2009.

NDA 22-407 was originally submitted on January 23, 2009, in support of 10 mg/kg of TLV administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days, for the requested indication of treatment of adults with NP caused by susceptible strains of Gram-positive bacteria. The initial application received a complete response (CR) on November 23, 2009, primarily because the two Phase 3 trials used a

clinical response endpoint, for which data from the historical literature were inadequate to justify a noninferiority (NI) margin and therefore the trials were not found to be adequate and well-controlled. However, as discussed at a meeting of the Anti-infective Drugs Advisory Committee (AIDAC) on July 16, 2008, historical data were available to support an NI margin for an endpoint of all-cause mortality. For additional information regarding the first cycle review, please refer to all relevant reviews by discipline from that cycle.

The applicant submitted a complete response in June 2010, which included additional mortality data and analyses of 28 day all-cause mortality for both Phase 3 trials; telavancin was not noninferior to vancomycin (VAN) using a 10% NI margin in one of the two trials as the upper bound of the 95% CI of the difference was 13.5%. In addition, TLV-treated subjects who had acute renal failure or renal impairment at baseline were more likely to die compared to vancomycin-treated subjects. Theravance was issued a CR letter on December 21, 2010, for the primary deficiency that only one study demonstrated noninferiority to vancomycin and wasn't adequate on its own to support a HABP/VABP indication, as well as other concerns including uncertainty that subjects had the disease of interest, uncertainty about comparing TLV-treated subjects with historical controls, questions about the appropriateness of pooling of the two Phase 3 trials as subjects differed with respect to some baseline comorbidities, and problems with diagnosis of renal failure. For additional information regarding the second cycle review, please refer to all relevant reviews by discipline for that cycle.

At the time of the issuance of the second CR letter, the Agency's current thinking was that two adequate and well-controlled trials demonstrating evidence of safety and efficacy for HABP/VABP were needed. However, based on comments (primarily regarding infeasibility of conducting two trials for this indication) to the docket in reference to the Draft Guidance for Industry titled "Guidance for Industry, Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment" and subsequent discussion of these comments and the Draft Guidance at a meeting of the AIDAC in November 2011, the Agency's thinking evolved such that one adequate and well-controlled trial in HABP/VABP providing evidence of efficacy and safety, together with supportive evidence, would be adequate to receive approval for this indication.

After receipt of the second CR letter, Theravance submitted a request for Formal Dispute Resolution (FDRR) to the Director of the Office of Antimicrobial Products, Dr. Edward Cox, on August 24, 2011. The FDRR was denied by Dr. Cox on October 14, 2011. Theravance submitted an appeal to the FDRR to the Director of the Office of New Drugs, Dr. John Jenkins, on December 6, 2011. Dr. Jenkins denied the appeal on February 2, 2012. However, he recommended resubmission of NDA 22-407 that included all new analyses that Theravance believed were informative to the interpretation of the data, as well as responses to the deficiencies contained in the December 21, 2010 CR letter. He also advised that the application be discussed publicly at a meeting of the AIDAC, to which Theravance had agreed in a meeting with FDA on January 20, 2012. The application was resubmitted on July 12, 2012.

This memo will summarize important findings and conclusions by review discipline. For further details, please refer to discipline specific reviews and the CDTL memo.

2.0 Product Quality

No new chemistry, manufacturing, and controls (CMC) information was included in this NDA. However, the CMC reviewer, Mark Seggel, does not recommend approval due to an overall recommendation of Withhold issued by the Office of Compliance on January 9, 2013. This recommendation is based on the significant cGMP issues identified at the drug product manufacturing site, (b) (4)

The applicant cross-referenced NDA 22-110 for information concerning the drug product and drug substance. In correspondence dated August 12, 2012, the applicant confirmed that (b) (4) would not be available until late 2012 or early 2013 for manufacturing activities. Notably, (b) (4) has repeatedly had issues with cGMPs and on (b) (4) announced the voluntary shutdown of manufacturing and distribution at its site in (b) (4) due to significant manufacturing and quality concerns. The company notified FDA as soon as they made the decision to shut down. Manufacturing and distribution of all products from this site are currently on hold; however, products already in distribution will remain on the market until further analysis is available.

According to colleagues from the Office of Compliance, (b) (4) entered into a consent decree on January 7, 2013. Theravance is aware of issues at (b) (4), but they have yet to bring a new manufacturing facility on board. However, under the terms of the consent decree, (b) (4) may not distribute any remaining lots of telavancin on site at (b) (4)

Further recent discussion with the Office of Regulatory Policy and the Office of Chief Counsel resulted in the determination that the NDA cannot be approved because it does not meet the standards for approval under Section 505 of the Federal Food Drug & Cosmetic Act (FD&C Act). Specifically, as provided in 505(d), the Agency will refuse to approve the application if “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity” of the product.

I concur with the CMC reviewer that the application cannot be approved until Theravance has addressed the CMC issue and an acceptable manufacturer for the drug product has been identified. The Office of New Drug Quality Assurance is working closely with the applicant to qualify a new manufacturer for telavancin.

3.0 Nonclinical Pharmacology/Toxicology

No new pharmacology/toxicology information was submitted with this resubmission.

4.0 Clinical Pharmacology

The clinical pharmacology reviewer, Ryan Owen, finds that NDA 22-407 is acceptable from his perspective.

Although no new clinical pharmacology information was contained in this resubmission, the medical officer requested assistance from clinical pharmacology to determine an appropriate CrCl cutoff for use of TLV in the treatment of HABP/VABP, given that there was a relationship between decreasing renal function and mortality noted in the two Phase 3 clinical trials for HABP/VABP, which will be discussed further below in the sections on Clinical Efficacy and Safety.

The requested analysis was to examine clinical outcome as a function of exposure in the PK subset and baseline renal function. The result of this analysis found no clear trend between TLV exposure and the ultimate clinical outcome. This assessment supports the applicant's exploratory PK analysis showing no relationship between AUC₀₋₂₄ and clinical outcome or mortality.

5.0 Clinical Microbiology

The clinical microbiology reviewer concludes that, from his perspective, the NDA may be approved provided the applicant makes the changes in the microbiology subsection of the proposed label recommended by DAIP. Clinical microbiology data included in this application were: in vitro drug characteristics (including mechanism of action, drug interaction, and development of resistance), pharmacokinetic/pharmacodynamic analysis, and correlation of in vitro activity with clinical outcomes. Important conclusions from the microbiology review are:

- Distributions of TLV MICs from survey studies and clinical studies found a higher percentage of isolates of *Staphylococcus aureus* and *Enterococcus faecalis* with higher TLV MICs among the clinical isolates compared to the survey isolates, particularly among those with higher MICs. This may imply developing resistance; therefore, continued surveillance for resistance is warranted.
- Correlation studies comparing the disk diffusion method of susceptibility testing with the MIC method support the zone size recommendations of the applicant.
- Data from reference laboratory reports suggest that susceptibility testing of TLV, using solid media techniques, may result in values that are difficult to reproduce or vary from acceptable quality control ranges. Therefore, susceptibility testing by the agar test method is not recommended.
- Data from quality control studies do not support vancomycin as a class-representative surrogate for TLV susceptibility testing.
- *Streptococcus pneumoniae* should be removed from the proposed indication for HABP/VABP since it is not a major etiologic agent for this infection.

6.0 Summary of Clinical Efficacy

The statistical reviewer, Scott Komo, and the CDTL, Benjamin Lorenz, conclude that TLV is effective for the treatment of HABP/VABP and that the application may be approved. However, due to concerns about increased mortality in subjects with a baseline estimated CrCl \leq 50 mL/min, they recommend limitation of the indication to HABP/VABP caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in patients with CrCl > 50 mL/min.

The applicant conducted two Phase 3 trials of identical design (0015 and 0019) in patients with Gram-positive HABP/VABP. The trials were randomized, double-blind, active-controlled, multicenter, and multinational. Subjects with Gram-positive HABP/VABP were randomized 1:1 to receive either TLV 10 mg/kg IV q 24 h or VAN 1 g IV q 12 h for 7 to 21 days. Study 0015 enrolled 761 subjects and Study 0019 enrolled 771 subjects. The prespecified primary efficacy analysis was clinical response at the test-of-cure (TOC) assessment, which occurred 7-14 days after the last dose of study drug. The noninferiority margin (TLV-VAN) was prospectively set at 20%. For the noninferiority analyses, the as-treated (AT) and clinically evaluable (CE) populations were considered coprimary.

The results of the applicant's prespecified primary analysis are shown in Table 1. Note that to address the Agency's concern regarding uncertainty whether subjects had the disease of interest, only subjects who fulfilled American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines for diagnosis of HABP/VABP were included in both the FDA and applicant's analyses.

Table 1: Clinical Cure at Test of Cure – CE & AT-ATS/IDSA Analysis Sets, Studies 0015 and 0019

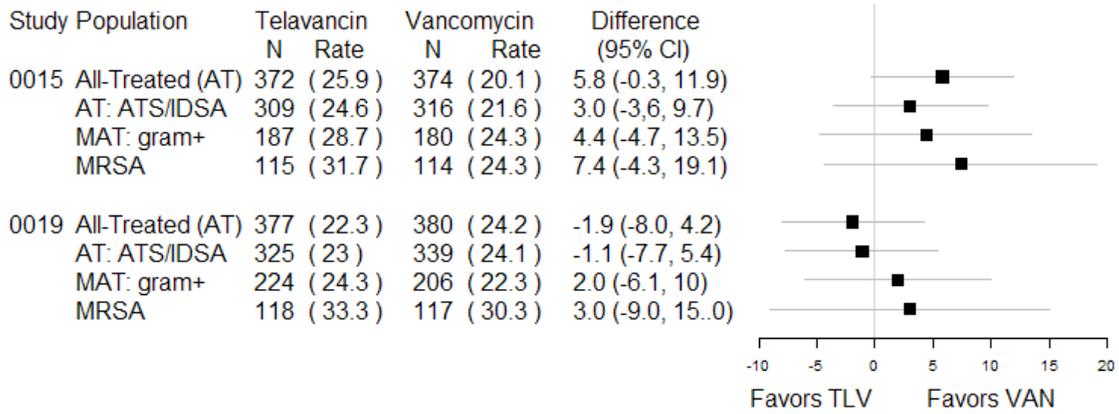
| <u>Population</u> | <u>0015</u> | | | <u>0019</u> | | |
|---------------------------|---------------------|---------------------|----------------------------|---------------------|---------------------|----------------------------|
| | Telavancin N (%) | Vancomycin N (%) | Difference (%) (95% CI) | 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) |
| ATS/IDSA MAT – MRSA | 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) |
| | 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

As discussed previously, the utility of clinical response as a primary endpoint is problematic due to the inability to justify an NI margin. Therefore, analyses of 28-day all-cause mortality were also conducted, as historical evidence of treatment effect is available to support and NI margin for an all-cause mortality endpoint. Since TLV has activity only against Gram-positive pathogens, only subjects who had at least one Gram-positive organism isolated at baseline were included in the analysis population. Figure 1 shows the Kaplan Meier estimates of 28-day all-cause mortality for four analysis populations: AT, AT (ATS/IDSA), microbiologically AT who had at least one Gram

positive organism isolated at baseline (MAT: gram +), and subjects from whom MRSA was isolated. The FDA analysis focused on the ATS/IDSA MAT population (subjects who had at least one Gram-positive pathogen at baseline) for the outcome of mortality.

Figure 1: 28-Day All-Cause Mortality (Based on K-M estimates)

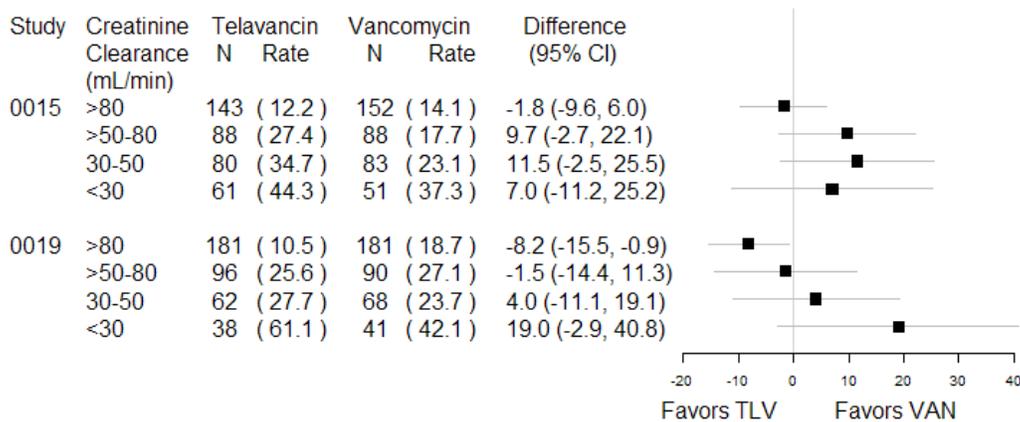


Source: FDA Statistical Review

For the MAT population, the upper bound of the 95% CI of the treatment difference for study 0015 is 13.5, while for 0019 it is 10.0. Therefore, only one study meets the currently recommended NI margin of 10%. Subjects enrolled in 0015 had more comorbidities at baseline; specifically, more subjects had baseline renal impairment and risk factors for renal impairment including diabetes, CHF, age ≥ 75 years, among others.

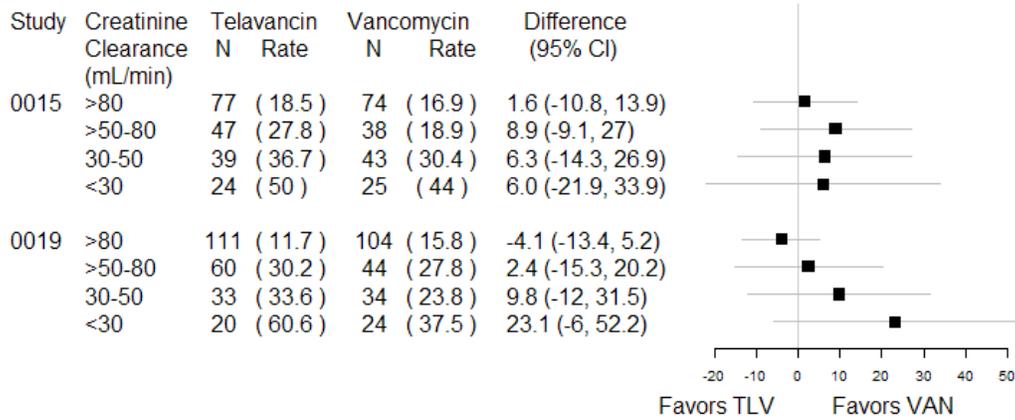
Because of the finding of reduced efficacy of TLV in subjects with baseline renal impairment in the cSSSI trials, analyses were performed to evaluate whether baseline renal impairment was also an effect modifier for mortality in the HABP/VABP trials. The results of these analyses for the AT and MAT are shown in Figures 2 and 3 below.

Figure 2: 28-day All-Cause Mortality (based on K-M estimates) by Baseline Creatinine Clearance (AT Population)



Source: FDA Statistical Review

Figure 3: 28-day All-Cause Mortality (based on K-M estimates) by Baseline Creatinine Clearance (MAT Population: gram +)



Source: FDA Statistical Review

The trend for decreased efficacy of TLV compared to VAN is more marked in 0019 compared to 0015 for both analysis populations. In 0015, TLV-treated subjects with a baseline CrCl <80 mL/min fare worse compared to those treated with VAN. However, in study 0019, efficacy doesn't appear to decline until subjects have a baseline CrCl ≤50 mL/min. When these findings are considered together with the information from the skin trials such that TLV-subjects with baseline CrCl ≤50 mL/min responded worse compared to those treated with VAN, it is reasonable to use the same cutoff of ≤50 mL/min to warn prescribers of the increased mortality seen in the HABP/VABP trials in the package insert.

I concur with the statistical and CDTL conclusions that sufficient evidence of the efficacy of TLV for the treatment of HABP/VABP has been provided for patients with CrCl > 50 mL/min and when other options are not available and that the labeling should include a boxed warning about the increased mortality in patients with CrCl < 50 mL/min. Based on labeling discussions with the applicant, the indication will include methicillin-susceptible *Staphylococcus aureus* (MSSA) as there may be rare circumstances when alternate therapy is not available for specific patients, either due to allergy/intolerance or resistance.

7.0 Summary of Clinical Safety

The CDTL, Benjamin Lorenz, finds that sufficient evidence for the safety of TLV for the treatment of patients with HABP/VABP caused by MSSA or MRSA has been provided, with certain caveats that include moving the nephrotoxicity warning from the Warnings and Precautions section of the package insert to a boxed warning. He also recommends including the information on increased mortality in TLV-treated subjects compared to VAN-treated subjects with baseline CrCl < 50 mL/min to the boxed warning as well. I concur with his conclusions and recommendations regarding labeling.

Serious adverse events were reported in 31% of patients treated with TLV and 26% of patients who received VAN. Treatment discontinuations due to adverse events occurred in 8% (60/751) of patients who received TLV, the most common events being acute renal failure and electrocardiogram QTc interval prolonged (~1% each). Treatment discontinuations due to adverse events occurred in 5% (40/752) of VAN-patients, the most common events being septic shock and multi-organ failure (<1%).

The treatment-emergent adverse reactions that occurred most commonly in TLV-treated subjects included nausea, vomiting and diarrhea. The rates for all three were 5% compared to 4% for VAN-treated subjects. More TLV-treated subjects had a treatment-emergent renal adverse event compared to VAN-treated subjects (10% vs. 8%, respectively). These events included blood creatinine increased, acute renal failure, chronic renal failure, renal impairment, renal insufficiency, and renal tubular acidosis. Of the patients who had at least one renal adverse event, 54% in each treatment group recovered completely, recovered with sequelae, or were improving at the last visit from the renal AE. Three percent of TLV-treated patients and 2% of VAN-treated patients experienced at least one serious renal adverse event. Renal adverse events resulted in discontinuation of study medication in 14 TLV-treated patients (2%) and 7 VAN-treated patients (1%). Increases in serum creatinine to 1.5 times baseline occurred more frequently among TLV-treated patients (16%) compared with VAN-treated patients (10%).

8.0 Advisory Committee

The NDA for TLV for the treatment of HABP/VABP in adults was presented at a meeting of the Anti-Infective Drugs Advisory Committee on November 29, 2012.

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

1. *Due to the discussions that transpired at the meeting, the wording of question #1 was modified to the following:*

Do the results provide substantial evidence of the safety and effectiveness of telavancin for the requested indication of treatment of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible isolates of the following Gram positive microorganisms: *Staphylococcus aureus* (both MSSA and MRSA) and *Streptococcus pneumoniae*? **(Vote)**

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

Six members voted “yes” while nine members voted “no”. Reasons given for the “no” votes included the higher mortality rates seen in subjects with impaired renal function at baseline which made the product not suitable for administration for such patients.

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

(Vote)

- a. If yes, please provide recommendations concerning labeling, particularly labeling concerning the use in patients with renal dysfunction.
- b. If no, what additional studies/analyses are needed?

Thirteen members voted “yes” while two voted “no.” Many members recommended a limited indication, such as for subjects with MRSA and baseline CrCl either >30 mL/min or >50 mL/min.

3. 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? **(Discussion)**

Most members recommended adequate description in product labeling regarding the nephrotoxicity issue.

9.0 Pediatrics

The applicant submitted a pediatric plan requesting a deferral of all pediatric age groups. PREA is triggered because this is a new indication. The applicant's proposed pediatric plan was presented to the Pediatric Research Committee (PeRC) on December 19, 2012. Although the application will receive a CR action this cycle, PeRC's recommendations were to propose a waiver for neonates and infants since patients with CrCl<50 mL/min should not receive TLV. A repeat PK study could be included in the applicant's proposed Phase 3 study enrolling children older than neonates and infants.

10.0 Other Regulatory Issues

The application was presented to Dr. Janet Woodcock and others at a Center Director's briefing on January 23, 2013. It was at this meeting that agreement was reached that NDA 22-407 could not be approved because of the status of (b) (4), according to section 505(d) of the FD&C Act, despite the fact that sufficient evidence of safety and efficacy had been provided by the applicant.

11.0 Regulatory Action

I concur with the recommendations and conclusions of the review team that the applicant has addressed the clinical and statistical deficiencies outlined in the December 21, 2010 complete response letter and has provided sufficient evidence of safety and efficacy of TLV for a limited indication of treatment of hospital-acquired and ventilator-associated bacterial pneumonia in adults caused by *Staphylococcus aureus* and should be reserved for use when alternative treatments are not suitable.

However, the NDA may not be approved on the basis that there is no assurance that “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity” of the product. Therefore, the applicant shall be issued a complete response letter with the following deficiency:

We have completed our review of this application, as amended, and we have determined that, from a clinical and statistical perspective, the data submitted to the Agency are adequate to demonstrate the safety and efficacy of the product for the indication under review (Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia). The application is not approvable however, because it does not meet the standards for approval under Section 505 of the Federal Food Drug & Cosmetic Act (FD&C Act). Specifically, as provided in 505(d), the Agency will refuse to approve the application if “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity” of the product.

Your NDA indicates that (b) (4) will manufacture telavancin at (b) (4). FDA has determined that (b) (4) has violated the FD&C Act by manufacturing, processing, packing, labeling, holding, and distributing drug products in violation of current good manufacturing practices (“cGMPs”) at its (b) (4) site. (b) (4) the Department of Justice, on the Agency’s behalf, filed a Consent Decree of Permanent Injunction against (b) (4) in the United States District Court for the (b) (4) that precludes (b) (4) from, among other things, manufacturing, processing, packing, labeling, holding, or distributing drugs until a remediation plan has been implemented and numerous conditions are met.

FDA is unable to approve an application in the absence of an appropriate manufacturing facility and process. Before NDA 22-407 can be approved, it will be necessary for you to have an acceptable manufacturing facility.

Katherine A. Laessig, M.D.

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/s/

KATHERINE A LAESSIG
02/22/2013

Office Director Decisional Memo

| | |
|--|---|
| Date | 02/22/2013 |
| From | Edward M. Cox, MD, MPH |
| Subject | Office Director Decisional Memo |
| NDA # | 22-407 |
| Applicant Name | Theravance, Inc. |
| Date of Re-Submission | July 12, 2012 |
| PDUFA Goal Date | January 12, 2013 |
| Proposed Proprietary Name / Established (USAN) Name | Vibativ telavancin hydrochloride |
| Dosage Forms / Strength | lyophilized powder for injection |
| Proposed Indication | Vibativ is indicated for the treatment of patients with nosocomial pneumonia caused by susceptible isolates of the following Gram positive microorganisms - <i>Staphylococcus aureus</i> (including methicillin-susceptible and methicillin-resistant strains) - <i>Streptococcus pneumoniae</i> (b) (4) |
| Indication | VIBATIV is indicated for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP), caused by susceptible isolates of <i>Staphylococcus aureus</i> (including methicillin-susceptible and -resistant isolates). VIBATIV should be reserved for use when alternative treatments are not suitable. |
| Action | Complete Response |

Introduction

Vibativ (telavancin) is a lipoglycopeptide antibacterial drug derived from vancomycin. Vibativ (telavancin) was first approved under NDA 22-110 for the treatment of complicated skin and skin structure infections (cSSSI) on September 11, 2009. This NDA 22-407 was initially received on January 23, 2009, prior to the initial approval of NDA 22-110 and hence was submitted as an NDA. Additional information on the regulatory history for NDA 22-110 and NDA 22-407 is provided in the section titled, Regulatory History.

Other drugs approved with a predominantly Gram-positive spectrum of activity including methicillin-resistant *Staphylococcus aureus* that are indicated for either nosocomial pneumonia or serious or severe infections caused by susceptible strains of methicillin-resistant *Staphylococcus aureus* infections are linezolid and vancomycin. Other drugs with an indication for nosocomial pneumonia include piperacillin/tazobactam and levofloxacin.

Regulatory History

NDA 22-110

NDA 22-110 Theravance's Vibativ (telavancin) for treatment of complicated skin and skin structure infections (cSSSI) was first submitted on December 19, 2006 and received an action of approvable on October 19, 2007. The deficiencies for this first cycle included deviations from cGMP at (b) (4) missing financial disclosure information for three sub-investigators; and several issues regarding whether there was an acceptable benefit-risk ratio for telavancin.

NDA 22-110 (for cSSSI) was re-submitted on January 21, 2008 (first re-submission). During the period of review, the application was presented to the Anti-Infective Drugs Advisory Committee on November 19, 2008. The Action on the second review cycle was a complete response on February 20, 2009 that noted that the following items needed to be provided to address deficiencies in the application (1) additional data from their completed clinical trials in patients with skin infections and nosocomial pneumonia were needed to further characterize adverse events related to renal impairment; (2) the need to submit a REMS; (3) the need to develop a pregnancy registry to evaluate for teratogenicity.

NDA 22-110 (for cSSSI) was re-submitted and received on March 13, 2009 (second re-submission). The deficiencies from the complete response letter of February 20, 2009 were addressed. Theravance's Vibativ (telavancin) for the treatment of cSSSI was approved on September 11, 2009.

NDA 22-407

The initial submission of NDA 22-407 for Vibativ (telavancin) for the treatment of *nosocomial pneumonia (NP)* was received on January 23, 2009. On January 23, 2009, NDA 22-110 was not an approved NDA; therefore in accordance with CDER's *Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*¹ the application was submitted as an NDA rather than as an efficacy supplement. The application received a complete response action on November 23, 2009 noting the following information should be submitted to address deficiencies (1) additional data on mortality, (2) a rationale for pooling mortality data across studies, (3) consideration of appropriate inclusion criteria to identify patients with nosocomial pneumonia for any future trial, (4) additional data from patients with penicillin non-susceptible isolates of *S. pneumoniae*, and a pediatric plan.

Theravance re-submitted NDA 22-407 on June 30, 2010 (first re-submission). The applicant received a complete response action on December 21, 2010 with the following deficiencies, (1) a lack of substantial evidence of efficacy for the treatment of nosocomial pneumonia (NP), (2) the criteria for selection of patients for the NP clinical trials, (3) questions on the appropriateness of the determination of the non-inferiority margin for the applicant's NP clinical trials, (4) the lack of scientific support for pooling the results of the two NP studies

¹ <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf>

and for the post hoc inclusion of selected patient prognostic factors, (5) lack of standardized definitions for assessing renal failure.

Theravance next submitted a request for formal dispute resolution (FDR) for NDA 22-407 for NP to the Office of Antimicrobial Products that was received on August 25, 2011.

Theravance's appeal to OAP was denied on October 14, 2011. The response to Theravance's request for formal dispute resolution discussed the science of non-inferiority clinical trial designs. The response noted that the historical evidence supports a considerable treatment effect on mortality for patients with NP and that to date a quantitative treatment effect for clinical response has not been determined for NP. The response notes the value of having the application discussed before the FDA's Anti-Infective Drugs Advisory Committee and notes a number of scientific issues that would benefit from discussion at an Advisory Committee meeting.

Theravance next submitted a request for formal dispute resolution (FDR) for NDA 22-407 to the Office of New Drugs that was received on December 7, 2011. The appeal to OND was denied on February 17, 2012. The recommendation in the response letter from OND was to resubmit the application for further review by the Agency and presentation to an Anti-Infective Drugs Advisory Committee (AIDAC) meeting. The response also noted a number of complex scientific issues that would benefit from discussion at an AIDAC meeting:

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).

The response letter also states that the Agency should 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.

NDA 22-407 was re-submitted on July 12, 2012.

At a teleconference on December 22, 2012 the issue of the status of the manufacturing of telavancin was discussed; this led to Theravance asking that FDA convert their NDA 22-407 to an efficacy supplement to NDA 22-110 because of the cGMP deficiencies at (b) (4)

(b) (4) the manufacturer of telavancin. In a subsequent letter to FDA on December 26, 2012, Theravance re-stated to the Agency that the Agency could convert NDA 22-407 to an efficacy supplement to their approved NDA, NDA 22-110. At a teleconference on January 7, 2013 the Agency explained to Theravance that the Agency cannot convert NDA 22-407 to an efficacy supplement to NDA 22-110 and that if an applicant wants to submit an efficacy supplement to their approved NDA, this would require the applicant (Theravance) to make the necessary submissions. (b) (4)

In the sections that follow, this memorandum will focus on selected issues from the review of NDA 22-407. The review team has reviewed the issues in detail in their respective disciplines. For a detailed discussion, the reader is referred to the individual discipline specific reviews, the Cross-Discipline Team Leader Review, and the Deputy Division Director Summary Review, for this cycle and previous review cycles.

Chemistry, Manufacturing, and Controls (CMC) & Product Quality

The CMC for Theravance's Vibativ (telavancin) was first reviewed under NDA 22-110 for treatment of complicated skin and skin structure infections (for CSSSI). At the time of the initial submission of December 19, 2006, the first cycle of review led to an approvable action which included a deficiency of "FDA inspection of the (b) (4) revealed significant deviations from the Current Good Manufacturing Practice regulations. A satisfactory resolution of these violations is required before this application can be approved." The CMC deficiency was subsequently addressed and the application was approved in September of 2009 for the treatment of complicated skin and skin structure infections (cSSSI).

The issue of the GMP status of manufacturing for Theravance's Vibativ (telavancin) has been a topic of considerable discussion during the review of NDA 22-407. (b) (4) is the manufacturer of Vibativ (telavancin) for NDA 22-407. The European Medicines Agency has suspended the marketing authorization for Vibativ (telavancin) because of the (b) (4)² NDA 22-407 has been discussed extensively with ONDQA and the Office of Compliance, at a CDER Center Director briefing, and with our Office of Chief Counsel and CDER's Office of Regulatory Policy.

NDA 22-407 indicates that (b) (4), will manufacture telavancin a (b) (4) (b) (4) FDA has determined that (b) (4) has violated the FD&C Act by manufacturing, processing, packing, labeling, holding, and distributing drug products in violation of current good manufacturing practice ("CGMP") at its (b) (4) site (b) (4) United States District Court for the (b) (4) approved a Consent Decree of Permanent Injunction against (b) (4) that precludes (b) (4) from, among other things, manufacturing, processing, packing, labeling, holding, or distributing non-medically necessary drugs until a remediation plan has been implemented and numerous conditions are met.

² http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/001240/WC500131172.pdf

FDA is unable to approve an application in the absence of an adequate manufacturing facility and process. Before NDA 22-407 can be approved, it will be necessary for Theravance to have a manufacturing facility that has methods, facility and controls that are adequate to preserve the drug's identity, strength, quality, purity, stability, and bioavailability.

As noted in the Complete Response letter:

We have completed our review of this application, as amended, and we have determined that, from a clinical and statistical perspective, the data submitted to the Agency are adequate to demonstrate the safety and efficacy of the product for the indication under review (Hospital-Acquired Bacterial Pneumonia/Ventilator-Associated Bacterial Pneumonia). The application is not approvable however, because it does not meet the standards for approval under Section 505 of the Federal Food Drug & Cosmetic Act (FD&C Act). Specifically, as provided in 505(d), the Agency will refuse to approve the application if “the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity” of the product. See 21 CFR 314.110(a); 314.125(b)(1).

ONDQA has been working with Theravance to facilitate the qualification of a new manufacturing facility to address the manufacturing deficiency noted for NDA 22-407.

Pharmacology Toxicology

There are no new pharmacology toxicology studies included in this resubmission.

Microbiology

The Clinical Microbiology Reviewer recommends approval. The proposed susceptibility interpretive criteria are found to be acceptable. The reviewer also recommends that *Streptococcus pneumoniae* be removed from the label for the indication of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia.

Clinical Pharmacology

The Clinical Pharmacology reviewer finds that the application is acceptable from a Clinical Pharmacology standpoint. The review notes that no new clinical pharmacology data were submitted in the current re-submission. The clinical pharmacology review also evaluated the proposed dosage adjustments in the setting of moderate and severe renal function and found that the proposed dosage adjustment resulted in comparable telavancin exposures.

Clinical and Statistical

The clinical reviewer, statistical reviewers and Deputy Division Director find that there is substantial evidence of efficacy for telavancin and recommend approval for treatment of HABP/VABP with a limited indication. Following additional discussion the indication for telavancin is for the treatment of HABP/VABP caused by susceptible isolates of *Staphylococcus aureus* when alternative treatments are not suitable. For more details, please see the respective reviews. Analyses evaluating effect of baseline creatinine clearance found

an increased mortality rate in the subgroups of patients with estimated baseline creatinine clearance less than or equal to 50 mL/min. Analyses performed by the statistical reviewer evaluating outcomes in the subset of patients from US sites, also support using a creatinine clearance of ≤ 50 mL/min, rather than the Applicant's proposal to use creatinine clearance of ≤ 30 mL/min. In addition nephrotoxicity was observed in the HABP/VABP trials and the cSSSI trials of telavancin. Renal adverse events were more likely to occur in patients with baseline comorbidities known to predispose patients to kidney dysfunction or in patients who received concomitant medications known to affect kidney function. The information on increased mortality in patients with creatinine clearance ≤ 50 mL/min and nephrotoxicity will be included in the boxed warning. The Warnings and Precautions section, Adverse Reactions, and Clinical Trials section adequately describe the information on HABP/VABP and the safety of telavancin. In addition the Medication Guide will be updated to include additional information related to the HABP/VABP indication. We are also requiring a REMS that includes a Medication Guide, a communication plan, and a timetable for assessments of the REMS.

The recommendation from the review team for an indication for HABP/VABP when alternative treatments are not suitable and prominent inclusion of the increased mortality in the setting of baseline renal compromise is consistent with the advice from the Anti-Infective Drugs Advisory Committee (AIDAC) meeting of November 29, 2012.

Summary

I concur with the assessments of the review team and the Deputy Division Director that the clinical and statistical deficiencies for the hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia indication have been addressed; that the data support an indication for HABP/VABP for *Staphylococcus aureus* when alternative treatments are not suitable and that the finding of increased mortality with baseline creatinine clearance ≤ 50 mL/min and the risk of nephrotoxicity should be included in the boxed warning. I also concur with the assessment of the CMC reviewers that there remains an outstanding manufacturing deficiency. As noted in the section of this review summarizing CMC, NDA 22-407 indicates that (b) (4) will manufacture telavancin at (b) (4) facility in (b) (4). FDA has determined that (b) (4) has violated the FD&C Act by manufacturing, processing, packing, labeling, holding, and distributing drug products in violation of current good manufacturing practice ("CGMP") at its (b) (4) site. (b) (4), United States District Court for the (b) (4) approved a Consent Decree of Permanent Injunction against (b) (4) that precludes (b) (4) from, among other things, manufacturing, processing, packing, labeling, holding, or distributing non-medically necessary drugs until a remediation plan has been implemented and numerous conditions are met. FDA is unable to approve an application in the absence of an adequate manufacturing facility and process. Before NDA 22-407 can be approved, it will be necessary for Theravance to have a manufacturing facility that has methods, facility and controls that are adequate to preserve the drug's identity, strength, quality, purity, stability, and bioavailability.

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/s/

EDWARD M COX
02/22/2013

Cross-Discipline Team Leader / Medical Officer Review

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| Date | February 1, 2013 |
| From | Benjamin Lorenz, MD |
| Subject | Cross-Discipline Team Leader Review Medical Officer Review |
| NDA/BLA # Supplement# | 022-407, R3 |
| Applicant | Theravance, Inc |
| Date of Submission | July 12, 2012 |
| PDUFA Goal Date | January 12, 2013 |
| Proprietary Name / Established (USAN) names | Vibativ (telavancin hydrochloride) |
| Dose forms / Strength | Sterile, lyophilized powder, 250 mg, 750 mg Recommended dose: 10 mg/kg IV every 24 hours |
| Proposed Indications(s) | Nosocomial pneumonia |
| Recommended: | Complete Response |

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1. Introduction

Vibativ[®] (telavancin for injection) was first approved on September 11, 2009 for use in 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), the Applicant conducted two Phase 3 trials (0015 and 0019, also referred to as the **A**ssessment of **T**elavancin for **H**ospital-acquired **P**neumonia or “ATTAIN” trials), which enrolled patients with NP 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, however, 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. 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.

On January 23, 2009, seeking approval of telavancin for the indication of NP, the Applicant submitted NDA 022-407 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 review division concluded 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 NP 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).

2. Background

2.1. 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. Like members of the glycopeptide class, telavancin appears to inhibit peptidoglycan synthesis and this activity may be enhanced, compared to vancomycin.

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.

2.2. 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).

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, 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 022-407 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. Due to this difference, 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.

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.

3. CMC/Device

According to evaluations of the Office of Compliance and ONDQA team, the current manufacturing facility for the VIBATIV drug product, (b) (4) (b) (4) in (b) (4) is not acceptable. Problems include microbial contamination and particulate matter. As of January 9, 2013, the current Establishment Evaluation System (EES) status for (b) (4) is "withhold".

(b) (4)

(b) (4) Certificates of analyses for release testing performed by (b) (4) on these two lots found that they met the release specifications when tested in November 2011. Violations reported at (b) (4) included deficiencies in sterility assurance. The third lot has been held and is being investigated due to (b) (4). Currently Theravance estimates that there are small amounts of residual quantities of telavancin in the supply chain. Assessments of whether other products manufactured at (b) (4) around the same time frame for intravenous administration, like telavancin, have been released and whether there have been any adverse events reported are underway. Telavancin remains indexed on the list of drugs in shortage, with remaining inventories dwindling, so information thus far has been limited.

In accordance with cGMP guidelines, the Applicant is required to demonstrate readiness for manufacturing; however, (b) (4) has ceased operation under consent decree. (b) (4) signed the consent decree with the FDA, and has been filed by the Department of Justice in federal court (b) (4). The remaining lots will likely fall under and be subject to the terms of the consent decree. Furthermore, although an initial assessment of the first batch at a new contract manufacturer, Hospira's McPherson facility in Kansas, is planned to be complete by mid-February, this site is not yet considered viable. Estimates for readiness to obtain approval for this manufacturing site may be somewhere between Q2 2013 and Q1 2014.

From a CMC standpoint, ONDQA does not recommend the approval of NDA 22-407 due to the Office of Compliance overall recommendation of withhold. Please refer to the chemistry review dated January 11, 2013 by Mark Seggel and Rapti Madurawe (ONDQA/DNDQA II/Branch V), including the attached EES for further details.

4. Nonclinical Pharmacology/Toxicology

There is no new nonclinical pharmacology/toxicology information provided in this submission.

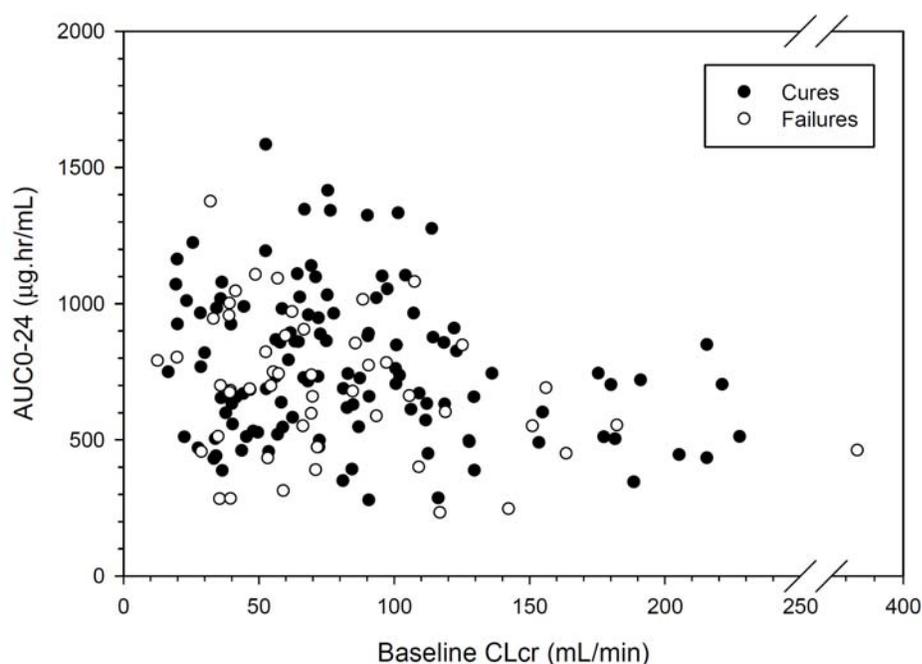
5. Clinical Pharmacology/Biopharmaceutics

Although no new clinical pharmacology information was submitted in this 12 July 2012 NDA resubmission, the Clinical Pharmacology team, Ryan Owen, Ph.D. and team leader, Kimberly Bergman, Pharm.D., reviewed the Applicant's proposed warning for use in patients with a CrCl <30 mL/min. The Applicant determined 30 mL/min due to the observation of increased mortality, and also provided clinical cure rates stratified by CrCl in order to justify an appropriate threshold for the purposes of providing a warning in the USPI. However, given the differing recommendations between the approved cSSSI (CrCl <50 mL/min) and the proposed nosocomial pneumonia (<50 mL/min)

indications, the Clinical Pharmacology analysis compared clinical outcomes as a function of exposure (in the PK subset) and baseline renal function.

The following figure (Figure 1) shows pooled PK and outcome data from Studies 0015 and 0019. AUC_{0-24} is shown on the y-axis and baseline renal function is shown on the x-axis. Clinical cures are indicated with dark circles, and clinical failures are indicated with open circles. For the purposes of this analysis, missing data were assigned as failures. There is no clear trend with respect to the relationship of baseline CrCl, the resulting telavancin exposure, and the ultimate clinical outcome. This assessment supports the Applicant's exploratory PK analysis showing no relationship between AUC_{0-24} and clinical cure or mortality.

Figure 1: Relationship between Baseline Renal Function and Telavancin Exposure Stratified by Clinical Outcome



CDTL comment: Please refer to Dr. Owen's Clinical Pharmacology review for full details. This analysis shows that the observations of increased mortality in NP trials, as well as observations of decreased clinical cure rates in cSSSI, do not appear to be a function of exposure, and that dosing adjustments as currently recommended in the label as well as the adjustments used in Studies 0015 and 0019, should appropriately and proportionately predict serum levels in patients with baseline renal impairment.

Due to the observation of reduced efficacy in patients with baseline renal impairment, one of the postmarketing commitments (PMC) with the approval of NDA 022-110 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 order to fulfill this PMC,

the Applicant submitted results of a Phase 1 open-label study to evaluate the effect of renal function on the biological activity of telavancin in May 2012. The study compared telavancin concentration in plasma obtained with a bioanalytical assay to results obtained with an antibiotic potency bioassay using serum samples obtained from subjects with normal renal function (estimated CrCl >80 mL/min), severe renal impairment (< 30 mL/min) and end-stage renal disease (ESRD) who were receiving hemodialysis. All 45 subjects (15 in each renal function group) received a single dose of 7.5 mg/kg telavancin and were followed for up to five days for safety assessments and determination of telavancin plasma concentration, serum antibiotic activity and hydroxypropyl-beta-cyclodextrin (HPβCD, an excipient and drug substance solubilizer) concentration. Conclusions from the results of the study suggest that there is no apparent effect of renal function on the biological activity of telavancin; however, clearance of HPβCD decreased with decreasing renal function. There was essentially no clearance of HPβCD in subjects with ESRD. Since cyclodextrins have previously been shown to have nephrotoxicity, and could potentially exacerbate acute and/or chronic renal insufficiency, the contribution of HPβCD in the excess mortality observed in Studies 0015 and 0019 in patients with moderate/severe renal impairment, but does not necessarily account for the observation of decreased clinical response in the cSSSI studies.

One issue raised in studies published this year, suggest that the mg/kg dose based on total body weight (TBW) rather than ideal body weight (IBW) adjustments, especially in the setting of renal impairment, may overestimate the dose needed for appropriate renal adjustment in patients with morbidly obese patients based on BMI. This is discussed further in Section 7 (Clinical Safety).

6. Clinical Microbiology

The Clinical Microbiology review, completed by Kerry Snow, is based largely on the original submission (23 January 2009). No additional clinical microbiology data or reports were included in later submissions.

The data provided by the Applicant support the proposed breakpoints for the susceptibility breakpoints for all pathogens included in the proposed indications.

In keeping with the AIDAC recommendation for a limited approval, the clinical microbiology review recommends that “*Streptococcus pneumoniae* should be removed from the proposed indications for telavancin for the treatment of nosocomial pneumonia, including ventilator-associated pneumonia (VAP)”.

CDTL/MO comment: *The following tables, summarize the baseline susceptibility of Gram-positive respiratory and blood pathogens (Table 1 and Table 2, respectively) for telavancin and vancomycin. Although approximately two-thirds of all S. aureus isolates were MRSA, the maximum vancomycin MIC from a S. aureus isolate was noted to be 2*

µg/mL, and, therefore, provides no information for efficacy in the treatment of NP caused by vancomycin-intermediate S. aureus (VISA, MIC = 4-8 µg/ml) or even vancomycin-resistant (VRSA, MIC ≥ 16 µg/ml) S. aureus with telavancin.

Table 1: Susceptibility of Gram-Positive Baseline Respiratory Pathogens to Telavancin and Vancomycin – MAT Analysis Set, Studies 0015 and 0019

| | Minimum Inhibitory Concentration (µg/mL) | | | | | | | |
|---|--|-------------------|-------------------|--------------|------------|-------------------|-------------------|---------------|
| | N | Telavancin | | | Vancomycin | | | |
| | | 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 |

Note: MIC90 values are not presented when sample size is less than 10

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

Table 2: Susceptibility of Gram-Positive Baseline Blood Pathogens to Telavancin and Vancomycin – MAT Analysis Set, Studies 0015 and 0019

| | Minimum Inhibitory Concentration (µg/mL) | | | | | | | |
|---|--|-------------------|-------------------|--------------|------------|-------------------|-------------------|-------------|
| | N | Telavancin | | | Vancomycin | | | |
| | | MIC ₅₀ | MIC ₉₀ | Range | N | MIC ₅₀ | MIC ₉₀ | Range |
| Organisms From Telavancin-treated Patients | | | | | | | | |
| STAPHYLOCOCCUS AUREUS | 29 | 0.25 | 0.5 | 0.12 - 0.5 | 29 | 1 | 1 | 0.5 - 2 |
| - MRSA | 16 | 0.5 | 0.5 | 0.12 - 0.5 | 16 | 1 | 1 | 0.5 - 2 |
| - MSSA | 13 | 0.25 | 0.5 | 0.12 - 0.5 | 13 | 0.5 | 1 | 0.5 - 1 |
| ENTEROCOCCUS FAECALIS | 5 | 1 | - | 0.5 - 1 | 5 | 2 | - | ≤ 0.5 - 2 |
| STREPTOCOCCUS PNEUMONIAE | 5 | 0.015 | - | 0.015 - 0.03 | 5 | 0.25 | - | 0.25 - 0.5 |
| Organisms from Vancomycin-treated Patients | | | | | | | | |
| STAPHYLOCOCCUS AUREUS | 34 | 0.5 | 0.5 | 0.06 - 1 | 34 | 1 | 1 | 0.5 - 2 |
| - MRSA | 24 | 0.5 | 0.5 | 0.06 - 1 | 24 | 1 | 1 | 0.5 - 2 |
| - MSSA | 10 | 0.25 | 0.5 | 0.12 - 0.5 | 10 | 1 | 1 | 0.5 - 1 |
| ENTEROCOCCUS FAECALIS | 4 | 1 | - | 0.5 - 1 | 4 | 1 | - | ≤ 0.5 - 1 |
| ENTEROCOCCUS FAECIUM | 2 | 0.5 | - | 0.12 - 0.5 | 2 | 64 | - | ≤ 0.5 - 128 |
| STREPTOCOCCUS PNEUMONIAE | 3 | 0.015 | - | 0.015 - 0.03 | 3 | 0.25 | - | 0.25 - 0.25 |

Note: MIC90 values are not presented when sample size is less than 10

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

7. Clinical/Statistical—Efficacy

During the second cycle review, the Division was unable to conclude that there was substantial evidence of efficacy, despite the substantial amount of missing mortality data that had been recovered for Studies 0015 and 0019. In the CR letter dated December 21, 2010, the reasons for taking this action were as follows: For the population of interest (i.e. patients with nosocomial pneumonia caused by Gram-positive bacteria), in Study 0015 did not demonstrate noninferiority of 28-day all-cause mortality with telavancin relative to vancomycin (as shown in the following table, Table 3). When the same analysis population was assessed in Study 0019, the observed treatment difference was 2.0% (telavancin: 24.3%; vancomycin: 22.3%) and the upper bound of the 95% CI is 10.0%, (-6.1%, 10.0%), and did not provide sufficient evidence for the noninferiority of telavancin to vancomycin.

Table 3: Estimated 28-Day All-Cause Mortality – Studies 0015 and 0019, MAT Population Excluding Patients with only Gram-Negative Pathogens Isolated at Baseline

| Study | Treatment | Estimated K-M Mortality at 28 Days (%) | Difference (%) (TLV – VAN) 95% CI |
|-------|-----------|--|-----------------------------------|
| 0015 | TLV | 28.7 | 4.4 |
| | VAN | 24.3 | (-4.7, 13.5) |
| 0019 | TLV | 24.3 | 2.0 |
| | VAN | 22.3 | (-6.1, 10.0) |

Lost to follow-up and deaths occurring after Day 28 are censored
Source: Statistical Reviewer

The Division also expressed concern regarding the appropriateness of pooling of patients across the two Phase 3 trials because subjects in study 0015 had more potential risk factors for mortality (e.g., diabetes mellitus and renal impairment/failure) than the subjects in study 0019. Additionally, the diagnosis of renal failure was left to the discretion of the investigator, and in some cases it was unclear whether some of the patients may have had acute as well as chronic renal failure.

As discussed in Section 2.2, this third cycle review addresses issues enumerated in the Division's CR letter and, in the process of the discussion leading to the meeting of the AIDAC, additional post hoc analyses that have been conducted. Although the Agency prefers to use all-cause mortality as the primary endpoint, this review will make use of all the available data to determine whether the benefits of telavancin outweigh its risks in the treatment of HABP/VABP.

7.1. Statistical Analysis Plan

7.1.1. Objectives

Original Study Objectives

The primary objective of these studies, as stated in the protocol, was as follows:

- To compare the efficacy and safety of telavancin with vancomycin in the treatment of adults with Gram-positive HAP with an emphasis on patients with infections due to MRSA

A key secondary objective of these studies, as stated in the protocol, was as follows:

- To pool the data from these studies and assess the superiority of telavancin to vancomycin in patients with MRSA infections

Post-Hoc Objectives

The primary objective of the post-hoc analyses was to demonstrate the noninferiority of telavancin to vancomycin in the treatment, with respect to all-cause mortality, for patients with hospital acquired pneumonia, by ATS/IDSA criteria.

Secondary objectives included the following.

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

7.1.2. Endpoints

Primary Endpoint

- The primary endpoint is all-cause mortality evaluated at Day 28

Secondary Endpoints

- Clinical response at Follow-up (TOC) visit
- By-pathogen clinical response at the Follow-up (TOC) visit
- MRSA-specific clinical response at the Follow-up (TOC) visit
- By-MIC clinical response at the Follow-up (TOC) visit

7.1.3. Analysis Sets

Patients who were randomized but did not receive any study medication were not included in the efficacy analyses. Four analysis sets were prospectively defined for efficacy-related summaries. In all four analysis sets, patients were grouped according to the treatment to which they were randomized. Descriptions and samples sizes are shown in the following table (Table 4).

Table 4: Sample Sizes of Prospectively Defined Analysis Sets

| Abbreviation | Description | Sample Size |
|--------------|--|--------------|
| AT | All subjects who received any amount of study medication | 1503 (100%) |
| CE | Subjects in the AT population who adhered to the protocol | 654 (43.5%) |
| MAT | Subjects in the AT population who also had a baseline pathogen identified from baseline respiratory cultures known to cause pneumonia. | 1089 (72.5%) |
| ME | Subjects in the CE Population who also had a Gram-positive baseline respiratory pathogen. | 480 (31.9%) |

Source: NDA-022-407, 2.5 Clinical Overview, v3.0, Table 6

CDTL/MO comment: *In this reviewer’s opinion, the primary analysis set should be defined as patients in the MAT population who had at least one Gram-positive organism identified (which may include patients with mixed infections, but excludes those with Gram-negative only). This would be equivalent to the microbiologic ITT or per the Applicant’s terminology: the “Per Protocol (PP)” analysis set. Using the ATS/IDSA guidelines, however, can serve as an exploratory analysis in order to demonstrate activity in a patient population more likely to have the disease being studied (NP). Ideally these populations should not vary significantly from the pre-specified analysis sets. The PP (Gram-positive) population, however, minimizes the potential introduction of bias with post hoc subgroup analysis. Furthermore, inclusion of patients who had only Gram-negative isolates could confound the drug effect of the telavancin due to the adjunctive therapy given and potentially bias the results toward falsely concluding noninferiority.*

The Applicant also included additional post-hoc analysis sets, which are summarized in Table 5.

Table 5: Sample Sizes of Post-Hoc Defined Analysis Sets

| Abbreviation | Description | Sample Size |
|----------------|--|--------------|
| AT-ATS/IDSA | Patients in the AT set who met ATS/IDSA criteria | 1289 (85.5%) |
| MAT-ATS/IDSA | Patients in the MAT set who met ATS/IDSA criteria | 951 (63.3%) |
| PP | Patients in the MAT set who had at least one Gram+ baseline respiratory pathogen (may include mixed infections) | 797 (53.0%) |
| PP-ATS/IDSA | Patients in the PP set who met ATS/IDSA criteria | 694 (46.2%) |
| PP2-ATS/IDSA | Patients in the PP-ATS/IDSA set who had a reliable respiratory sample and CrCl ≥ 30 mL/min | 553 (36.8%) |
| MPP | Patients with only Gram+ baseline respiratory pathogens | 527 (35.1%) |
| MPP-ATS/IDSA | Patients in the MPP set who met ATS/IDSA criteria | 449 (29.9%) |
| MRSA | Patients who had MRSA identified as at least one baseline respiratory pathogen (may include mixed) | 464 (30.9%) |
| MRSA-ATS/IDSA | Patients in the MRSA set who met ATS/IDSA criteria | 400 (26.6%) |
| MMRSA | Patients with only MRSA isolated as a respiratory pathogen | 295 (19.6%) |
| MMRSA-ATS/IDSA | Patients in the MMRSA set who met ATS/IDSA criteria | 245 (16.3%) |

Source: NDA-022-407, 2.5 Clinical Overview, v3.0, Table 7

The primary analysis set defined for the post-hoc analysis was as follows:

- **All-Treated ATS/IDSA (AT-ATS/IDSA):** Patients in the AT analysis set who met ATS/IDSA pneumonia criteria.

The target analysis set, also defined post-hoc:

- **PP2-ATS/IDSA:** The PP2-ATS/IDSA analysis set, which the Applicant suggested should be the “target” analysis set, was defined as the population that comprised of patients with a baseline pathogen isolated from a reliable respiratory sample, met the ATS/IDSA criteria and excludes patients with baseline moderate to severe renal impairment (CrCl ≥ 30 mL/min).

7.2. Clinical Response

For all patients randomized into the studies, a Follow-up Visit was to be conducted 7 to 14 days after the last dose of study medication. For a clinical outcome for all patients in the AT analysis set a blinded test-of-cure (TOC) assessment was conducted only for those patients who were evaluated as a clinical cure or indeterminate at the EOT Visit.

For purposes of analysis, a clinical response of failure at EOT was extrapolated to the TOC evaluation. The investigator was to assess the patient’s clinical response at TOC as cure, failure, or indeterminate defined as follows:

- Failure: At least one of the following:
 - Relapsed pneumonia with the same Gram-positive organism after termination of study medication
 - Death after the end of study medication therapy attributable to primary infection (i.e., pneumonia) (as judged by the investigator)
- Cure:
 - Signs and symptoms of pneumonia resolved, and
 - Baseline radiographic findings improved or did not progress (see below)
- Indeterminate: Inability to determine outcome

Of note, failures at EOT were carried forward to TOC.

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

Table 6: Clinical Response at TOC

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

*95% CI calculated based on Agresti-Caffo method
Source: NDA 22-407, Summary of Clinical Efficacy, v3.0, Table 57

CDTL/MO comment: As Dr. Scott Komo discusses in his statistical review, there is still concern about the validity and reliability of the clinical cure endpoint. 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, Dr. Komo identified patients who were considered clinical cures at the TOC assessment but subsequently died by

Day 28. As defined, 33 patients, whom the investigator classified as clinical cures at the TOC assessment, died within 28 days. More details of these patients by study are shown in Table 7. Many of the deaths in the assigned as “cure” group occurred in close temporal proximity to the TOC assessment. Although these TOC assessments of “failure” by the investigator were meant to be assigned if subsequent death was attributable to primary infection, many of the deaths could not be ruled out as infection-related.

Table 7: Clinical Cures at TOC and Deaths by Day 28

| | Pooled | | Study 0015 | | Study 0019 | |
|--|----------------|----------------|----------------|----------------|----------------|----------------|
| | TLV (N=749) | VAN (N=754) | TLV (N=372) | VAN (N=374) | TLV (N=377) | VAN (N=380) |
| Subjects who died before Day 28 | 178 (24%) | 164 (22%) | 95 (26%) | 74 (20%) | 83 (22%) | 90 (24%) |
| Subjects with cure at TOC | 441 (59%) | 449 (60%) | 214 (58%) | 221 (59%) | 227 (60%) | 228 (60%) |
| Subjects with Cure at TOC but died before Day 28 | 17 | 16 | 11 | 5 | 6 | 11 |

Source: Statistical Reviewer

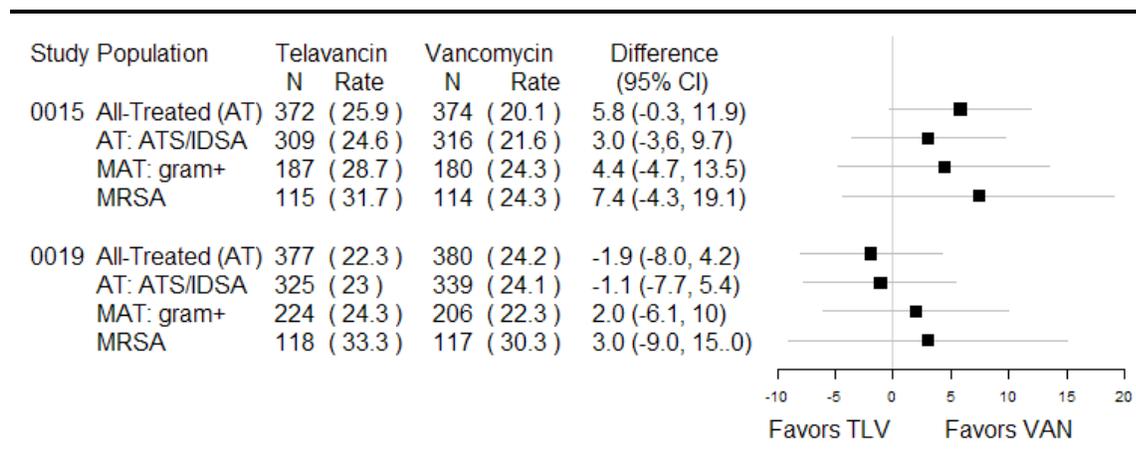
CDTL/MO Comment: *The interpretation of the results based on clinical response as described in Table 6 and Table 7 is limited as we have not been able to justify a noninferiority margin for the endpoint of clinical response based on the historical literature. In addition, there are concerns regarding 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.*

7.3. Mortality

The 28-day all-cause mortality results for the AT and the Agency-defined primary analysis population (patients in the MAT set who had at least one Gram-positive pathogen isolated at baseline, or the PP analysis set, as defined by the Applicant) are presented 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%. In the MAT-Gram+ population (or the PP analysis set), the estimated mortality rate difference in Study 0015 is 4.4% (telavancin: 28.7%; vancomycin: 24.3%) with the corresponding upper bound of 95% CI of at 13.5%, which is higher than a non-inferiority margin of 10%. For Study

0019, estimated mortality rate difference is 2.0% (telavancin: 24.3%; vancomycin: 22.3%) with the corresponding upper bound of 95% CI of at 10.0%.

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

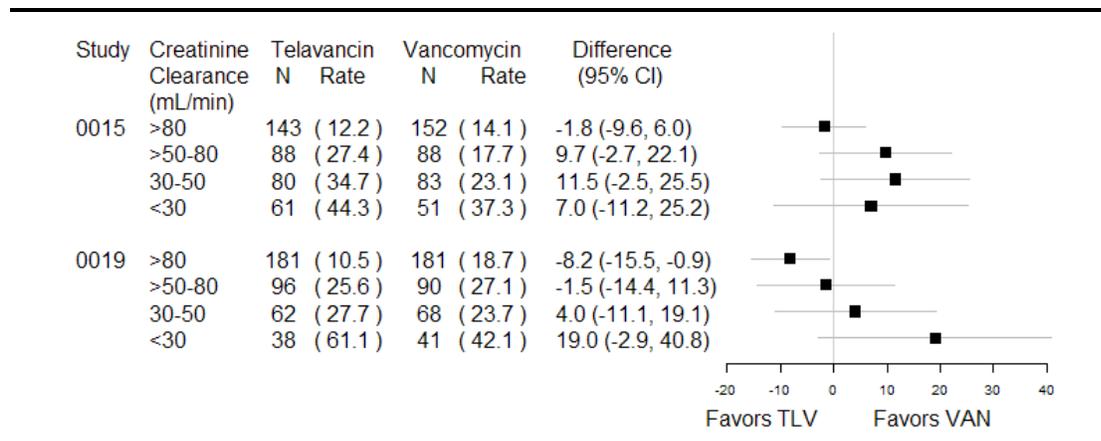


Source: Statistics Reviewer

7.4. Outcomes by Special Patient Populations

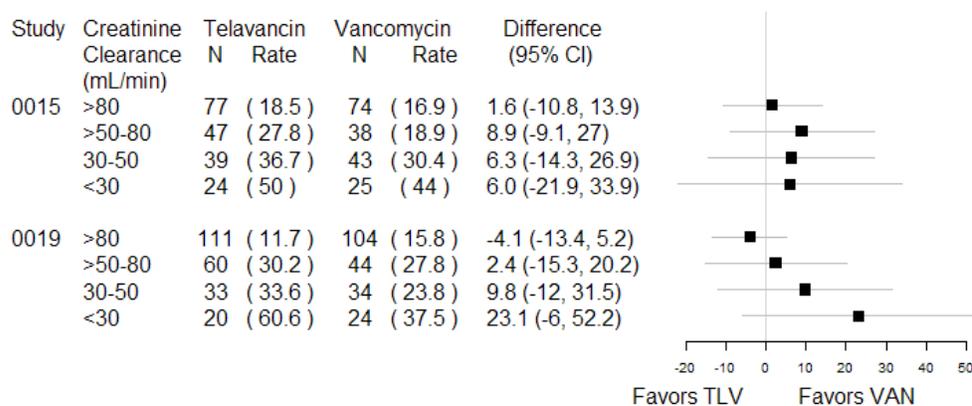
Exploratory analyses have been conducted and shown here to determine what potential effect modifiers may play a role in the observations of decreased mortality in patients treated with telavancin. Approximately one third of each treatment group had moderate to severe renal impairment. In an effort to examine the Applicant’s proposal to include a warning in the label for use when patients have a CrCl < 30 mL/min, as opposed to the cSSSI indication which warns against decreased efficacy in patients with a CrCl < 50 mL/min, the following figures (Figure 3 and Figure 4) show mortality in the AT and PP analysis sets, respectively, as stratified by baseline CrCl estimates.

Figure 3: 28-Day Mortality (K-M estimates) Stratified by Baseline CrCl (AT set)



Source: Statistics Reviewer

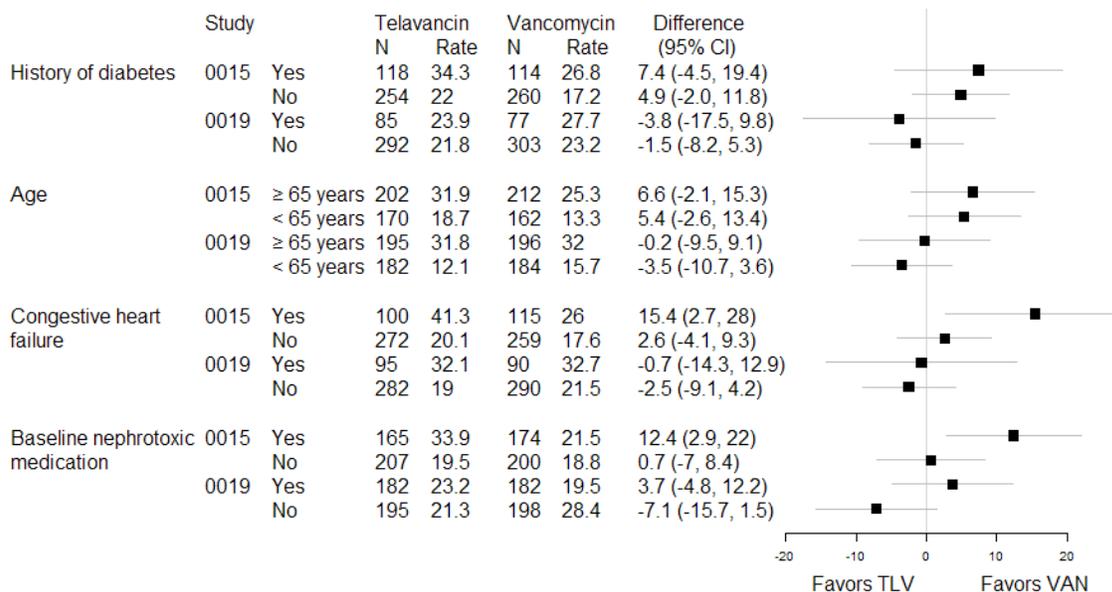
Figure 4: 28-Day Mortality (K-M estimates) Stratified by Baseline CrCl (PP set)



Source: Statistics Reviewer

The following figure, Figure 5, describes mortality by other risk factors that may also affect renal injury.

Figure 5: 28-Day All-Cause Mortality — Other Risk Factors for Renal Injury (AT set)



Source: Statistics Reviewer

CDTL/MO Comments: Much of the risk associated with these factors, diabetes, age ≥65, CHF and baseline use of other nephrotoxic medications, appear to have had the greatest impact in Study 0015 (in fact, the association of mortality was statistically significant with CHF and use of other nephrotoxic medications). Although statistical significance was not shown for any of these factors in Study 0019, higher relative mortality with telavancin compared to vancomycin was still concerning for age ≥65, CHF and nephrotoxic medications.

The following table, Table 8, summarizes a sensitivity analysis of mortality data in order to account for the potential outcomes of the missing mortality data (after recovery). The two patient populations presented are the AT and PP (MAT with at least one Gram-positive organism identified), and censored patients were either classified as alive or dead.

Table 8: Sensitivity Analysis: Mortality of Censored Patients Classified as Alive or Dead

| | Study 0015 | | | Study 0019 | | |
|-----------------------|----------------|----------------|------------------------|----------------|----------------|------------------------|
| | TLV | VAN | Difference (95% CI) | TLV | VAN | Difference (95% CI) |
| Missing: Alive | | | | | | |
| AT | 25.5% n=372 | 19.8% n=374 | 5.8% (-0.2%, 11.7%) | 22.0% n=377 | 23.7% n=380 | -1.7% (-7.6%, 4.3%) |
| PP | 28.3% n=187 | 23.9% n=180 | 4.5% (-4.5%, 13.4%) | 24.1% n=224 | 21.8% n=206 | 2.3% (-5.7%, 10.2%) |
| Missing: Dead | | | | | | |
| AT | 30.6% n=372 | 27.0% n=374 | 3.6% (-2.9%, 10.1%) | 26.3% n=377 | 28.4% n=380 | -2.2% (-8.5%, 4.2%) |
| PP | 31.6% n=187 | 31.1% n=180 | 0.4% (-9.1%, 9.9%) | 27.7% n=224 | 27.7% n=206 | <0.1% (-8.5%, 8.5%) |

Source: ISE, v2.0, Supporting Table 167 and 169

CDTL/MO Comments: *Regardless of patient population or whether all missing patients were considered alive or dead, the upper bound of the 95% CI in Study 0015 was above or barely within (in the PP set, when censored patients were classified as dead, the upper bound was 9.9%) the 10% non-inferiority margin. The caveat in the interpretation of this analysis, however, is that applying the same classification to missing patients in both study groups assumes that mortality in each group are equivalent for all missing patients and drives the conclusions toward the finding of non-inferiority. There still remains concern, however, that in Study 0015, telavancin did not provide a survival benefit when compared to vancomycin.*

Further analysis of mortality as a safety endpoint will be discussed in the next section (Section 8). Please also refer to Dr. Komo's statistical review for more details regarding his discussion of the analysis of efficacy.

8. Safety

Alfred Sorbello DO, MPH completed the safety review of the original submission of NDA 022-407. He highlighted concerns regarding the imbalance in mortality in Study 0015 with more deaths occurring in the telavancin treatment group (although this finding was based on incomplete mortality data). Additionally, nephrotoxicity was noted as the most significant safety issue for telavancin in NDA 022-110 reviews and was reflected in the currently approved label. Dr. Janice Pohlman reviewed safety as part of the review for the second-cycle submission. For additional details, please refer to Dr. Sorbello's

primary safety review of NDA 022-407 and Dr. Pohlman’s December 20, 2010 second-cycle safety review.

This safety review will cover: (1) additional mortality analyses in the safety population, with a focus on a risk/benefit determination, specifically in the setting of baseline renal insufficiency, (2) post-marketing experience since the review of the second-cycle submission, and (3) a review of current literature regarding current prescribing practices and safety investigations of telavancin.

8.1. Additional Mortality Analysis

Revisiting the concerns from the second-cycle review in this current submission, now with both recovery of mortality and a computation of baseline renal function (creatinine clearance) for all patients, the Applicant submitted their justification for labeling with the following observation that in the NP studies: “higher mortality rates and lower cure rates in patients with preexisting severe renal impairment treated with telavancin relative to vancomycin have been observed.”

As noted in Dr. Pohlman’s second-cycle safety review, acute renal failure (ARF) at baseline was the only variable that showed an interaction with treatment. However, in Studies 0015 and 0019, there was no prespecified definition for acute renal failure and the diagnosis was left to the discretion of the investigator.

Table 9: Kaplan-Meier estimates of 28-Day All-Cause Mortality by Acute Renal Failure at Baseline* — AT Population

| ARF at Baseline | Study 0015 | | | Study 0019 | | |
|-----------------|--|------|------------------------------|--|------|-------------------------------|
| | Estimated K-M Mortality at 28 Days (%) | | Difference %TLV-VAN (95% CI) | Estimated K-M Mortality at 28 Days (%) | | Difference % TLV-VAN (95% CI) |
| | TLV | VAN | | TLV | VAN | |
| YES | 51.2 | 22.9 | 28 (7.9, 48.7) | 65.1 | 44.8 | 20.3 (-4.8, 45.3) |
| NO | 22.5 | 19.8 | 2.7 (-3.6, 8.9) | 18.8 | 22.2 | -3.4 (-9.5, 2.6) |

FDA Statistician Table, *(ARF) as determined by the Investigator

Although the increase in mortality associated with telavancin compared to vancomycin in the setting of ARF was statistically significant in Study 0015, the definition of ARF lacked standardization, since the diagnosis of ARF was left to the discretion of the investigator and involved only checking a box on the case report form. It is unclear whether some of these patients may have had acute on top of chronic renal failure.

In addition to exploratory pharmacometric analyses (to correlate exposure levels in patients with NP who were cured at TOC and patients who were not—please refer to Section 5: review of Clinical Pharmacology/Biopharmaceutics), the Applicant also presented analyses of clinical cure rates and 28-day all-cause mortality according to initial dose of study medication and baseline creatinine clearance. The Applicant’s

analysis led them to propose the following warning in association with the NP indication:

(b) (4)

The arrival of this population of patients, in whom the maximal benefit in terms of clinical response and survival would demonstrate the lowest risk, was derived from a targeted analysis set (the PP2-ATS/IDSA) in which patients had a reliable respiratory sample with at least Gram-positive baseline pathogen isolated.

MO/CDTL Comment: For the purposes of this review and in the opinion of this reviewer, the determination of an appropriate CrCl rate, below which a benefit/risk threshold can be justified, should be derived from the as-treated safety population. Exploratory analyses have been conducted in special patient populations elsewhere (please refer to the review by Dr. Scott Komo and Section 7 of this review) for the purposes of demonstrating a treatment effect, but for this safety review, mortality will be considered only as a safety endpoint without inferential testing.

Table 10: 28-Day Mortality* by CKD Stage – As Treated Safety Population

| CrCl (mL/min) | Study 0015 | | Study 0019 | | Total | |
|---------------|-------------------|-------------------|-------------------|-------------------|---------------------------|---------------------------|
| | TLV N=372 | VAN N=374 | TLV N=379 | VAN N=378 | TLV N=751 | VAN N=752 |
| ≥60 | 28/196 (14.3%) | 31/207 (15.0%) | 34/250 (13.6%) | 48/244 (19.7%) | 62/446 (13.9%) | 79/451 (17.5%) |
| <60 | 67/176 (38.1%) | 43/167 (25.7%) | 50/129 (38.8%) | 41/134 (30.6%) | 117/305 (38.4%) | 84/301 (27.9%) |
| ≥50 | 41/231 (17.7%) | 36/240 (15.0%) | 45/279 (16.1%) | 56/270 (20.7%) | 86/510 (16.9%) | 92/510 (18.0%) |
| <50 | 54/141 (38.3%) | 38/134 (28.4%) | 39/100 (39.0%) | 33/108 (30.6%) | 93/241 (38.6%) | 71/242 (29.3%) |
| ≥30 | 68/311 (21.9%) | 55/323 (17.0%) | 61/341 (17.9%) | 72/337 (21.4%) | 129/652 (19.8%) | 127/660 (19.2%) |
| <30 | 27/61 (44.3%) | 19/51 (37.3%) | 23/38 (60.5%) | 17/41 (41.5%) | 50/99 (50.5%) | 36/92 (39.1%) |

*observed mortality only, missing patients (5.6% of total population) imputed as survivors

The table above, Table 10, shows all-cause mortality by baseline CrCl in the as-treated safety population. The cutoff values of 30 and 60 mL/min were chosen to correlate with the criteria for established for staging chronic kidney disease. The cutoff value of 50 mL/min was chosen because this is the value, below which dosing modification is recommended in the current label. The same dosing modifications were used in the ATTAIN trials. For patients with CrCl estimates under 60, 50 and 30 mL/min, the differences between overall mortality rates (both studies combined) of the telavancin and vancomycin treatment groups were: 10.5%, 9.3% and 11.4%, respectively. Based on these three thresholds, the survival advantage of vancomycin was maintained across

each cutoff point, and there does not appear to be a particular CrCl rate under which the differences between telavancin and vancomycin expand. However, mortality rates in the telavancin are as high as 60.5% in Study 0019 among patients with baseline CrCl of 30 mL/min. In comparison, the overall mortality rate, as demonstrated in the all-treated telavancin population was 24.1%.

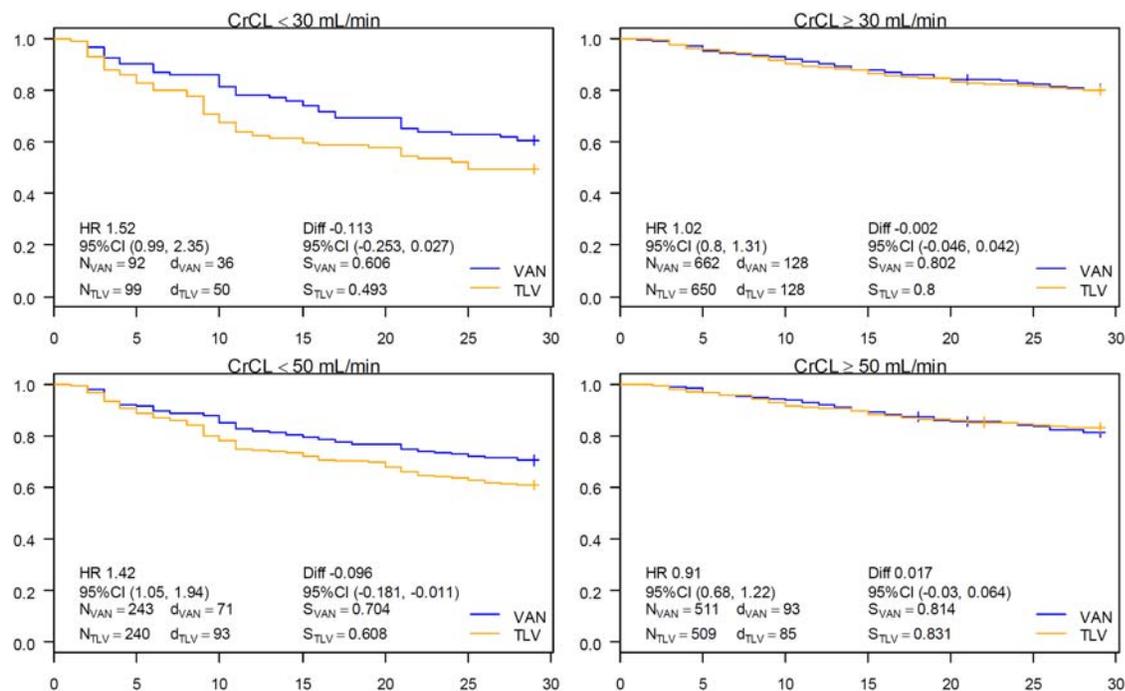
MO/CDTL Comment: *As previously mentioned, this analysis was not meant to account for other factors that may increase mortality risk, but does show a consistent effect at any degree of baseline renal impairment upon mortality.*

The following figures, ***MO/CDTL Comment:*** *These curves demonstrate substantially higher mortality in the telavancin groups of patients with CrCL <30 mL/min, <50 mL, as well as the following strata: 30-50 mL/min and 50-80 mL/min.*

Figure 6 and Figure 7, are from the Applicant's supporting analysis of Kaplan-Meier survival curves by creatinine clearance.

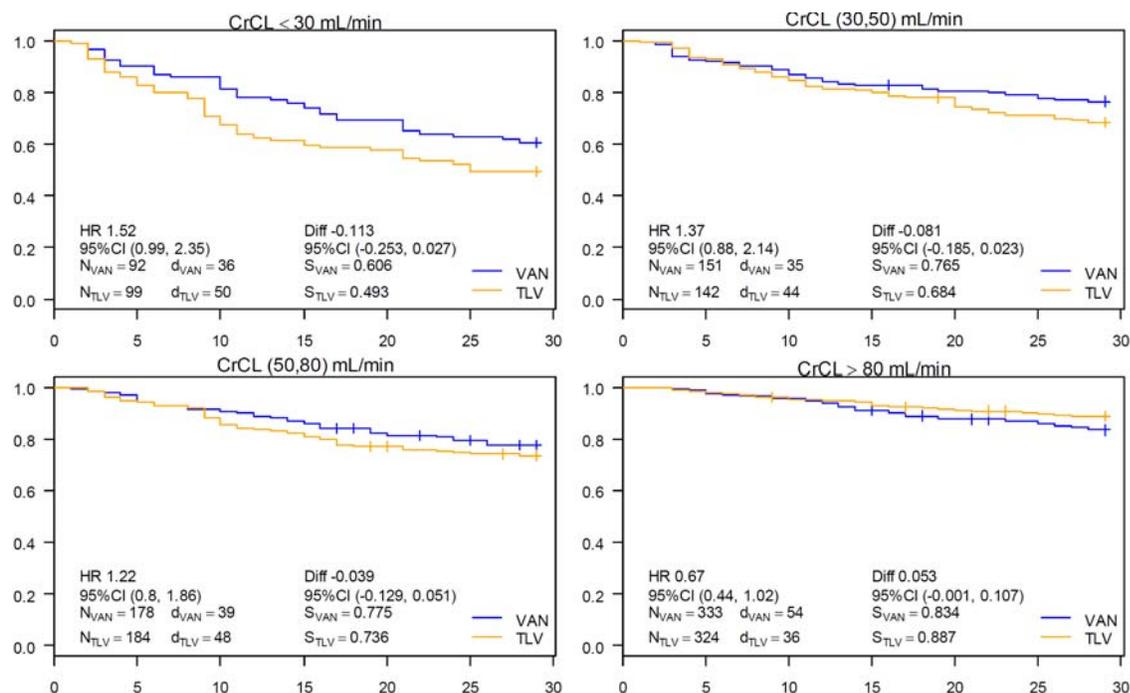
MO/CDTL Comment: *These curves demonstrate substantially higher mortality in the telavancin groups of patients with CrCL <30 mL/min, <50 mL, as well as the following strata: 30-50 mL/min and 50-80 mL/min.*

Figure 6: Kaplan-Meier Survival Curves by CrCL (Part 1) – AT Analysis Set



Source: Supporting figure 13 (ISE, Version 2.0, 28JUN2012)

Figure 7: Kaplan-Meier Survival Curves by CrCL (Part 2) – AT Analysis Set



Source: Supporting figure 14 (ISE, Version 2.0, 28JUN2012)

8.2. Post-Marketing Experience

MedWatch submissions for spontaneous reports for marketed product have been submitted under the NDA 022-110 (in parallel to NDA 022-407) throughout the NDA review period. Of note, however, Vibativ has been on a voluntary distribution hold since mid-November 2011 owing to manufacturing difficulties at the contract drug product manufacturer, which have been discussed in Section 3. This distribution hold has limited drug product availability since, and as a result little new safety data has been spontaneously reported since late 2011. Also, during this reporting period Astellas USA transferred responsibility for marketing to Theravance on 31 Mar 2012.

Periodic Safety Update Reports (PSURs) were submitted on 10 May 2012 and 10 November 2012. Approved NDA 22-110 was last updated with a Periodic Adverse Drug Experience Report (PADER) on 10 April 2012. The following table, Table 11, summarizes the estimated cumulative market experience to date.

Table 11: Cumulative Market Experience Exposure

| PSUR | Period | Patient-Years |
|------|----------------------------|---------------|
| 1 | 11-Sep-2009 to 10-Mar-2010 | 1,009 |
| 2 | 11-Mar-2010 to 11-Sep-2010 | 496 |
| 3 | 12-Sep-2010 to 11-Mar-2011 | 1,406 |
| 4 | 12-Mar-2011 to 11-Sep-2011 | 1,868 |
| 5 | 12-Sep-2011 to 11-Mar-2012 | 119 |
| 6 | 12-Mar-2012 to 11-Sep-2012 | 0 |
| | Total | 4,898 |

PSUR #5: Two deaths were reported during this review period:

Case ID # 2012US001833: a female of unknown age who suffered from acute lymphocytic leukemia (ALL). A pharmacist reported that the patient had developed MDR and subsequently died while on telavancin therapy. Causality was not assessed and time lines were not reported.

MO Comment: *Due to lack of additional information, causality can not be determined.*

Case ID #2012US002502: (unknown age/gender) Patient had a baseline creatinine of 2.1 mg/dL. After 5 days on telavancin for sepsis, creatinine increased to 3.4 mg/dL. Patient died (b) (6) after initiation of hemodialysis. Potential confounders: chronic kidney disease, diabetes, IV contrast dye, supratherapeutic vancomycin levels.

MO Comment: *In spite of a number of potential concomitant comorbidities and receipt of other potentially nephrotoxic drug in addition to telavancin, there remains a probable contributory effect of telavancin to this patient's progression of renal failure and subsequent death.*

Targeted medical events: During this reporting period, in the SOC “blood and lymphatic system disorders”, there was one report of thrombocytopenia and one report of platelets decreased. In the SOC “cardiac disorders”, there was one case of ventricular tachycardia. In the SOC “renal and urinary disorders” there were 12 cases, including acute renal failure (8), renal failure (2), renal impairment (1) and tubulointerstitial nephritis (1). Also, in the SOC “investigations” without renal events, 4 cases of “blood creatinine increased” were reported.

PSUR #6: During this reporting period there was one case with fatal outcome:

Case ID #2012000265: (US) a 43 y/o female who suffered from acute myeloid leukemia (AML). She was hospitalized (b) (6) for induction chemotherapy with idarubicin and cytarabine. Her course was complicated by pancytopenia, pneumonia and a partial SBO. Her RML pneumonia was presumed bacterial or fungal of etiology. She received telavancin on 19 July 2012 (one dose) after a culture revealed a vancomycin-resistant *Enterococcus faecium*. She was then transferred to a palliative care unit for pain management and failure to respond to chemotherapy. The Investigator assessed the patient’s death as not related to telavancin.

MO Comment: *This reviewer agrees with the Investigator’s assessment. The refractory hematologic abnormalities and fatal outcome were most likely attributable to the chemotherapy and progression of her AML.*

8.3. Literature Review

In a review of recent literature regarding telavancin, the following articles were retrieved:

- Twilla JD, Gelfand MS, Cleveland KO, Utery JB. Telavancin for the treatment of methicillin-resistant *Staphylococcus aureus* osteomyelitis. *J Antimicrob Chemother.* 2011; 66:2675-7.

This was a case series of four patients with MRSA osteomyelitis who failed standard vancomycin therapy and were successfully retreated with telavancin and surgical intervention. In one of these patients, serum creatinine levels increase during treatment. This patient had several episodes of MRSA bacteremia with MRI evidence of discitis, T8-9 osteomyelitis, and an extensive paravertebral phlegmon with cord compromise. By the fourth episode of bacteremia, the daptomycin MIC had increased to 4 mg/L. Vancomycin and linezolid MICs were 2 mg/L and 0.5 mg/L, respectively. After laminectomy and evacuation telavancin 10 mg/kg IV daily was begun. After 4 weeks, there was noted to be a rise in serum creatinine to 2.5 mg/dL and development of eosinophiluria. Therapy was changed to tigecycline 50 mg IV every 12hr. Subsequent to 5 weeks of antibiotic therapy, the spine was stabilized with pedicle screws and rods. Post-operatively the patient received 2 weeks of tigecycline followed by 2 weeks of

linezolid 600 mg orally twice daily, had improvement of the serum creatinine to 1.5 mg/dL and demonstrated no evidence of recurrence 1 month after completing therapy.

- Marcos LA, *et al.* Acute renal insufficiency during telavancin therapy in clinical practice. *J Antimicrob Chemother.* 2012; 67: 723-6.

This was a retrospective cohort study from 1 September 2009 to 1 December 2010 that included 21 adult patients who received at least three doses of telavancin at the Barnes-Jewish Hospital in St. Louis. These appear to also represent patients who were reported to the FDA through MedWatch and included in my 15 July 2011 safety review for NDA 022-110 (cSSSI indication). Seven of 21 patients (33%) developed acute renal insufficiency during therapy. Patients who developed acute renal insufficiency had a mean GFR reduction of 56 mL/min/1.73 m². In the univariate analysis, high body mass index (BMI) (p=0.025), use of intravenous contrast dye (p=0.017) and prior serum vancomycin trough levels >20 mg/L (p=0.017) were associated with developing acute renal insufficiency. Two patients required hemodialysis; two had persistent renal insufficiency.

The authors found the association of higher BMI with development of acute renal insufficiency is “intriguing, since telavancin dosing is calculated based on actual body weight rather than ideal body weight. This association needs to be studied further in larger studies before any recommendations can be made on dosing of telavancin in patients with higher BMI.”

- Pai MP. *J Antimicrob Chemother.* 2012; 67: 1300-3.

In a comment to the authors of the study mentioned above, “the dosage of telavancin is based on total body weight (TBW), but the [CrCl] value used to adjust its dose is estimated using the Cockcroft–Gault equation with ideal body weight (IBW). Marcos *et al.* indicated that the telavancin dose was based on the estimated [CrCl] using the Cockcroft–Gault equation and TBW, which is inconsistent with the telavancin product label. This is an important distinction because TBW overestimates kidney function, while IBW underestimates kidney function in patients with a high BMI.”

Marcos clarified that patients received the adjusted dose of telavancin according to CrCl calculated using IBW, not TBW, and none was overdosed with telavancin for their degree of renal function based on label recommendations.

MO/CDTL comment: *As discussed in Section 5 (Clinical Pharmacology) and the Clinical Pharmacology review for NDA 022-110, there did not appear to be any clinically relevant differences observed in the PK of telavancin in obese patients (BMI >35) and non-obese patients (BMI <35). Also in the analysis presented above from this NDA (022-407), there was no correlation between exposure level using this CrCl formula and either clinical cure.*

It should be noted that the approved label also specifies IBW in the Cockcroft-Gault calculation, but only does so in section 12.3. Section 12.3 of the approved label also specifies how IBW was calculated. The Applicant's proposed label provides more detail regarding the IBW and the Cockcroft-Gault calculation in the Highlights section and Section 2.3, Patients with Renal Impairment.

The following table, Table 12, presents an analysis of the exposure rates of patients in the PK subset. Exposure of telavancin is somewhat higher in morbidly obese patients, but is consistent across renal function groups. The range of exposures in the obese and renally impaired population falls entirely within the range of the obese and non-renally impaired population. This is consistent with the analysis in the pharmacometric review by Hao Zhu, Ph.D. of NDA 022-110, which concluded that "No clinically relevant differences were observed in the pharmacokinetics of telavancin in obese subjects, defined as subjects with BMI of 35 or greater and non-obese subjects, BMI of less than 35."

Table 12: Mean AUC₀₋₂₄ by different populations within the PK subset (combined data from Studies 0015 and 0019)

| Population within the PK subset N = 168 | AUC ₀₋₂₄ All Baseline Renal Mean (SD) [min, max] | AUC ₀₋₂₄ >50 mL/min at baseline only [min, max] | AUC ₀₋₂₄ <50 mL/min at baseline only [min, max] |
|--|--|---|---|
| Morbidly Obese (>35 BMI) N = 18 | 958.2 (228.8) [347, 1343] | 932.3 (252.2) [347, 1343] | 1048 (72.8) [981, 1160] |
| <35 BMI Only N = 150 | 717.5 (258.6) [230, 1582] | 717.1 (260.6) [230, 1582] | 718.4 (256.6) [281, 1373] |
| All PK subset patients N = 168 | 743.3 (265.6) [230, 1582] | 742.0 (267.7) [230, 1582] | 746.5 (263.2) [281, 1373] |

Of note, the Applicant stated, that: "there is a trend to higher mortality with doses of telavancin that are higher than protocol-recommended. This deserves further exploration as it is likely multifactorial" (page 292, Integrated Summary of Effectiveness NDA 22-407, Version 2.0, 28 June 2012)

Table 13: K-M Estimates of Mortality by BMI and Creatinine Clearance – AT Safety Population)

| | Telavancin | | Vancomycin | |
|-------------------|------------------|------------------|------------------|------------------|
| | CrCl (ml/min) | | CrCl (ml/min) | |
| | ≤50 | >50 | ≤50 | >50 |
| Study 0015 | | | | |
| BMI >35 | 29.9% (N=17) | 14.1% (N=29) | 14.3% (N=14) | 6.7% (N=15) |
| BMI ≤35 | 40.0% (N=124) | 18.6% (N=202) | 30.3% (N=120) | 16.0% (N=225) |
| Study 0019 | | | | |
| BMI >35 | 39.1% (N=8) | 16.3% (N=12) | 0.0% (N=5) | 12.5% (N=8) |
| BMI ≤35 | 50.0% (N=93) | 8.3% (N =266) | 32.4% (N=103) | 21.5% (N=262) |

In the table above, Table 13, mortality rates were about twice those in the respective vancomycin groups when stratified by CrCl (>50 and ≤50 ml/min). Only a few number of patients were morbidly obese (BMI >35), so inferential testing was not done. Taking the analyses of these two tables together, however, it is does not appear that mortality rates are related to aberrations in exposure levels due to dosing adjustments for BMI and/or CrCl. The increased rates in mortality, associated with CrCl and BMI, respectively, however, between telavancin and vancomycin groups as noted here, may also reflect other co-morbidities that independently increase risk of death.

9. Advisory Committee Meeting

The Anti-Infectives Advisory Committee (AIDAC) convened for the discussion of NDA 022-407 on November 29, 2012.

Questions to the Committee (due to the discussions that transpired at the meeting, the wording of question #1):

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 the requested indication of treatment of nosocomial pneumonia, including ventilator-associated pneumonia, caused by susceptible isolates of the following microorganisms: *Staphylococcus aureus* (both MSSA and MRSA) and *Streptococcus pneumoniae*? **(Vote)**

YES: 6

NO: 9

ABSTAIN: 0

Committee Discussion: *The committee members who voted “Yes” noted that the data showed the drug to be as good as vancomycin for the requested indication and approval would provide patients and clinicians with an additional treatment option. However, a majority of committee members were concerned that telavancin had shown non-inferiority to vancomycin in only one of two studies and that the drug seemed to pose mortality risks in renally impaired patients. Several committee members noted that approval was not warranted for a Streptococcus pneumoniae indication, where effective treatments already exist.*

- a. If yes, please provide any recommendations concerning labeling.

Committee Discussion: *The committee suggested that information related to safe use in patients with renal impairment be included in the product labeling. One member noted that labeling should reflect the mortality data according to baseline renal function and creatinine clearance levels found in the Applicants data.*

- b. If no, what additional studies/analyses are needed?

Committee Discussion: *Some of the committee members who voted “No” stated that additional data showing noninferiority to vancomycin and more evidence to establish threshold creatinine clearance levels to guide the use of telavancin in patients with renal impairment are needed.*

2. Do the results provide substantial evidence of the safety and effectiveness of telavancin for the treatment of nosocomial pneumonia when other alternatives are not suitable? (Vote)

YES: 13 NO: 2 ABSTAIN: 0

Committee Discussion: *The majority of the committee noted that approval should be limited for the treatment of nosocomial pneumonia due to MRSA and certain cases of MSSA (e.g., β -lactam allergy). A few committee members did not agree that there is substantial evidence of the safety and effectiveness of telavancin (even when other alternatives are not suitable) due to remaining concerns about mortality risks in patients with renal impairment.*

- a. If yes, please provide recommendations concerning labeling, particularly labeling concerning the use in patients with renal dysfunction.

Committee Discussion: *The majority of committee members who voted “Yes” said use of the drug should be limited to situations where alternative treatments are not available, and should be reserved for use in nosocomial pneumonia caused by MRSA. These limitations should be included in the labeling. The committee strongly advised there be labeling related to use of telavancin in renal*

dysfunction and suggested further consideration of appropriate renal function threshold levels to be included in the labeling.

b. If no, what additional studies/analyses are needed?

Committee Discussion: *The committee agreed that additional analyses and discussions related to the appropriate renal function thresholds need to be conducted to properly label telavancin for use in renal impairment. Committee members were divided about whether a creatinine clearance below 30 mL/min, as favored by the Applicant's analysis or a creatinine clearance at or below 50 mL/min, as used in FDA analyses was most appropriate or predictive of drug treatment risk.*

3. 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? (Discussion)

Committee Discussion: *The committee recommended that warnings regarding telavancin for nosocomial pneumonia should be at least comparable to warnings included in the labeling of the drug for the cSSSI indication. They noted that the patients receiving telavancin for a nosocomial pneumonia indication would generally be sicker and more medically vulnerable, thus labeling should advise extreme caution when using the drug in patients with CrCl levels between 30 mL/min to 50 mL/min. Several committee members noted that the renal effects would likely be a manageable toxicity, and all committee members advised more analysis regarding nephrotoxicity and explicit warnings related to the degree of renal impairment. One member expressed concern with the Applicant's data showing congestive heart failure and multiple organ failure that was not discussed at the meeting, and noted that these should be looked at more closely to see if there is a safety issue. Another committee member pointed out the need for pediatric studies of agents for this indication.*

10. Pediatrics

Of note, the PMC for pediatric development with the approved cSSSI indication (NDA 022-110) is currently in a deferred status. The Applicant's plan to fulfill this PMC was submitted on September 23, 2008, and had been deferred under PREA according to the NDA 022-110 approval letter, dated 11 September 2009. According to the latest Annual Report, no subjects have been enrolled. Owing to difficulties at the drug product manufacturer, (b) (4) resulting in a hold on distribution since November 2011, telavancin has had limited new patient exposure.

Currently, the pediatric development plan for nosocomial pneumonia, which was submitted on December 22, 2009, includes a synopsis of planned nonclinical juvenile toxicity and clinical (safety/PK) studies. The nonclinical study is a six-week repeat dose toxicity study in CrI:CD(SD) neonatal rats with a six-week recovery phase. The objective of this study is the identification of safety issues related to the use of telavancin during early development.

Study reports for these nonclinical studies are pending. Meanwhile, the Applicant has proposed the following four clinical studies for the pediatric development plan in this NDA (022-407):



Pediatric studies are planned [redacted] (b) (4) and will be informed by the relevant non-clinical juvenile toxicology studies. The proposed study schedule is presented below.

Table 14: Proposed Pediatric Study Schedule

(b) (4)

PeRC Comments and Recommendations: *The Committee was concerned about the need for the single-dose studies and whether it was ethical to delay enrollment in a Phase 3 trial, since it was unclear what potential safety/PK information could be gleaned from a single dose study. However, they also recognized that dose selection and initiation of enrollment of each age group would be based on data from previous PK assessments (PK modeling) supplemented with accumulating PK and safety data from the finalized cohorts within the same study. Their recommendations were as follows:*

- *Age groups should be enrolled sequentially, so older cohorts are entered first.*
- *Consider waiver for neonates and infants, since entry criteria would exclude patients with CrCl <60mL/min. This criterion would essentially exclude neonates since most would not have reached a GFR of that level.*
- *Consider need for the repeat-dose PK study, or if it can be embedded in the proposed pediatric Phase 3 study.*
- *Consider a review by the ethics panel when full protocols are submitted.*

11. Other Relevant Regulatory Issues

No other relevant regulatory issues.

12. Labeling

Indication:

- Using GFI-recommended terminology for the indication, and change “nosocomial pneumonia” (NP) to “hospital-acquired and ventilator-associated bacterial pneumonia” (HABP/VABP).
- List the cSSSI indication first and limited HABP/VABP indication (for *Staphylococcus aureus* only, and when alternatives are not available) second.

Warnings/Precautions:

- Include increased risk for mortality with moderate/severe renal impairment (CrCl <50 mL/min) and nephrotoxicity along with fetal risk in the boxed warning.
- Also mention potential risk in patients with CHF and multi-organ failure

Adverse Events:

- Most common AEs should list only identified terms that occurred more frequently than the comparator.

Clinical Studies section:

- Demographics can be summarized in text rather than a table.
- The proposed label included [REDACTED] (b) (4) is not necessary and should be omitted. [REDACTED] (b) (4)
- The Gram-positive MAT population (patient with at least one Gram-positive isolate identified) showing of 28-all cause mortality, using KM estimates, should be the population presented. ATS/IDSA criteria were meant to be applied as an exploratory analysis, not to be considered the “target” population.
- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

13. Recommendations and Risk-Benefit Assessment

13.1. Recommended Regulatory Action

Based on the clinical review, post-marketing safety review and additional statistical analysis of Studies 0015 and 0019, as a medical officer and cross-discipline team leader, this reviewer recommends that Vibativ™ (telavancin for injection) should not be approved as proposed for the treatment of nosocomial pneumonia in adults caused by susceptible strains of Gram-positive pathogens. However, when accompanied by a boxed warning in the prescribing information, indicating an increased risk of nephrotoxicity and in patients treated for nosocomial pneumonia with moderate/severe renal impairment (creatinine clearance less than 50 mL/min) an increased risk of mortality, telavancin should be approved for use only when susceptible isolates of *Staphylococcus aureus* are strongly suspected or confirmed and alternatives are not available. Use of telavancin should be reserved for use when MRSA is proven or suspected and other antibacterial agents such as linezolid or vancomycin are not suitable, or in certain cases of MSSA, such as when β -lactams cannot be used due to allergy. While this application remains approvable under the aforementioned conditions, the NDA for this indication (NP or HABP/VABP) remains deficient in providing a viable manufacturing site ((b) (4) site is currently under a distribution hold). The proposed new manufacturing site, Hospira McPherson, has not yet been fully assessed, however, and the Applicant would require readiness at a viable manufacturing site under cGMP before the NDA goal date.

13.2. Risk/Benefit Assessment

Considering the totality of data in Studies 0015 and 0019, including the analyses of clinical cure, 28-day all-cause mortality, and outcomes in various exploratory subsets, there is insufficient evidence of effectiveness for the requested treatment indication of nosocomial pneumonia, particularly when weighed against the potential safety risks. Additional analysis, including post-marketing safety experience with telavancin (under NDA 022-110) and further post hoc exploration into specific patient populations in the NP trials where telavancin is likely to have the most benefit (i.e., patients with NP where a Gram-positive organism, or MRSA, was identified), continues to yield concerns about the use of clinical cure as a primary endpoint, and the demonstration of mortality benefit in the patient population proposed by the Applicant. Furthermore, telavancin has demonstrated a more significant risk of nephrotoxicity compared to vancomycin, in both the cSSSI and NP trials, particularly in patients who may already have a comorbid risk for renal injury or have concomitantly received another nephrotoxic drug. When taking into account these risk factors, however, clinicians may be able to safely prescribe telavancin, particularly when alternatives, such as vancomycin or linezolid, are not available. This reviewer also agrees with the Anti-Infective Drugs Advisory Committee recommendation for a more limited approval, whereby telavancin should only be used for treatment of HABP/VABP caused by *Staphylococcus aureus*, considering that safer

and more effective treatments for pneumococcal pneumonia already exist. The use of telavancin should, therefore, be reserved for use when MRSA is proven or suspected and other antibacterial agents are not suitable, or in certain cases of MSSA, such as when β -lactams cannot be used due to allergy.

At the Advisory Committee meeting on November 29, 2012, there was also a discussion of the appropriate creatinine clearance, below which telavancin could be safely prescribed (<30 mL/min or <50 mL/min). Although no clear consensus was reached on this question, the clearance of 50 mL/min is currently approved in the US Prescribing Information, both as a guideline, for when prescribers should consider a dosage adjustment, and for which decreased efficacy was observed when treating complicated skin and skin structure infections. In the opinion of this reviewer, however, the increase in mortality was more evident in patients whose baseline creatinine clearance was <50 mL/min, as opposed to the proposed <30 mL/min. Creatinine clearance calculation may not always accurately estimate a glomerular filtration rate, particularly in the acute setting, but alerting prescribers to the risk when CrCl is under 50 mL/min is more clear and consistent (with the currently approved dosing recommendations and warnings/precautions) when making a safety/risk determination for individual patients.

13.3. Recommendation for Postmarketing Risk Evaluation and Management Strategies

As of March 2011, under NDA 022-110, the Applicant has completed an 18-month assessment report. The goals of these REMS are to avoid unintended exposure of pregnant women to Vibativ, and include:

- Educating healthcare professionals (HCPs) and patients on the potential risk of fetal development toxicity if women are exposed to Vibativ while pregnant.
- Informing HCPs that a serum pregnancy test should be performed before initiating therapy with Vibativ in women of childbearing potential.
- Informing HCPs that women of childbearing potential, including those being treated in the outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during Vibativ use.

(b) (4)

(b) (4)

Under this NDA (022-407), the Applicant has proposed the following goals:

(b) (4)

In addition to merging the goals and objectives of NDA 022-110 and NDA 022-407 (the two indications would share the same USPI), the proposed goals should be amended to reflect a creatinine clearance of 50 mL/min, rather than 30 mL/min, below which increased mortality was observed and risk may outweigh the anticipated benefit. The REMS should also include an additional goal of reducing the risk of nephrotoxicity, and inform HCPs regarding the potential risks of nephrotoxicity, and the increased mortality that was observed, particularly in association with moderate/severe baseline renal insufficiency, congestive heart failure and the concomitant use of nephrotoxic agents.

13.4. Recommendation for other Postmarketing Requirements and Commitments

As discussed in Section 10, PMCs should be merged with the proposed pediatric plan for NDA 022-110. A complete pediatric plan has been submitted, and in accord with the recommendations from the PeRC meeting:

- Age groups should be enrolled sequentially, so older cohorts are entered first.
- Consider a waiver for neonates and infants, since entry criteria would exclude patients with CrCl <60mL/min. This criterion would essentially exclude neonates since most would not have reached a GFR of that level.
- Consider need for the repeat-dose PK study, or if it can be embedded in the proposed pediatric Phase 3 study.
- Consider a review by the ethics panel when full protocols are submitted.

13.5. Recommended Comments to Applicant

No additional comments.

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/s/

BENJAMIN D LORENZ
02/01/2013

M E M O R A N D U M**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

DATE: 12-21-10

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

TO: Division File

SUBJECT: Deputy Division Director's Decisional Memo for NDA 22-407 Class II resubmission, telavancin for intravenous infusion 10 mg/kg every 24 hours (Tradename VIBATIV™) for nosocomial pneumonia (NP)

1.0 Background

Telavancin (TLV) is an injectable, lipoglycopeptide antibacterial agent, produced by chemical modification of vancomycin. Its mechanism of action is via inhibition of bacterial wall synthesis by interfering with peptidoglycan synthesis and cross-linking. TLV also causes disruption of the functional integrity of the cell membrane by depolarizing the membrane. It has activity against Gram-positive bacteria including *Staphylococcus aureus* and *Streptococcus pneumoniae*, that may cause nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP). TLV was approved for the treatment of complicated skin and skin structure infections (cSSSI) caused by designated, TLV-susceptible, Gram-positive organisms including methicillin-resistant *S. aureus* on September 11, 2009.

The applicant, Theravance, Inc., has submitted this class II resubmission in response to a complete response (CR) letter issued by DAIOP on November 23, 2009. NDA 22-407 was submitted on January 23, 2009, in support of 10 mg/kg of TLV administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days, for the requested indication of treatment of adults with NP caused by susceptible strains of Gram-positive bacteria. The submission contained the data and results from two phase 3 clinical trials of NP. The November 23, 2009, CR letter cited the following deficiencies:

"The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia (NP). Both

trials were designed and powered for a clinical response endpoint. However, as discussed at the FDA Anti-infective Drugs' Advisory Committee meeting for NDA 22-171 on July 16, 2008, the published scientific literature (identified to date) does not permit interpretation of non-inferiority studies of antibacterial drugs for NP and ventilator-associated pneumonia (VAP) using clinical response as the primary endpoint due to the lack of scientific data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. Published historical evidence will only permit interpretation of non-inferiority studies for NP and VAP using all-cause mortality as the primary endpoint.

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

For additional information regarding the first cycle, please refer to all relevant reviews by discipline. The information in this resubmission includes re-analyses for mortality for two analysis populations: the primary analysis population – the full, As-Randomized (AT) population, and a supportive analysis population – that subset of the AT population who met the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) criteria for nosocomial pneumonia – “chest x-ray plus two clinical features” (CXR+2F). In addition, microbiological subsets of interest were also evaluated in the mortality analysis. These include 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. The resubmission also includes a safety update. There is no new CMC, pharmacology/toxicology, clinical pharmacology, or microbiology information in this submission. This memo will summarize the clinical efficacy and safety reviews. For further details, please refer to the biometrics review by Dr. Scott Komo, the clinical efficacy review by Dr. Benjamin Lorenz, and the Cross-Disciplinary Team Leader (CDTL) memo by Dr. Janice Pohlman.

2.0 Summary of Efficacy

Drs. Komo, Lorenz, and Pohlman have recommended issuance of another complete response letter because the new mortality analyses do not demonstrate the non-inferiority of TLV to VAN for the treatment of NP, nor have the concerns identified in the original review regarding uncertainty that the subjects had the disease of interest been rectified (see the first cycle medical officer review by Dr. Alfred Sorbello). Due to the baseline differences in patient populations with respect to risk factors for mortality, specifically renal insufficiency/failure and diabetes mellitus, it is not appropriate to pool studies 0015 and 0019.

Since telavancin has activity against Gram-positive pathogens only, the analysis population of interest is the one containing subjects from whom Gram-positive organisms were isolated from respiratory tract specimens. The following table illustrates the estimated 28-day all-cause mortality for this population for both trials.

Table 1: Estimated 28-Day All-Cause Mortality – Studies 0015 and 0019, MAT Population Excluding Patients with only Gram-Negative Pathogens Isolated at Baseline

| Study | Treatment | Estimated K-M Mortality at 28 Days (%) | Difference (%) (TLV – VAN) 95% CI |
|-------|-----------|--|-----------------------------------|
| 0015 | TLV | 28.7 | 4.4 |
| | VAN | 24.3 | (-4.7, 13.5) |
| 0019 | TLV | 24.3 | 2.0 |
| | VAN | 22.3 | (-6.1, 10.0) |

Deaths occurring after Study Day 28 have been censored
Source: MO review

Study 0015 does not demonstrate the non-inferiority of TLV to VAN when using a margin of 10%, which is supported by the historical evidence of treatment effect and discussed in the draft guidance for industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment. Study 0019 just meets the 10% margin, but in the absence of other supportive evidence, is not sufficient. When this analysis population is further refined to eliminate subjects who received either potentially active antibacterial therapy prior to enrollment, or received potentially active concomitant antibacterial therapy during the study period, or those with inadequate respiratory specimens or chest radiographs, the confidence intervals only become wider. Consequently, the treatment effect of TLV becomes even more difficult to discern.

An additional efficacy and safety concern is the mortality analysis by presence or absence of acute renal failure, as depicted in Table 2.

Table 2: 28-Day Adjusted Hazard Ratios for Telavancin vs. Vancomycin by Presence of Acute Renal Failure at Baseline – AT Population

| Study | ARF | N | Hazard Ratio | 95% CI |
|--------------------------------|-----|------|--------------|------------------|
| 0015 | Yes | 78 | 2.483 | (1.082, 5.700) |
| | No | 668 | 1.072 | (0.764, 1.506) |
| 0019 | Yes | 59 | 2.558 | (1.239, 5.285) |
| | No | 698 | 0.880 | (0.629, 1.230) |
| Combined (Stratified) Model | Yes | 137 | 2.360 | (1.379, 4.038) |
| | No | 1366 | 0.987 | (0.779, 1.250) |

Source: MO review

Subjects treated with TLV who had acute renal failure were more likely to die compared to VAN-treated subjects. Decreased efficacy was seen in the cSSSI trials among subjects with impaired renal function who received TLV compared to those who received VAN, and the product carries a Warning and Precaution to that effect. There was also an interaction between treatment and baseline chronic renal failure in the AT population for Study 0019, with an estimated mortality difference of 31% for subjects with chronic renal failure at baseline, compared to a difference of -2.6% for those who did not.

The Applicant included an analysis of post-hoc selected risk factors for mortality in their submission. This analysis was problematic because of potential bias due to its post hoc nature. Another analysis attempted to compare the treatment effect of TLV for NP with a historical control group that was generated from multiple studies in the published literature. These studies contained insufficient information on the baseline characteristics of the patients that are necessary to make conclusions regarding the comparability to subjects in the TLV NP trials.

3.0 Summary of Safety

The safety update in this submission referenced the post-marketing Periodic Adverse Drug Experience Report (PADER) submitted to NDA 22-110 on April 12, 2010, along with the results of a literature review for safety information related to TLV covering the period from November 2, 2009, to May 31, 2010. In addition to the PADER included in the submission, two additional PADERs for the periods March 11-June 10, 2010 and June 11-September 10, 2010 were also reviewed. There were no new clinical trial safety data to review. The literature review did not identify any new safety issues. Renal events were the most common serious adverse events reported in all three PADERs, and there were a handful of reports for dysgeusia (described in the package insert), rash and pruritis, and leucopenia. The cases of skin disorders and leucopenia were too poorly documented to determine any relationship to TLV. No new safety information needs to be added to the package insert at this time.

4.0 Recommended Regulatory Action

I concur with the findings and conclusions of the review team. Per 21 CFR 314.126, there is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, suggested in its proposed labeling. The applicant will be issued a complete response delineating the following deficiencies, and the means to address them:

1. While a substantial amount of missing mortality data has been recovered and provided for analysis, the analysis in the population of interest in Study 0015 does not demonstrate non-inferiority of telavancin relative to vancomycin. While the 10% NI margin is met in study 0019, in the absence of other supportive information, it is not sufficient evidence evidence.
2. The method of selection of patients does not provide adequate assurance that they had the disease being studied due to uncertainties with respect to interpretations of chest radiographs and adequacy of respiratory tract specimens.
3. Your analysis method that compares the telavancin-treated patients from the phase 3 trials to the historical studies of patients receiving inadequate, inappropriate, and delayed therapy is problematic. Specifically, there is inadequate information about the baseline characteristics of the control group to permit comparisons with the patients from the telavancin trials.
4. The pooling of patients across the two phase 3 trials is not appropriate because subjects in study 0015 had more potential risk factors for mortality, e.g. diabetes mellitus and renal impairment/failure, than the subjects in study 0019.
5. The inclusion of post hoc selected prognostic risk factors for mortality in the analyses is not acceptable because they may bias the results.
6. The diagnosis of renal failure was left to the discretion of the investigator, and in some cases it was unclear whether some of the patients may have had acute as well as chronic renal failure. For patients with potential risk factors, renal status should have been more specifically defined by standardized measures at entry and followed more closely for at least 28 days.

In order to address these deficiencies, the applicant needs to conduct at least two adequate and well-controlled studies to demonstrate the safety and efficacy of telavancin in patients with hospital-acquired bacterial pneumonia.

Katherine A. Laessig, MD

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/s/

KATHERINE A LAESSIG
12/21/2010

CLINICAL REVIEW

Application Type NDA
Application Number(s) 22-407
Priority or Standard Standard

Submit Date(s) June 30, 2010
Received Date(s) June 30, 2010
PDUFA Goal Date December 30, 2010
Division / Office Division of Anti-Infective and
Ophthalmology Products/
Office of Antimicrobial
Products

Reviewer Name(s) Benjamin Lorenz, MD
Review Completion Date December 21, 2010

Established Name Telavancin for injection
Trade Name VibativTM
Therapeutic Class Systemic antimicrobial
Applicant Theravance, Inc

Formulation(s) Intravenous infusion
Dosing Regimen 10 mg/kg every 24 hours
Indication(s) Nosocomial pneumonia
Intended Population(s) Adult patients

Recommendation on Regulatory Action

Based on the clinical review of the newly submitted safety and efficacy data, this FDA Medical Officer recommends that VIBATIV™ (telavancin) should not be approved for the treatment of nosocomial pneumonia in adults caused by susceptible strains of Gram-positive pathogens. The design and execution of these studies did not yield a conclusive assessment of drug effect. A substantial amount of data was recovered to conduct additional analyses of mortality at the 28-day time point; however telavancin failed to demonstrate noninferiority compared to vancomycin using a 10% margin in both of the two controlled clinical trials. The differences in baseline characteristics make it unsuitable to combine the two trials. Even though the patient selection methods did not provide adequate assurance that they had the disease being studied, the difference in mortality rates between treatment groups in both trials decreased when a more stringent definition of nosocomial pneumonia was applied. Noninferiority was not demonstrated in either patients who had methicillin-resistant *Staphylococcus aureus* (MRSA) isolated, or when excluding patients who had only Gram-negative organisms isolated. The increased mortality in patients with acute renal failure also raised concerns that telavancin was inferior to vancomycin and that the drug may not be safe to administer in some subpopulations.

Although the Applicant attempted to fulfill the deficiencies noted in the November 23, 2009 Complete Response letter, many of the issues have not been appropriately addressed. To address these deficiencies, the Applicant should perform adequate and well-controlled studies to demonstrate the efficacy and safety of telavancin in patients with nosocomial pneumonia. The inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever > 38°C, leukocytosis or leukopenia, and purulent respiratory secretions. Chest radiograph interpretation should be performed and/or validated by a qualified health care provider (i.e. radiologist, pulmonologist, intensive care physician) not involved in enrollment of patients in the trial. Uniform criteria should be applied to assess the quality of respiratory specimens for culture and subsequent pathogen identification. The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol. In Studies 0015 and 0019, the diagnosis of renal failure was left to the discretion of the investigator, and in some cases it is unclear whether some of the patients may have had acute as well as chronic renal failure. For patients with potential risk factors, renal status should be more specifically defined by standardized measures at entry and followed more closely for at least 28 days in future clinical trials.

Risk Benefit Assessment

Based on a review of the updated all-cause mortality data, the risk-benefit assessment is unfavorable and indicative of a mortality imbalance with higher death rates and odds ratios for death in the telavancin treatment group in one (Study 0015) of the two trials. In the review of the original NDA, there were concerns regarding the imbalance in serious renal adverse events with more events in the telavancin treatment group. Reanalysis of the mortality data, with recovered vital status at Day 28, shows that there is a statistically significant increase in mortality in telavancin relative to vancomycin for patients with baseline ARF that is replicated in both trials. Since there is no unequivocal evidence of efficacy, especially in patients with comorbid conditions and infections caused by MRSA, it is the clinical opinion of this Medical Officer that the risks of treatment of nosocomial pneumonia with telavancin do not outweigh the benefits.

Introduction and Regulatory Background

Telavancin 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). In two Phase 3 clinical trials of patients with cSSSIs suspected to be caused by Gram-positive bacterial pathogens telavancin demonstrated non-inferiority to vancomycin. However, telavancin did not demonstrate superiority compared to vancomycin in the treatment of patients with MRSA as the baseline pathogen. Renal toxicity, teratogenicity, and potential for QTc prolongation were problematic safety issues identified in the review of NDA 22-110. One of the postmarketing study commitments was to determine if there may be some effect of renal function on the activity of telavancin that may explain the decreased efficacy of telavancin in patients with renal impairment.

In pursuit of the indication for the treatment of nosocomial pneumonia (NP) the Applicant conducted two Phase 3 clinical trials (0015 and 0019) of noninferiority design given the acronym ATAIN (**A**ssessment of **T**elavancin for **H**ospital-acquired **P**neumonia). These trials compared the safety and efficacy of telavancin and vancomycin in the treatment of adult patients with hospital-acquired pneumonia (HAP) with a focus on patients with infections due to MRSA. Accordingly, the design was intended to enrich the population with patients who had HAP due to Gram-positive pathogens. The design of these studies was originally based on the specifications outlined in the 1998 FDA *Guidance for Industry: Nosocomial Pneumonia—Developing Antimicrobial Drugs for Treatment and Developing Antimicrobial Drugs—General Considerations for Clinical Trials*. Discussions on the development of telavancin for the treatment of nosocomial pneumonia began in July 12, 2004 during an end of Phase 2 meeting, in which proposals for Phase 3 studies in HAP were submitted to the Agency.

Prior to final closure of the clinical database, the final Statistical Analysis Plan for Studies 0015 and 0019 was submitted to the FDA on November 12, 2007. At the Pre-NDA Meeting for the HAP indication held on March 6, 2008, it was agreed that the Integrated Summary of Safety (ISS) for the current submission only include the data from Studies 0015 and 0019 in hospital-acquired pneumonia. At a meeting of the Anti-infective Drugs Advisory Committee (AIDAC) to discuss the doripenem NDA submission (NDA 22-171) on July 16, 2008, the FDA presented an approach to justification of a noninferiority margin for the indication of nosocomial pneumonia (including ventilator-associated pneumonia) based on all-cause mortality as the primary endpoint. The two trials (Studies 0015 and 0019) were designed based on a 20% noninferiority margin (14% post hoc margin) for a clinical response efficacy endpoint, and the Applicant planned to pool the study populations to achieve sufficient statistical power.

On January 23, 2009, the Applicant submitted NDA 22-407 for the use of telavancin for the treatment of nosocomial pneumonia to the FDA; however, upon review the Medical Officer, found that “despite identical trial designs the two study populations differed substantially with respect to the frequencies of various baseline characteristics and comorbid conditions that could potentially affect the risk for mortality making it inadvisable to pool them.” Since there was inadequate data to reach a conclusion regarding the efficacy of the drug, the Applicant was asked to submit additional mortality data to the Division. Additionally, while historical evidence only permitted interpretation of non-inferiority studies for NP and VAP using all-cause mortality at 28 days as the primary endpoint, the Medical Officer’s review pointed out that the criteria utilized inclusion criteria that 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*:

The inclusion criterion regarding radiographic findings “consistent with a diagnosis of pneumonia” was problematic in such patients as they may have other non-infectious illnesses (such as atelectasis, congestive heart failure, pulmonary embolism with infarct, pulmonary contusion, and chemical aspiration) that may produce x-ray findings that may mimic pneumonia. Confirmation of the Investigators’ interpretation of chest radiographs by a radiologist was not required. The lack of radiologists’ confirmation of the chest x-ray findings that were reported by Investigators adds to the dilemma of assessing whether enrolled patients actually had the disease being studied.

Consequently, the Medical Officer recommended that telavancin should not be approved for the treatment of nosocomial pneumonia. The Division issued a Complete Response (CR) letter to Theravance on November 23, 2009 with the following recommendations for resubmission of the ATTAIN trials to address these issues:

- 1) Submit all available all-cause mortality data and account fully for censored information.
- 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) Verify that the study population contains patients who met the ATS/IDSA criteria for nosocomial pneumonia – “chest x-ray plus two clinical features” (CXR+2F).

The Applicant responded to the CR on December 21, 2009. However, on January 26, 2010, the Division advised the Applicant that it did not consider the resubmission to be a complete response. The Applicant and Division discussed the deficiencies in the submission during a face-to-face meeting on March 15, 2010. The following statement was made in response to the question in the Briefing Document regarding concerns about combining evidence in the primary analysis population:

There were significant differences in prognostic factors and baseline severity for the study populations in Studies 0015 and 0019. Due to differences in patient comorbidities, lack of adequate microbiological data, and other uncertainties with the data, the studies should not be combined to make inferences on mortality. Furthermore, the mortality rate difference between treatment arms does not appear to be the same in studies 0015 and 0019.

The present resubmission incorporates the direction provided by the Division with regard to the analysis of mortality in nosocomial pneumonia. Re-analyses have been performed for two analysis populations: the primary analysis population – the full, As-Randomized (AT) population, and a supportive analysis population – that subset of the AT population who met the ATS/IDSA criteria for nosocomial pneumonia – “chest x-ray plus two clinical features” (CXR+2F). In addition, microbiological subsets of interest were also evaluated in the mortality analysis. These include 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.

This review will focus on the efficacy analysis. For further details on the statistical plan and analysis, please refer to the Statistical Review and Evaluation by Scott Komo, DrPH and the safety analysis by Janice Pohlman, MD, MPH, Clinical Team Leader.

Review of Efficacy

Objectives

The overall goal for the analyses of mortality was to provide evidence of the efficacy of telavancin for the treatment of nosocomial pneumonia for the purposes of a regulatory assessment. The specific objectives are as follows:

Primary

- Objective 1: Demonstrate the superiority of treatment of NP with telavancin to imputed placebo mortality rates obtained from historical data, for both Study 0015 and Study 0019.
- Objective 2: Estimate the relative mortality rates of telavancin vs. vancomycin using regression analysis to adjust mortality rates for predictive factors, in both Study 0015 and Study 0019 and for the two studies combined.

Secondary

- Objective 3: Demonstrate that telavancin preserves a proportion of the benefit (the noninferiority margin) of vancomycin treatment relative to placebo using a 10% noninferiority margin, for both Study 0015 and Study 0019 and for the two studies combined.
- Objective 4: Compare telavancin mortality rates with vancomycin in microbiological-defined subgroups, for both Study 0015 and Study 0019 and for the two studies combined.

Inclusion and Exclusion Criteria

The study entry criteria suggested by the FDA (as a sensitivity analysis for evaluating consistency of effect to that observed in the primary analysis) assure that patients had the highest possible clinical likelihood and radiographic evidence of nosocomial pneumonia (NP). Patients at risk of poor outcomes, such as the elderly (≥ 65 years) or patients with comorbid conditions such as severe renal impairment (CrCL < 30 mL/min) were also included. The only exclusion criteria that limited the severity of illness were related to probability of imminent death (refractory shock, profound neutropenia) and likelihood of ventricular arrhythmia due to QT prolongation.

Statistical Analysis Plan

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. Based on the 1998 FDA guidance documents, Studies 0015 and 0019 were each originally designed as active-controlled, noninferiority trials with a primary endpoint of clinical response at test of cure (TOC). The noninferiority margin (telavancin – vancomycin) was prospectively set at 20%. All-cause mortality was a secondary efficacy endpoint. Ultimately, after the Complete Response (CR) letter to the Applicant on November 23, 2009, the statistical analysis in this submission was revised to incorporate the direction provided with regard to mortality in nosocomial pneumonia. The Applicant prepared a post-hoc plan for the analysis of all-cause mortality, relying on FDA comments provided during and after the initial review period for NDA 22-407 with respect to the choice of analysis population(s), selection of appropriate time points, accounting for the inclusion of censored data, choice of the appropriate metric for comparing treatments, and calculation of the noninferiority margin.

Re-analyses were performed for two analysis populations: the primary analysis population – the full, As-Randomized (AT) population, and a supportive analysis population – that subset of the AT population who met the ATS/IDSA criteria for nosocomial pneumonia (the CXR+2F population). In addition, microbiological subsets of interest were also evaluated in the mortality analysis. These include the original 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. The analysis methods included determination of Kaplan-Meier survival estimates that accounted for subjects whose mortality data were censored (unknown at the landmark reporting time, e.g., 28 days) and use of a proportional hazards regression model to identify and account for predictive factors and any treatment-effect modifiers related to mortality. In addition to presentation of the results of Studies 0015 and 0019, the application also references confirmatory evidence of telavancin's effectiveness from approved NDA 22-110 for complicated skin and skin structure infections caused by *Staphylococcus aureus* (including MRSA).

The Applicant listed the following justifications for pooling data from the two studies:

- The protocols were identical in all respects.
- The studies were conducted concurrently.
- The statistical analysis plan called for combining the studies for the analysis of an efficacy endpoint (clinical response in patients with MRSA).
- There was no difference between treatment groups for 30 of 31 baseline characteristics; the lone exception was baseline vasopressor use.
- Confidence intervals for the all-cause mortality rates overlap.
- Multivariate regression analysis suggests that multiple variables are related to vital status.

• There is not a statistically significant interaction between study and treatment ($p = 0.45$). This result supports combining Studies 0015 and 0019 for more precise estimation of results. After adjustment for significant factors predictive of mortality, an interpretable model was obtained that statistically segregated risk between the two treatment groups.

Reviewer Comments: *Although demographics were similar between both treatment groups after randomization with respect to age, gender, race/ethnicity, body mass index, baseline renal function (serum creatinine), hemodialysis, acute renal failure, mechanical ventilation at baseline, and incidence of VAP; patients differed significantly between the two studies (Study 0015 and Study 0019 with treatment groups combined) when comparing the history of diabetes, baseline creatinine clearance and renal failure:*

Table 1: Baseline characteristics by Trial (AT Population, treatment arms combined)

| | Study 0015 (N=746) | | Study 0019 (N=757) | | p-value |
|-----------------------------|-----------------------|-------|-----------------------|-------|---------|
| | n | % | n | % | |
| History of diabetes | 232 | 31.1% | 162 | 21.4% | <0.0001 |
| Chronic renal failure | 67 | 9.0% | 28 | 3.7% | <0.0001 |
| Baseline 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 |

Despite identical trial designs, these baseline characteristics and co-morbid conditions are independent predictors of mortality, so the degree of discrepancy as shown here makes it unsuitable to combine the two studies. Please also refer to the Statistical Review by Scott Komo for further details, including concerns with the Applicant's strategy to demonstrate efficacy by comparing the telavancin treatment groups from the current trials to a historical control.

Analysis of Primary Endpoint(s)

The primary analysis population for analysis of all-cause mortality in Studies 0015 and 0019 was the All-Treated (AT) population, which is the same as the population prospectively defined in the protocols and statistical analysis plans for each study and also used for analyses presented in the ISE submitted in the original NDA 22-407, as described in Section 1.2.

The AT population comprises all randomized patients who received any treatment and is based on the treatment group assigned by randomization, regardless of the study medication actually received. In Study 0015, all patients received treatment according to randomization. In Study 0019, two patients who were randomized to vancomycin actually received telavancin.

Analysis of Secondary Endpoints(s)

The guidelines of the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) describe the criteria for an analysis population of interest, which was referenced by the Agency as a population to consider in the design of future studies in NP. This population is defined by the presence of a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) at baseline among patients in the AT population and is referred to in this document as the “Chest X-Ray Plus Two Features” (AT CXR+2F) population.

Subpopulations

In addition to the analysis populations described above, supportive microbiologically defined subgroups were analyzed. The Modified All-Treated (MAT) analysis group was prospectively defined in the protocols and statistical analysis plans for each study and used for analyses presented in the ISE submitted in the original NDA 22-407, as described in Section 1.2. The MAT population comprises all patients in the AT population who also had a baseline pathogen identified. The following subsets of patients in the MAT population and their complements were also analyzed, as summarized in Table 2-1 of the ISE addendum (see Table 2 below):

- Any Gram-positive, including mixed Gram-positive/Gram-negative pathogens
- Gram-positive only, excluding any patients with mixed infection

Table 2: Description of Analysis Groups for Mortality Analysis in Studies 0015 and 0019

| Analysis Populations | Description |
|--|---|
| All-Treated (AT) | All patients who received any amount of study medication, according to treatment assigned at randomization |
| Chest X-Ray Plus Two Clinical Features (AT CXR+2F) | All patients in the AT population who also had a new or progressive radiographic infiltrate plus at least two of three clinical features (fever greater than 38°C, leukocytosis or leukopenia, and purulent secretions) at baseline |
| Analysis Subgroups | |
| Modified All-Treated (MAT) | All patients in the AT population who also had a baseline pathogen identified ^a |
| MAT, Any Gram-Positive | Subgroup of all patients in the MAT population who also had a baseline Gram-positive pathogen identified, i.e., patients with Gram-positive or mixed Gram-positive/Gram-negative infections ^a |
| MAT, Only Gram-Positive | Subgroup of all patients in the MAT population who also had a baseline Gram-positive pathogen and no Gram-negative pathogen identified ^a |

^a A baseline pathogen was defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, endotracheal aspirate (ETA), blind bronchial suctioning (BBS), bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB). 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 would qualify a patient for the MAT population.

Characteristics of the Study Populations

Additional subgroup analyses were undertaken based on targeted microbiological profiles. The number and percentage of patients in each analysis group are summarized by study in the following table.

Table 3: Analysis Populations, Studies 0015 and 0019

| | Number of Patients | | | | | |
|----------------------------------|--------------------|----------------|----------------|----------------|----------------|----------------|
| | Study 0015 | | Study 0019 | | Total | |
| | TLV (N=372) | VAN (N=374) | TLV (N=377) | VAN (N=380) | TLV (N=749) | VAN (N=754) |
| Analysis Populations | | | | | | |
| All-Treated (AT) | 372 (100%) | 374 (100%) | 377 (100%) | 380 (100%) | 749 (100%) | 754 (100%) |
| AT CXR+2F | 309 (83%) | 316 (84%) | 325 (86%) | 339 (89%) | 634 (85%) | 655 (87%) |
| Microbiological Subgroups | | | | | | |
| Modified All-Treated (MAT) | 257 (69%) | 247 (66%) | 303 (80%) | 282 (74%) | 560 (75%) | 529 (70%) |
| MAT, Any Gram-Positive | 184 (49%) | 175 (47%) | 213 (56%) | 199 (52%) | 397 (53%) | 374 (50%) |
| MAT, Only Gram-Positive | 136 (37%) | 134 (36%) | 125 (33%) | 124 (33%) | 261 (35%) | 258 (34%) |

Adapted from ISE addendum Table 2-2

Two patients (both in Study 0019) who were randomized to the vancomycin treatment group actually received telavancin. To address this discrepancy, ancillary analyses of mortality were performed using the As-Treated (AsTx) population, which is defined as all randomized patients who received any treatment; patients are assigned to treatment groups on the basis of treatment actually received. This population is the same as the Safety population characterized in the original NDA.

The reliability of the sputum and endotracheal aspirate (ETA) samples for determining the etiological diagnosis by culture for this analysis was defined using the following strict microscopic criteria:

- Reliable sputum: WBCs >25, SECs <10/LPF
Potentially unreliable sputum: all others
- Reliable ETA: reliable SECs < 10/LPF
Potentially unreliable ETA: all others

From the 1503 patients, 658 sputum samples and 617 endotracheal aspirate samples (ETAs) were obtained, and 233 patients underwent bronchoalveolar lavage (BAL), mini-bronchoalveolar lavage, or protected specimen brush (PSB), or other more invasive sampling methods. The samples were obtained from 819 (54.5%) patients who were not ventilated, 257 (17.1%) who had tracheal intubation but did not meet criteria for VAP, and 427 (28.4%) with VAP.

Table 4: Summary of Respiratory Sampling in Studies 0015 and 0019 – AT Population

| | Number of Patients | | | | | |
|---|--------------------|----------------|----------------|----------------|----------------|----------------|
| | Study 0015 | | Study 0019 | | Total | |
| | TLV (N=372) | VAN (N=374) | TLV (N=377) | VAN (N=380) | TLV (N=749) | VAN (N=754) |
| Patients with sputum samples | 169 (45%) | 174 (47%) | 151 (40%) | 164 (43%) | 320 (43%) | 338 (45%) |
| Reliable | 101 (60%) | 107 (61%) | 113 (75%) | 123 (75%) | 214 (67%) | 230 (68%) |
| Potentially unreliable | 68 (40%) | 67 (39%) | 38 (25%) | 41 (25%) | 106 (33%) | 108 (32%) |
| Patients with ETA samples | 132 (35%) | 134 (36%) | 171 (45%) | 180 (47%) | 303 (40%) | 314 (42%) |
| Reliable | 103 (78%) | 114 (85%) | 141 (82%) | 158 (88%) | 244 (81%) | 272 (87%) |
| Potentially unreliable | 29 (22%) | 20 (15%) | 30 (18%) | 22 (12%) | 59 (19%) | 42 (13%) |
| Patients with samples from other invasive procedures* | 68 (18%) | 62 (17%) | 61 (16%) | 42 (11%) | 129 (17%) | 104 (14%) |
| Patients with no samples | 9 (2%) | 11 (3%) | 8 (2%) | 7 (2%) | 17 (2%) | 18 (2%) |

Adapted from ISE addendum Table 3-1

Reviewer’s comments: *Several issues remain that have also been previously discussed by Dr. Sorbello in his review of the original submission. Based on the quality of assessments for collection of microbiological specimens, and the range of specimens that could be erroneously interpreted (up to 40% as shown in the telavancin arm for sputum samples in Study 0015), this will limit the ability to appropriately assign the microbiologically evaluable population for efficacy assessment.*

The chest radiographs in Studies 0015 and 0019 were to be interpreted by the investigator or a radiologist to avoid delay given the urgency to commence antibiotic therapy early in this critically ill population. 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 a radiologist. While 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 and source documents being received. The documents and CRF data were submitted to an independent radiology core laboratory (RadPharm, Inc. 100 Overlook Center Princeton, New Jersey, USA) for a treatment-blinded review. The documentation was assessed and then compared with data from the chest radiograph CRF (Pulmonary Radiography Log) for each patient. Each radiology report was assessed as either consistent with the CRF data, not consistent with the CRF data, or providing insufficient information to make possible a determination.

Table 5: Independent Core Radiology Data – AT Population

| | Study 0015 | | Study 0019 | | Total |
|---|------------|----------|------------|----------|-----------|
| | TLV | VAN | TLV | VAN | |
| Pretreatment Radiographs Reviewed | 337 | 326 | 309 | 309 | 1281 |
| Radiological report type | | | | | |
| Site radiologist's report, n (%) | 297 (88) | 291 (89) | 247 (80) | 256 (83) | 1091 (85) |
| Investigator source document, n (%) | 37 (11) | 31 (10) | 55 (18) | 47 (15) | 170 (13) |
| Unknown* source document, n (%) | 3 (1) | 4 (1) | 7 (2) | 6 (2) | 20 (2) |
| Core Radiology Adjudication | | | | | |
| Consistent with pneumonia diagnosis (%) | 312 (93) | 308 (94) | 291 (94) | 293 (95) | 1204 (94) |
| Not consistent with pneumonia diagnosis (%) | 12 (3) | 8 (3) | 6 (2) | 7 (2) | 33 (3) |
| Insufficient information to determine (%) | 13 (4) | 10 (3) | 12 (4) | 9 (3) | 44 (3) |

Adapted from ISE addendum Tables 3-3 and 3-4

Reviewer's comments: *Of the 1503 patients in the AT population, 1281 (85%) had a pretreatment radiograph reviewed for consistency with pneumonia. In Study 0015, 663 of 749 (89%) and in Study 0019, 618 of 754 (82%) were reviewed. After adjudication at an independent laboratory, a total of only 1204 (80%; 83% of Study 0015 patients and 77% of Study 0019 patients) were found to be consistent with pneumonia. This is concerning, because as many as 20% of patients lack confirmation of radiologic evidence of pneumonia. These data combined with the uncertainty of the presence of fever as determined by axillary temperature (please refer to Dr. Sorbello's review), and the degree of reliability of respiratory specimens for the determination of microbiologic etiology, still raises concern about the whether patients were appropriately diagnosed with nosocomial pneumonia.*

Concomitant Medications

Since the studies were designed to compare the efficacy of two drugs with activity against Gram-positive pathogens, the use of concomitant Gram-negative therapy was left to the Investigator's discretion. Some of these agents also had overlapping gram-positive activity so their use could potentially confound the efficacy analysis for the trials. The protocol specified that patients not requiring potentially effective antibiotic (PEA) following availability of culture results should have the PEA discontinued as soon as possible. However, a delay in the availability of culture results or a physician decision to continue medication based on the patient's clinical condition led to more prolonged use in some cases. Only systemic and inhaled antibiotics were evaluated for potential effectiveness. Aztreonam, metronidazole, and colistin were defined a priori as not potentially effective against Gram-positive pathogens. Piperacillin/tazobactam and carbapenems were defined a priori as potentially effective against MSSA but not potentially effective against MRSA.

In the analysis presented in the original NDA 22-407 ISE, patients who had received a PEA during the course of study treatment during >2 calendar days were defined as non-

evaluable and were not included in the CE or ME analysis populations. As reported in the NDA, PEA use during >2 calendar days resulted in exclusion from the evaluable population in ~24% of the AT population (original ISE, Table 5-10). The proportion of patients who received PEA during >1 calendar day adds 23 patients (telavancin, 6 patients; vancomycin, 17 patients) to this group and brings the proportion excluded to 25% of the AT population (Table 3-5).

Table 6: Impact of Varying Allowable Durations of Potentially Effective Concomitant Antibiotics (PEA) – Studies 0015 and 0019, AT Population

| | Number of Patients | | | | | |
|-----------------------------------|--------------------|----------------|----------------|----------------|----------------|----------------|
| | Study 0015 | | Study 0019 | | Total | |
| | TLV (N=372) | VAN (N=374) | TLV (N=377) | VAN (N=380) | TLV (N=749) | VAN (N=754) |
| Allowable Duration for PEA | | | | | | |
| 2 Calendar Days | 109 (29%) | 97 (26%) | 61 (16%) | 87 (23%) | 170 (23%) | 184 (24%) |
| 1 Calendar Day | 114 (31%) | 108 (29%) | 62 (16%) | 93 (24%) | 176 (23%) | 201 (27%) |

Adapted from ISE addendum Table 3-5

Reviewer’s Comments: *The rates of PEA leading to exclusion were higher in Study 0015; however, more patients in the vancomycin group of Study 0019 received PEA. In both treatment groups of Study 0015, 77 patients (17.5%) received piperacillin/tazobactam, 6 (1.4%) received cefepime, and 4 (0.91%) received imipenem. Most (74%) received aztreonam, and only 2 patients received gram-negative therapy with potential activity against MRSA (clindamycin, doxycycline). The usage was similar in Study 0019, with 56 (13%) receiving piperacillin/tazobactam, 4 (0.93%) receiving cefepime, 7 (1.63%) receiving imipenem and 5 (1.2%) receiving meropenem. Only 2 patients received clindamycin. Overall this usage history appears consistent with the goals of the protocol to limit the usage of PEA against MRSA; however, usage of PEA against all Gram-positive pathogens does appear to constrain the CE or ME analysis populations.*

In addition, there was a concern raised in Dr. Fred Sorbello’s review of the original NDA that should be reiterated here: For patients with mixed infections who were considered evaluable for efficacy analysis in the AT population, PEA also needs to be assessed with respect to activity against baseline Gram-negative organisms and the potential impact of inadequate Gram-negative coverage on clinical response and mortality outcomes. One potential bias could arise when patients whose pre-treatment respiratory tract and blood cultures had no growth, but subsequent respiratory tract cultures grew Gram-negative bacteria. These patients should not be classified as having received inadequate initial Gram-negative therapy if the bacterial isolates were colonizers and did not require treatment with antibacterial agents.

Analysis of All-Cause Mortality

In order to fulfill the first request of the November 23, 2009 Complete Response letter, the Applicant retrospectively collected data for 28-day survival status. In the original NDA, there was incomplete survival information for nearly 35% of patients in Study 0015 and 29% of patients in Study 0019. In this submission, incomplete survival data was reduced to 6% in Study 0015 and 5% in Study 0019. Patients with missing data at Day 28 were designated as censored observations.

Analysis of 28-day all-cause mortality is summarized in the table below:

Table 7: Vital Status at Day 28 by Study – AT Population

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

Adapted from ISE addendum Table 4-1

For analysis purposes, survival curves (Kaplan-Meier product limit estimates) were created through Day 28 from the first dose of study medication. All of the Kaplan-Meier figures also contain a log-rank p-value, which were intended to establish an indication of similarity or dissimilarity of survival functions. Ninety-five percent confidence intervals are given for the survival differences (TLV – VAN). Also, hazard rates and their confidence intervals are presented. Estimates of mortality using this approach were summarized in the following table:

Table 8: Estimated 28-Day All-Cause Mortality – Studies 0015 and 0019, AT Population

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

Deaths occurring after Study Day 28 have been censored

Adapted from ISE addendum Table 4-2

Reviewer’s Comments: For the reasons previously discussed (lack of similarity with baseline characteristics) the data from these two studies were not suitable for a pooled analysis. The results are not statistically significant (using the $p < 0.05$ threshold) for the AT population in Study 0015, but the telavancin mortality rate is higher by 5.8%.

Furthermore, the upper bound of the 95% confidence interval is higher than the non-inferiority margin of 10% specified in the November 2010 Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment.

Since both telavancin and vancomycin have only Gram-positive activity, supportive analyses were also performed on subpopulations including the microbiologically modified all-treated group (MAT). All-cause mortality was estimated in patients excluding those with only Gram-negative pathogens at baseline, which is summarized in the following table:

Table 9: Estimated 28-Day All-Cause Mortality – Studies 0015 and 0019, MAT Population Excluding Patients with only Gram-Negative Pathogens Isolated at Baseline

| Study | Treatment | Estimated K-M Mortality at 28 Days (%) | Difference (%) (TLV – VAN) 95% CI |
|-------|-----------|--|-----------------------------------|
| 0015 | TLV | 28.7 | 4.4 |
| | VAN | 24.3 | (-4.7, 13.5) |
| 0019 | TLV | 24.3 | 2.0 |
| | VAN | 22.3 | (-6.1, 10.0) |

Deaths occurring after Study Day 28 have been censored
 Adapted from ISE addendum Table 4-2

Reviewer’s Comments: *The mortality findings for Study 0015 are not favorable in this subgroup with a difference of 4.4% higher than vancomycin. Although not significantly higher (with a -4.7% lower bound), the upper bound of the 95% CI is markedly higher than the allowable 10% margin. For Study 0019, the findings are similar, but the upper bound of the 95% CI reached 10.0%.*

Because MRSA is an important and emerging etiologic pathogen in nosocomial pneumonia, the all-cause mortality was also stratified by patients who specifically had MRSA isolated at baseline.

Table 10: 28-Day All-Cause Mortality – MAT including only patients MRSA at baseline*

| | Study 0015 | | Study 0019 | |
|-----------------------|-------------|-------------|-------------|-------------|
| | TLV (n=115) | VAN (n=114) | TLV (n=118) | VAN (n=117) |
| Deaths at Day 28 (%) | 36 (31.3) | 27 (23.7) | 39 (33.0) | 35 (29.9) |
| Alive at Day 28 (%) | 76 (66.1) | 75 (65.8) | 75 (63.6) | 77 (65.8) |
| Lost of follow-up (%) | 3 (2.6) | 12 (10.5) | 4 (3.4) | 5 (4.3) |

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

Table 11: Estimated 28-Day All-Cause Mortality – MAT including only patients MRSA at baseline*

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

*Patients receiving a concomitant agent w/ MRSA activity were excluded

Reviewer’s Comments: *The subgroups are much smaller (study arm sizes range from 114 to 118), so statistical significance is even more difficult to achieve. Nevertheless, Kaplan-Meier mortality rates were consistently higher for patients in the telavancin arms of both Study 0015 (7.4%) and 0019 (3.0%) than the respective vancomycin arms.*

Additional analyses were also performed on the CXR+2F population. The Applicant provided this analysis and the 28-day all-cause mortality for this subgroup is summarized in the following tables:

Table 12: Summary of Vital Status at Day 28 by Study – AT CXR+2F Population

| | Study 0015 | | Study 0019 | |
|-----------------------|-------------|-------------|-------------|-------------|
| | TLV (n=309) | VAN (n=316) | TLV (n=325) | VAN (n=339) |
| Deaths at Day 28 (%) | 75 (24.3) | 67 (21.2) | 74 (22.8) | 80 (23.6) |
| Alive at Day 28 (%) | 216 (69.9) | 225 (71.2) | 238 (73.2) | 239 (70.5) |
| Lost of follow-up (%) | 18 (5.8) | 24 (7.6) | 13 (4.0) | 20 (5.9) |

Adapted from ISE addendum Table 4-12

Table 13: Estimated 28-Day All-Cause Mortality – Studies 0015 and 0019 – AT CXR+2F Population

| Study | Treatment | Estimated K-M Mortality at 28 Days (%) | Difference (%) (TLV – VAN) 95% CI |
|-------|-----------|--|-----------------------------------|
| 0015 | TLV | 21.6 | 3.0 |
| | VAN | 24.6 | (-3.6, 9.7) |
| 0019 | TLV | 24.1 | -1.1 |
| | VAN | 23.0 | (-7.7, 5.4) |

Deaths occurring after Study Day 28 have been censored

Adapted from ISE addendum Table 4-13

Reviewer’s Comments: *Narrowing the AT population to those with the radiologic and clinical features previously discussed may have enriched this subgroup of patients with those who were more likely to have the diagnosis of nosocomial pneumonia. The difference in mortality rates between treatment groups may appear similar, although this is a post-hoc subgroup analysis and the results may not be reliable.*

Table 14: 28-Day Adjusted Hazard Ratios for Telavancin vs. Vancomycin by Presence of Acute Renal Failure at Baseline – AT Population

| Study | ARF | N | Hazard Ratio | 95% CI |
|--------------------------------|-----|------|--------------|------------------|
| 0015 | Yes | 78 | 2.483 | (1.082, 5.700) |
| | No | 668 | 1.072 | (0.764, 1.506) |
| 0019 | Yes | 59 | 2.558 | (1.239, 5.285) |
| | No | 698 | 0.880 | (0.629, 1.230) |
| Combined (Stratified) Model | Yes | 137 | 2.360 | (1.379, 4.038) |
| | No | 1366 | 0.987 | (0.779, 1.250) |

Adapted from ISE addendum Table 4-6

Reviewer’s comments: *As the Applicant indicates in Section 4.4.1 and Table 4-6 of the ISE, there is a greater disparity in the number of patients with ARF at baseline between treatment groups (43 telavancin vs. 35 vancomycin) in Study 0015. In Study 0019, 30 telavancin patients were reported to have ARF at baseline compared with 29 vancomycin patients. There is a statistically significant increase in mortality in telavancin relative to vancomycin for patients with baseline ARF that is replicated in both trials. Since baseline renal disease (e.g. diabetes, chronic renal failure, baseline CrCl <50mL/min) appears to be an independent risk factor, this difference in treatment groups could have confounded results in other Study 0015 subgroups.*

Conclusions

The Applicant followed the recommendations set forth in the November 23, 2009 Complete Response letter. However, while mortality data was provided for a much more substantial proportion of the study population from Studies 0015 and 0019, the Applicant chose not to conduct new trials. Given the choice to reanalyze the data from these same studies, the ability to draw conclusions is restricted by many of the same concerns raised in the review of the original submission. Although more clinical and radiographic data was recovered and reanalyzed, it still remains unclear that a sufficient number of patients had the disease being studied. A substantial number of the patients also received agents for Gram-negative organisms with overlapping Gram-positive coverage, which may have confounded any potential treatment effect. Additionally, one of the weaknesses that remain was that even though each individual trial was not statistically powered for the 28-day mortality endpoint, the significant differences between baseline characteristics remain and make the trials unsuitable to be pooled. Telavancin failed to demonstrate noninferiority compared to vancomycin using a 10% margin in both of the two trials. Significant differences between characteristics of the study population and historical controls are also a problem when attempting to ascertain a treatment effect compared to a putative placebo. Subgroup analysis of patients with MRSA did not show any significant evidence of mortality benefit, and baseline prognostic factors, particularly renal risk factors, were found more frequently among

patients in Study 0015. Mortality was significantly higher for patients with baseline renal failure in both trials. Additional, adequate and well-controlled trials with more stringent inclusion criteria for the diagnosis of nosocomial pneumonia, and minimization to the extent possible of adjunctive antimicrobial therapy, will need to be conducted in order to demonstrate the efficacy and safety of telavancin in patients with hospital-acquired bacterial pneumonia. Safety issues such as nephrotoxicity remain an outstanding issue that should continue to be monitored. Based on the additional data presented in this submission, the clinical recommendation of this Medical Officer is that telavancin should not be used in the treatment of nosocomial pneumonia.

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

/s/

BENJAMIN D LORENZ
12/21/2010

JANICE K POHLMAN
12/21/2010

Cross-Discipline Team Leader Review

| | |
|--|---|
| Date | December 20, 2010 |
| From | Janice Pohlman, MD, MPH |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 22407 |
| Supplement# | |
| Applicant | Theravance, Inc |
| Date of Submission | June 30, 2010 |
| PDUFA Goal Date | December 30, 2010 |
| | |
| Proprietary Name / Established (USAN) names | Vibativ™ Telavancin hydrochloride |
| Dosage forms / Strength | Sterile, lyophilized powder, 250 mg, 750 mg Recommended dose: 10 mg/kg IV every 24 hours |
| Proposed Indication(s) | Nosocomial pneumonia |
| Recommended: | Complete Response |

1. Introduction

Vibativ™ (NDA 22110) was approved on September 11, 2010, for the treatment of complicated skin and skin structure infections (cSSSI) caused by susceptible isolates of designated bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Theravance, Inc. submitted NDA 22407 on January 23 2009, for the proposed indication of treatment of nosocomial pneumonia (NP) caused by susceptible strains of the following Gram positive bacteria: *Staphylococcus aureus* (including methicillin-sensitive and methicillin-resistant isolates) (MSSA and MRSA, respectively) and *Streptococcus pneumoniae*. The Division of Anti-Infective and Ophthalmology Products issued a complete response letter on November 23, 2009, outlining deficiencies and proposed remedies. Theravance, Inc. submitted a response to this letter to NDA 22407 on December 21, 2009, to which the Division responded with an incomplete response letter on January 26, 2010. Subsequently there were two meetings held between the Applicant and the Division, on March 15, 2010, and May 25, 2010. Based on discussion at the May 25, 2010 meeting, the Applicant submitted a complete response to NDA 22407 on June 30, 2010.

2. Background

The Applicant conducted two independent Phase 3 clinical trials of identical design, Study 0015 and Study 0019, in patients with NP caused by suspected or confirmed Gram positive bacteria, including MRSA. The trials were multicenter, randomized, double-blind, active-controlled trials. Patients were randomized 1:1 to receive either telavancin 10 mg/kg IV every 24 hours or vancomycin 1g IV every 12 hours for 7-21 days, with duration determined by the investigator based on the patient's clinical status. Randomization was stratified by geographic location, presence or absence of diabetes mellitus, and ventilatory status of the patient. Adjustment of telavancin and vancomycin doses for patients with renal impairment was performed by study personnel not involved in the clinical assessment of the patient. Patients could receive aztreonam or piperacillin/tazobactam for concomitant Gram negative coverage if necessary, although patients who received piperacillin/tazobactam were not clinically or microbiologically evaluable (Note: prior to a protocol amendment recommended by the FDA review team, patients could also receive imipenem for Gram negative coverage).

In order to enroll in the trial, patients were required to have clinical signs and symptoms consistent with pneumonia after at least 48 hours in an inpatient acute or chronic care facility, or acquired within seven days after being discharged from a hospital stay of ≥ 3 days. At least two of the following signs or symptoms were required: 1) cough, 2) purulent sputum or other deep respiratory specimen, 3) auscultatory findings of pneumonia, 4) dyspnea, tachypnea, or hypoxemia, 5) identification of an organism consistent with a respiratory pathogen isolated from an appropriate respiratory specimen or blood culture. Additionally, at least two of the following conditions must have been present: 1) fever ($>38^{\circ}\text{C}$) or hypothermia (rectal or core temperature $< 35^{\circ}\text{C}$), 2) respiratory rate > 30 breaths/minute, 3) pulse rate ≥ 120 beats/min, 4) altered mental status, 5) need for mechanical ventilation, 6) elevated total peripheral white blood cell (WBC) count $> 10,000$ cells/ mm^3 , $>15\%$ immature neutrophils (band forms) regardless of total peripheral WBC, or leukopenia with total WBC < 4500 cells/ mm^3 . Patients were also required to have a chest radiograph consistent with a diagnosis of pneumonia (progressive infiltrates, consolidation, or pleural effusion) within 48 hours prior to study and an appropriate respiratory specimen for Gram stain and culture.

The predefined primary endpoint was clinical response as assessed by the investigator at the Test-of-Cure (TOC) visit 7-14 days after the End of Therapy (EOT). The primary efficacy analysis was to initially test for clinical non-inferiority of telavancin by comparing the difference in clinical response rates of telavancin relative to vancomycin at TOC in the all-treated (AT) and clinically evaluable (CE) populations using a non-inferiority margin of 20%. If non-inferiority was demonstrated, 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. If the efficacy analyses of both identically designed trials demonstrated non-inferiority, a key secondary objective was to pool the data from

both trials to assess for superiority of telavancin to vancomycin in patients with MRSA infections.

Following completion of the trials, two public discussions relevant to clinical trial design in the evaluation of antimicrobial agents for treatment of NP took place and had a direct impact on the review of this application. The first was a meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) on July 16, 2008, during which NDA 22171 (doripenem) for treatment of NP, including ventilator-associated pneumonia (VAP), was presented. The Agency's presentation included a discussion of use of a non-inferiority trial design in NP trials and provided justification for a non-inferiority margin based on all-cause mortality to evaluate efficacy, rather than a clinical endpoint. The second discussion was a public workshop "Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)" (HAP/VAP workshop) co-sponsored by the Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) held on March 31-April 1, 2009 in Silver Spring, MD.

Based on a review of the literature, the Agency outlined the problem with the use of a clinical response endpoint in non-inferiority (NI) trials used to evaluate efficacy of treatment in NP. Based on literature reviewed to date, the lack of historical data for the clinical response endpoint does not allow for estimation of the treatment effect of antimicrobial agent over placebo. At the AIDAC meeting in July 2008, the Agency presented historical data from the literature supporting a 7% NI margin for the endpoint of all-cause mortality in clinical trials of NP. Additional information regarding the size of the NI margin which could be justified based on the historical literature was presented at the public workshop on HAP/VAP by the Agency. While the clearest evidence for treatment effect is based on an all-cause mortality endpoint, it is unclear as to appropriate timing of this assessment. The focus of discussion at the HAP/VAP workshop was based on assessment of all-cause mortality at 28 days post-randomization or initiation of therapy.

Following the discussions at the July 2008 AIDAC meeting and 2009 HAP/VAP workshop, the Applicant provided additional efficacy analyses based on all-cause mortality. The Applicant's initial assessment for all-cause mortality considered only deaths which occurred prior to the TOC visit (7-14 days after EOT) or within 28 days of the last dose of study medication (EOT). Therefore, the initial all-cause mortality analyses included in the application did not include 28-day post randomization mortality data for all patients.

Based on a FDA review team information request (February 25, 2009) related to the mortality endpoint at two possible timepoints (i.e. 28-day post-randomization and EOT + 28 days), an additional 17 deaths were identified by the Applicant and information was submitted to the NDA on March 26, 2009. The March mortality update was subsequently amended by a July 21, 2009 submission to the NDA. The Applicant

noted that while developing Kaplan-Meier analyses requested by the Agency (June 9, 2009) they identified additional sources for reported deaths that occurred outside the protocol-specified window (TOC or EOT+28 days), but within the FDA requested windows (i.e. 28-day post randomization and EOT + 28 days), from the clinical and serious adverse event (SAE) databases and from data collected in a pharmaco-economic substudy not analyzed by Theravance. An additional 34 deaths were identified, bringing the total to 51 deaths not initially reported in the NDA.

Mortality data at Day 28 was still unavailable for approximately 30% of the study populations. Narratives for the 51 deaths not initially identified were submitted to the NDA on August 13 and 14, 2009. This information was submitted late in the first review cycle and was not completely analyzed.

Dr. Alfred Sorbello noted in his clinical efficacy review of the original application that a number of methodologic problems with the way the study was designed and conducted may have adversely impacted interpretation of the data and non-inferiority determination. These factors included:

- Reliability of inclusion criteria in selecting a patient population in which patients actually had a diagnosis of NP. Examples of these criteria included:
 - Patients could be enrolled without any of the three important features of pneumonia: fever, leukocytosis, and/or purulent sputum.
 - The assessment of severity of disease by APACHE II and CPIS (if ventilated) scores where measured axillary temperatures were used with one degree added based on method of measurement.
 - The chest radiograph interpretation was not consistently performed by a radiologist.
- Failure of investigators to follow the protocol-specified de-escalation of concomitant Gram negative coverage (with possible overlapping Gram positive anti-bacterial activity).
- Lack of specified criteria to demonstrate adequacy of respiratory specimens for microbiological culture and pathogen determination.
- Applicant determinations with potential impact on the patient's clinical evaluability status and/or clinical outcome made after the medical monitor had been unblinded to treatment assignment.

Additionally, problems with use of a primary efficacy analysis based on clinical response were discussed.

- Use of a non-inferiority design based on clinical response without sufficient evidence for justification of the non-inferiority margin.
- The study was not designed, sized, or powered for a non-inferiority design using all-cause mortality as an endpoint.
- Mortality data for the 28-day post-randomization period and EOT + 28 days was not complete, rendering the analyses uninterpretable.

The Division issued a Complete Response (CR) letter to Theravance on 23 November 2009. The missing mortality data was cited as a deficiency. In their response, the

Applicant was to provide the missing mortality data and additional rationale for pooling the mortality analyses from the two trials. The Agency provided advice for design of a necessary subsequent trial(s).

In the incomplete response submitted to the Agency on December 21, 2009, the Applicant included vital status (i.e. dead or alive) information for 95% of patients 28 days post-randomization and for 90% of patients for 49 days post-randomization (period including the maximum treatment duration of 21 days plus 28 days of follow-up). To collect the additional data the Applicant had sent a letter of introduction to each investigator from whom vital status on participating patients was sought. Data were requested via specific data clarification forms (DCFs) sent to the clinical sites by (b) (4). The DCFs included entries for vital status, date last known to be alive or date of death, cause of death, and source of information. Sites that did not return forms were contacted by Theravance on a repeated basis until contact was made and DCFs were received, inability to comply with the request was confirmed, or the project deadline of October 30, 2009 occurred. Table 1 shows the vital status for patients at the 28-day and 49 day timepoints.

Table 1: Applicant All-treated Population

| | 0015 | | 0019 | | Total | |
|-------------|--------------|--------------|--------------|--------------|--------------|--------------|
| | TLV N=372 | VAN N=374 | TLV N=379 | VAN N=378 | TLV N=751 | VAN N=752 |
| 28 days | | | | | | |
| Dead | 95 (25.5) | 74 (19.8) | 84 (22.2) | 89 (23.5) | 179 (23.8) | 163 (21.7) |
| Alive | 258 (69.4) | 272 (72.7) | 278 (73.4) | 269 (71.2) | 536 (71.4) | 541 (71.9) |
| Lost to F/U | 19 (5.1) | 28 (7.5) | 17 (4.5) | 20 (5.3) | 36 (4.8) | 48 (6.4) |
| 49 Days | | | | | | |
| Dead | 114 (30.6) | 92 (24.6) | 100 (26.4) | 116 (30.7) | 214 (28.5) | 208 (27.7) |
| Alive | 234 (62.9) | 242 (64.7) | 257 (67.8) | 231 (61.1) | 491 (65.4) | 473(62.9) |
| Lost to F/U | 24 (6.5) | 40 (10.7) | 22 (5.8) | 31 (8.2) | 46 (6.1) | 71 (9.4) |

NDA 22407, December 20, 2009, Analysis of Mortality in Studies 0015 and 0019, Table 1

The Applicant also submitted a proportional hazards regression analysis model (also included with the subsequent complete response) for Studies 0015 and 0019 to adjust for multiple baseline factors associated with survival, including APACHE II score, creatinine clearance, MRSA infection, multilobar pneumonia, body mass index, bacteremia, cardiovascular morbidity, ARDS or ALI, and acute renal failure. This analysis will be discussed with the efficacy analysis of this memo.

The Division advised Theravance that it did not consider the submission to be a complete response on January 26, 2010. The Division noted that even if based on review, pooling of studies for a mortality endpoint was found to be acceptable, this would essentially provide evidence of efficacy from a single study. The Applicant was again advised about design elements that should be incorporated into a future trial(s) that were included in the complete response letter.

Theravance subsequently met on two occasions with Division reviewers (March 15 and May 25, 2010) to further discuss their application.

At the March meeting, there was discussion regarding the derivation of the treatment effect of antibacterial drugs relative to placebo and the clinically acceptable difference allowed. The Division informed the Applicant that these differences should be addressed in a future resubmission and also recommended that the Applicant consider another trial with design elements as suggested. The Division advised the Applicant that there was concern about combining evidence from Studies 0015 and 0019 due to differences in patient populations and lack of standardized microbiological evaluation.

At the second meeting in May, "M1", the treatment effect of antibacterial relative to placebo, was again discussed with the added caveat that the populations being studied should match those in the historical literature. The Applicant stated that they would provide detailed analysis in a resubmission about how the patients were similar to historical controls. The Division emphasized that the NI margin justification should be based on the relevant patient populations and pathogens. Much of the historical literature is based on patients with Gram negative bacterial pneumonia (primarily *Pseudomonas*) and not pneumonia due to MRSA. The Division also stated that the analysis should include only those patients with Gram positive bacterial pathogens, since telavancin lacks Gram negative activity. The Division advised Theravance that they should perform the analysis without adjusting for covariates as was done previously. The Applicant indicated that they would try to demonstrate that Studies 0015 and 019 can stand alone for a 10% NI margin and when combined, meet a 7% margin. The present resubmission incorporates the analysis of mortality based upon these discussions.

Following resubmission of this complete response, a new draft guidance document for development of drugs for treatment of hospital-acquired bacterial pneumonia, including ventilator associated pneumonia, has been posted on the FDA internet (November 26, 2010). This document recommends endpoint assessment at 28 days post-randomization and therefore no further discussion of the EOT+28 day endpoint will be included in the efficacy section of this review.

Discussion regarding information submitted and analyses of the June 30, 2010 submission will be further expanded upon in the efficacy and safety sections of this memo.

3. CMC/Device

There is no new CMC information provided in this submission

4. Nonclinical Pharmacology/Toxicology

There is no new nonclinical pharmacology/toxicology information provided in this submission.

5. Clinical Pharmacology/Biopharmaceutics

There is no new clinical pharmacology information provided in this submission.

6. Clinical Microbiology

There is no new clinical microbiology information provided in this submission.

7. Clinical/Statistical- Efficacy

Theravance, Inc was issued a complete response letter for their original NDA 22407, telavancin for treatment of NP submission. The complete response letter stated:

“The results of the two Phase 3 clinical trials (0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia (NP). Both trials were designed and powered for a clinical response endpoint.”

“Published historical evidence will only permit interpretation of non-inferiority trials for NP and VAP using all-cause mortality as the primary endpoint.”

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

The Applicant was advised that in order to resolve these deficiencies they would be required to:

- Submit all available all-cause mortality data and account fully for any censored information.
- Provide a scientific rationale for pooling all-cause mortality data across the two clinical trials. The rationale should address the consistency of the treatment difference for telavancin relative to vancomycin across the trials given the difference in the distribution of baseline prognostic factors for mortality between the two trials and the proportion of subjects whose mortality status is censored.
- In design of the new clinical trials advised for the NP indication, the Applicant was to consider the following:

- The study population should contain patients with a high likelihood of having the disease of interest.
- Chest radiograph interpretation should be performed by a blinded healthcare provider not directly involved in assessment of the patient for enrollment or subsequent care.
- Uniform criteria should be applied to identify the quality of sputum and endotracheal aspirate specimens for culture and subsequent pathogen identification.
- The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

The Applicant's resubmission on June 30, 2010 included:

- Information to support the adequacy of the NP diagnosis in patients enrolled in Studies 0015 and 0019
- Updated (more complete) mortality information (including vital status to 28 days post-randomization)
- Analysis strategy to demonstrate the treatment effect of telavancin using a historical control
- Rationale and methods used to pool the study populations for analysis by adjusting for baseline comorbidities associated with increased risk of death.

Study Population

Based upon concerns about the adequacy of the diagnosis of pneumonia and satisfactory performance of the inclusion/exclusion criteria contained in the clinical trial protocols, the Applicant provided the following information describing study population characteristics.

Severity of Illness

The Applicant included a review of key demographic and baseline characteristics to highlight the severely ill status of the patient population. Baseline comorbidities in the population included patients with underlying diabetes, COPD, hypertension, congestive heart failure, and renal insufficiency, along with factors such as a mean APACHE II score of 14 and half of the patients were > 65 years of age and in the ICU. Approximately 20% of the population had ventilator associated pneumonia at baseline. Due to FDA concerns about the accuracy of diagnosis of nosocomial pneumonia as defined by the trial inclusion criteria, the Applicant identified a secondary analysis population for the primary efficacy endpoint of 28 day all-cause mortality. This secondary analysis population, "Chest X-Ray + Two Clinical Features" (CXR+2F) was used to refine the population to be more consistent with the definition of NP outlined by the ATS/IDSA criteria.¹ The Applicant also performed analyses in subgroups outlined in Table 2 below.

¹ American Thoracic Society, Infectious Diseases Society of America. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-Associated, and Healthcare-associated Pneumonia. American Journal of Respiratory and Critical Care Medicine 2005;171:388-416.

Table 2: Applicant Analysis Populations

| Analysis Populations | Description |
|--|---|
| All-Treated (AT) | All patients who received any amount of study medication, according to treatment assigned at randomization. |
| Chest X-Ray Plus Two Clinical Features (AT CXR+2F) | All patients in the AT population who also had a new or progressive radiographic infiltrate plus at least two of three clinical features (fever >38°C, leukocytosis or leucopenia, and purulent secretions) at baseline |
| Analysis Subgroups | |
| Modified All-Treated (MAT) | All patients in the AT population who also had a baseline pathogen identified. |
| MAT, Any Gram Positive | Subgroup of all patients in the MAT population who also had a baseline Gram positive pathogen identified (i.e. patients with Gram positive or mixed gram positive, Gram negative infections) |
| MAT, Only Gram Positive | Subgroup of all patients in the MAT population who also had a baseline Gram positive pathogen and no Gram negative pathogen identified |
| NDA 22407, June 30, 2010, Summary of Clinical Efficacy, Table 28 A baseline pathogen was defined as an organism known to cause pneumonia identified from baseline respiratory cultures from sputum, endotracheal aspirate (ETA), blind bronchial suctioning (BBS), bronchoalveolar lavage (BAL), mini-BAL, or protected specimen brush (PSB). 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 would qualify a patient for the MAT population. | |

Adequacy of respiratory specimens:

The Applicant provided criteria for a uniform examination of sputum and endotracheal aspirates. A reliable sputum specimen was defined as having > 25 white blood cells and < 10 squamous epithelial cells per low power field. A reliable endotracheal aspirate was defined as having < 10 squamous epithelial cells per low power field. Reliability of cultures was also evaluated according to the number of respiratory pathogens isolated per specimen, with < 3 isolates considered to be a reliable specimen. Table 3 shows the percentage of types of specimens collected and the reliability of those specimens.

Table 3: Applicant All-Treated Population

| | 0015 | | 0019 | | Pooled | |
|---|--------------|--------------|--------------|--------------|--------------|--------------|
| | TLV N=372 | VAN N=374 | TLV N=377 | VAN N=380 | TLV N=749 | VAN N=754 |
| Patients with sputum sample | 169 (45%) | 174 (47%) | 151 (40%) | 164 (43%) | 320 (43%) | 338 (45%) |
| Reliable | 101 (60%) | 107 (61%) | 113 (75%) | 123 (75%) | 214 (67%) | 230 (68%) |
| Patients with ETA samples | 132 (35%) | 134 (36%) | 171 (45%) | 180 (47%) | 303 (40%) | 314 (42%) |
| Reliable | 103 (78%) | 114 (85%) | 141 (82%) | 158 (88%) | 244 (81%) | 272 (87%) |
| Patients with samples from other invasive procedures* | 68 (18%) | 62 (17%) | 61 (16%) | 42 (11%) | 129 (17%) | 104 (14%) |
| Patients with no respiratory samples | 9 (2%) | 11 (3%) | 8 (2%) | 7 (2%) | 17 (2%) | 18 (2%) |
| Source: NDA 22407, ISE, Table 3.1 pg 28. | | | | | | |
| * BAL, mini-BAL, protected specimen brush, blind bronchial suctioning | | | | | | |

While these criteria help to better define and qualify respiratory specimens for consideration, these criteria were not used in the initial analyses and many subsequent microbiologically defined analyses. Therefore the inference of “reliability” of microbiological specimens for analyses in the application is unclear.

Chest Radiographs

A chest radiograph (CXR) showing new pulmonary infiltrates is recommended (required) for defining pneumonia. The CXRs for these trials were to be interpreted by the investigator or radiologist to avoid delay in initiating antimicrobial therapy. In order to determine the concordance between the case report form (CRF) data and the CXR report or source documentation, the documents and CRF data were submitted by the Applicant to an independent radiology core laboratory for a treatment blinded review. Baseline reports or source documentation was obtained for 1281/1503 (85.2%) of randomized patients who took study drug. For 85% of those with source documentation, the documentation was a report by a radiologist. The findings indicated an 83% anatomical correlation of pulmonary pathology between source documents and CRF data. Consistency of the diagnosis of pneumonia was noted in 94% of patients.

This does not alleviate the problem of bias that may have been introduced by an investigator’s interpretation of a CXR and subsequent enrollment of patients in the trial.

Mortality Analysis

The Applicant has recovered a substantial amount of mortality data since revision of mortality data was made to the original application in July 22, 2009. The amount of missing mortality data has decreased from approximately 30% to 5% for the 28 day post-randomization period.

The Applicant analyzed 28 day all-cause mortality for the AT and CXR+2F populations. The primary analysis population was the AT population that included all patients who had received any dose of study medication. The results of this analysis are shown in Table 4 below:

Table 4: Summary of 28-day all-cause mortality (Applicant AT population)

| | 0015 | | 0019 | |
|----------------------|----------------|----------------|----------------|----------------|
| | TLV N=372 | VAN N=374 | TLV N=377 | VAN N=380 |
| Deaths | 95 (25.5%) | 74 (19.8%) | 83 (22.0%) | 90 (23.7%) |
| Alive | 258 (69.4%) | 272 (72.7%) | 277 (73.5%) | 270 (71.1%) |
| Lost to Follow-up | 19 (5.1) | 28 (7.5%) | 17 (4.5%) | 17 (4.5%) |

NDA 22407, ISE, Table 4.1, pg 51.

Table 5 shows the estimated difference in 28-day all-cause mortality for both trials.

Table 5: Estimated 28-Day All-Cause Mortality (AT Population)

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

Adapted from ISE Addendum, Table 4.2, pg 55

In study 0015, the estimated mortality difference is 5.8%, 95% CI (-0.3, 11.9) and for Study 0019 the estimated difference is -1.9%, 95% CI (-8.0, 4.42). As noted By Dr. Komo in his statistical review, the results for Study 0015 “are concerning because 1) the telavancin mortality rate is almost statistically significantly ($p < 0.05$) higher than vancomycin and 2) the upper bound of the 95% CI is markedly higher than the NI margin of 10% proposed in the Draft Guidance for Industry on Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment published on 11/2010.”

The following Tables 6 and 7, show the results of the mortality analysis in the more strictly defined CXR+2F population.

Table 6: Summary of 28-day all-cause mortality (AT population)

| | 0015 | | 0019 | |
|-------------------|---------------|---------------|---------------|---------------|
| | TLV N=309 | VAN N=316 | TLV N=327 | VAN N=337 |
| Deaths | 75 (24.3) | 67 (21.2) | 75 (22.9) | 79 (23.4) |
| Alive | 216 (69.9) | 225 (71.2) | 239 (73.1) | 238 (70.6) |
| Lost to Follow-up | 18 (5.8) | 24 (7.6) | 13 (4.0) | 20 (5.9) |

NDA 22407, ISE, Appendix 7, pg 125

Table 7: Estimated 28-Day All-Cause Mortality (AT Population)

| Study | Treatment | Estimated K-M Mortality at 28 Days (%) | Diff (%) (TLV-VANC) 95% CI |
|-------|-----------|--|----------------------------|
| 0015 | TLV | 24.6 | 3.0 (-3.6, 9.7) |
| | VAN | 21.6 | |
| 0019 | TLV | 23.1 | -0.9 (-7.3, 5.7) |
| | VAN | 24.0 | |

Adapted from ISE Addendum, Supporting Table 13, pg 128

The results of the CXR+2F analyses show that when a more stringent definition for NP is utilized the mortality imbalance decreases in both Study 0015 and Study 0019. This could potentially indicate that telavancin might perform better in a patient population more strictly defined to truly have NP.

Since telavancin and comparator (vancomycin) have no Gram negative activity, the FDA defined the primary analysis population as all patients who received any amount of treatment with study medication and had a Gram positive pathogen (either as a sole pathogen or in a mixed Gram positive and Gram negative bacterial infection) isolated from a baseline culture. Tables 8 and 9 below show the results of the 28-day all-cause mortality analysis in the FDA MAT population.

Table 8: Summary of 28-day all-cause mortality (FDA MAT population)

| | 0015 | | 0019 | |
|--------------------------|---------------|---------------|---------------|---------------|
| | TLV N=187 | VAN N=180 | TLV N=224 | VAN N=206 |
| Deaths | 53 (28.3) | 43 (23.9) | 54 (24.1) | 45 (21.8) |
| Alive | 128 (68.4) | 123 (68.3) | 161 (71.9) | 148 (71.8) |
| Lost to Follow-up | 6 (3.2) | 14 (7.8) | 9 (4.0) | 13 (6.3) |
| FDA Statistical Reviewer | | | | |

Table 9: Estimated 28-Day All-Cause Mortality (FDA MAT Population)

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

In the FDA analysis, there are a greater number of deaths in the telavancin treatment group in both trials. Study 0019 marginally demonstrated the noninferiority of telavancin to vancomycin with an observed difference in 28-day all-cause mortality rates of 2.0% (telavancin: 24.3%; vancomycin: 22.3%) and a corresponding 95% CI of (-6.1%, 10.0%).

FDA also looked at a subgroup of patients with MRSA at baseline, excluding patients who may have received overlapping antibacterial therapy with potential MRSA activity (i.e. doxycycline, clindamycin). Given telavancin's activity against MRSA, this is a subgroup of patients in whom there is a particular interest in outcome. The results of these analyses are consistent with those of the MAT population and are shown in Tables 10 and 11 below:

Table 10: 28-Day All-Cause Mortality (FDA MAT including only patients with MRSA at baseline excluding patients who may have received adjunctive agents with activity against MRSA)

| | 0015 | | 0019 | |
|--------------------------|--------------|--------------|--------------|--------------|
| | TLV N=115 | VAN N=114 | TLV N=118 | VAN N=116 |
| Deaths | 36 (31.3) | 27 (23.7) | 39 (33.0) | 34 (29.3) |
| Alive | 76 (66.1) | 75 (65.8) | 75 (63.6) | 77 (66.4) |
| Lost to Follow-up | 3 (2.6) | 12 (10.5) | 4 (3.4) | 5 (4.3) |
| FDA Statistical Reviewer | | | | |

Table 11: Estimated 28-Day All-Cause Mortality (FDA MAT including only patients with MRSA at baseline excluding patients who may have received adjunctive agents with activity against MRSA)

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

This subgroup analysis yields similar results to the FDA MAT analysis and shows that mortality was higher in the telavancin treatment groups in both trials although the width of the confidence intervals has increased due to a decrease in sample size.

Concomitant Antimicrobial Use

Approximately 25% of patients received concomitant potentially effective non-study antibacterial agents for > 2 days. A patient was defined as having received potentially effective antibiotic therapy if he/she was treated on 3 or more calendar days with one or more antibiotics that either 1) had activity against all of the patient's baseline Gram positive respiratory pathogens or, 2) if no baseline Gram positive respiratory pathogen had been identified, had activity against any Gram positive respiratory pathogen. Whether an individual patient had received PEAT was determined on a case-by-case basis by the Applicant's medical monitor. Use of PEAT affected about 25% of the AT population.

An additional subgroup analysis was performed by the FDA reviewers on the subgroup of FDA MAT patients who did not receiving concomitant potentially effective

Gram negative antibacterial treatment with overlapping Gram positive activity. The results of this analysis are shown in Table 12.

Table 12: 28-Day All-Cause Mortality (FDA MAT excluding patients who received adjunctive agents with overlapping Gram positive activity)

| | 0015 | | 0019 | |
|--------------------------|---------------|---------------|---------------|---------------|
| | TLV N=164 | VAN N=163 | TLV N=130 | VAN N=125 |
| Deaths | 47 (28.7) | 39 (23.9) | 47 (23.4) | 38 (20.5) |
| Alive | 112 (68.3) | 110 (67.5) | 146 (72.6) | 134 (72.4) |
| Lost to Follow-up | 5 (3.0) | 14 (8.6) | 8 (4.0) | 13 (7.0) |
| FDA Statistical Reviewer | | | | |

Table 13: Estimated 28-Day All-Cause Mortality (FDA MAT excluding patients who received adjunctive agents with overlapping Gram positive activity)

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

This subgroup analysis also yields similar results to the FDA MAT analysis and shows that mortality was higher in the telavancin treatment groups in both trials.

Analysis Strategy

In order to demonstrate the treatment effect of telavancin, the Applicant used superiority analyses to compare the treatment effect of telavancin to imputed placebo using historical data from trials of delayed or inappropriate antibacterial treatment of NP. A second analysis involved comparing vancomycin to this historical “placebo”. Subsequently an analysis that pooled data across the two trials (Studies 0015 and 0019) and controlled for prognostic factors provided an estimate of relative effect of telavancin compared to vancomycin.

Dr. Komo outlined in his statistical review the concerns with use of a historical control group to demonstrate effectiveness. He notes, “It is difficult to establish comparability of the treatment and control groups, which is essential to fulfill the major purpose of the control group, i.e. the ability to discriminate patient outcomes caused by treatment from outcomes caused by other factors.” The historical data utilized for the control group included all ten studies identified by the FDA, along with two additional studies as compared to the two studies used by Sorbello, et al to establish a NI margin.² Specific concerns with comparing telavancin treatment to treatment in the historical

² Sorbello A, Komo s, Valappil T. Noninferiority margin for clinical trials of antibacterial drugs for nosocomial pneumonia, Drug Information Journal 2010;44:165-176.

control include the fact that the telavancin trial population included a lower percentage of VAP patients (30%) and more patients with Gram positive (primarily MRSA) than Gram negative bacterial infections as seen in the historical literature. The lower incidence of VAP in the telavancin population is concerning because in Study 0019, the mortality rate was noted to be markedly higher for the VAP patients than for non-VAP patients, as noted on page 17 of Dr. Komo's review.

Pooling of Data from Studies 0015 and 0019

In his review of the original NDA 22407, Dr. Sorbello expressed his concern with pooling data from the two trials because he noted several cross-study differences in potential risk factors for mortality (page 125-127 of NDA 22407 clinical review). Such differences included more patients in Study 0015 with chronic renal failure, baseline CrCl < 50 mL/min, serum Cr > 1.2 mg/dL, hemodialysis, diabetic status (yes), acute respiratory distress syndrome (ARDS), healthcare-associated pneumonia (HCAP), torsades, history of atrial fibrillation, and history of myocardial infarction. In Study 0019, there were more patients with serum Cr ≤ 1.2 mg/dL, immunocompromised patients, patients with hospital-acquired pneumonia, organ failure at baseline, and history of left ventricular hypertrophy compared to study 0015.

The Applicant's rationale for pooling the two trials included:

- The trials were conducted under identical protocols
- The trials were conducted concurrently
- The statistical plan called for combining the trials for the purpose of analysis of efficacy (clinical response in patients with MRSA).
- There was no difference in 30 of 31 baseline characteristics
- The confidence intervals for all-cause mortality overlap

The Applicant used a multivariate proportional hazards regression model to identify baseline covariates predictive of mortality, then adjust treatment estimates for predictive covariates and treatment effect modifiers, and finally, to estimate adjusted hazard ratios. The Applicant found nine baseline characteristics related to outcome: APACHE II, creatinine clearance (CrCl), cardiovascular disease, MRSA infection, multilobar pneumonia, bacteremia, acute respiratory distress syndrome/acute lung injury, geographic region and acute renal failure. There was one interaction with treatment and that was ARF at baseline.

After adjusting for baseline covariates predictive of mortality, the Applicant combined data from Studies 0015 and 0019 because it provided a more precise estimate of hazards ratios for comparison of treatments using all available data. As noted by Dr. Komo, "The proposal for the comparison between telavancin and vancomycin to include post hoc selected variables assumed to predict mortality is problematic because it is a data-driven analysis and can bias the results and potentially inflate the overall type-1 error rate." "We view the analyses that include prognostic factors as exploratory."

For additional details on the efficacy review of the original NDA 22407, see the clinical review by Alfred, Sorbello, DO, MPH and statistical review by Scott Komo, DrPH. For additional details on the June 30, 2010 resubmission to NDA 22407, see the clinical review by Benjamin Lorenz, MD and statistical review by Scott Komo, DrPH.

8. Safety

The safety review of the original submission of NDA 22407 was also completed by Alfred Sorbello DO, MPH. Dr. Sorbello had concerns about the imbalance in mortality in Study 0015 with more deaths occurring in the telavancin treatment group (although this finding was based on incomplete mortality data). Dr. Sorbello also had concerns regarding the imbalance in serious renal adverse events with more events occurring in the telavancin treatment group. There were also noted to be an increased number of pulmonary emboli cases reported for the telavancin treatment group, although review of the narratives did not support a specific drug signal. For additional details, refer to Dr. Sorbello's safety review of NDA 22407.

The safety update in this submission referenced the post-marketing Periodic Adverse Drug Experience Report (PADER) submitted to NDA 22-110, April 12, 2010, along with the results of a literature review for safety information related to telavancin covering the period from November 2, 2009 to May 31, 2010.

There were no nonclinical or clinical trial safety data to review. The literature review did not identify any safety issues not previously described from the clinical trial database.

Postmarketing Experience

In addition to the PADER included with the submission, two additional PADERs encompassing the periods March 11, 2010-June 10, 2010 and June 11-September 10, 2010, for telavancin NDA 22110 were also reviewed.

The referenced PADER covered the time period December 11, 2009-March 10, 2010. During this time period, there were six initial 15-day alert reports for serious unlisted adverse drug experiences (ADEs). The following list contains those events with explanatory comments if available.

- Stroke (occurred while the patient was on telavancin, incomplete information)
- Accidental exposure (with questionable hypersensitivity reaction) while reconstituting sealed vials of telavancin
- Death secondary to staphylococcal bacteremia: 21 year old female with methicillin-resistant *Staphylococcus aureus* (MRSA) vertebral osteomyelitis, bacteremia, and pneumonia developed septic shock following a bone biopsy and required continuous renal replacement therapy to treat acute renal failure. Renal replacement therapy was ongoing at the time telavancin was first administered. The patient had received prior treatment with vancomycin and daptomycin (with possible rhabdomyolysis) for MRSA.

- Acute renal failure: male with MRSA osteomyelitis and a history of hypertension and diabetes mellitus (type II) developed acute renal failure with a creatinine of 5.9 on Day 3 of telavancin therapy. The patient required hospitalization for acute non-oliguric renal failure, became hypoxic, and was admitted to the intensive care unit for respiratory failure. He required hemodialysis until Day 7, with renal function subsequently reported as improving.
- Dyspnea and pruritus: possible anaphylactic reaction treated with diphenhydramine and methylprednisolone.
- Diarrhea (presumed *Clostridium difficile*): on Day 11 of telavancin therapy, the patient developed presumed *C. difficile* diarrhea and died 5 days later.

Skin and subcutaneous disorders (primarily rash and pruritus) and renal events (impairment and failure) were the most common serious events (by system organ class (SOC) during this period.

The second PADER covered the time period March 11, 2010-June 10, 2010. During this time period, there were two initial 15-day alert reports for serious unlisted adverse drug experiences. The following list contains those events with explanatory comments if available.

- Abnormal liver function tests: the patient was noted to have an elevation in alkaline phosphatase (143 to 220 on Day 8 of telavancin, no units or normal range reported), aspartate aminotransferase (85 to 231 on Day 8, no units or normal range reported), and alanine aminotransferase (68 to 331 on Day 9, no units or normal range reported) which required hospitalization. Liver function tests were noted to normalize while on telavancin (no values given).
- Cyanosis, abnormal ECG: the patient required hospitalization, causality was not assessed by the primary physician and no cardiac history or description of the abnormality was provided.

Renal events (6) were the most common serious adverse drug experiences reported during this period. Nervous system disorders (dysgeusia) and skin disorders (rash, pruritus) were the most common ADEs by SOC.

The third PADER covered the time period June 11, 2010-September 10, 2010. During this time period, there were ten initial 15-day alert reports for serious unlisted adverse drug experiences. The following list contains those events with explanatory comments if available.

- Leukopenia or decreased WBC (3 cases):
 - Poorly documented case of leukopenia and neutropenia with telavancin treatment that reportedly resolved with discontinuation and recurred upon rechallenge with telavancin.
 - Second case of poorly documented leukopenia and neutropenia.
 - Female patient with HIV infection and CNS lymphoma noted to have a decrease in WBC from 8.4 to 0.1 resulting in discontinuation of telavancin. No other useful information was reported, including any history of concomitant HIV medications or treatment for lymphoma.

- Hepatotoxicity, abnormal LFTs (2 cases):
 - Female hemodialysis patient treated with telavancin for osteomyelitis and discitis (presumed MRSA) who developed unspecified elevations in liver function tests 28 days after starting therapy. The abnormal labs resolved with discontinuation of telavancin.
 - 50 year old female receiving telavancin for staphylococcal bacteremia developed hepatotoxicity. One week into treatment, AST and ALT had reportedly increased to 5000, along with a slight elevation in alkaline phosphatase. She had been treated with vancomycin prior to telavancin treatment.
- Cyanosis, abnormal ECG (possible previous report): 76 year old male who developed cyanosis and abnormal ECG two days after receiving a single dose of telavancin for cellulitis and an abscess. There was no follow-up information on the ECG abnormality or underlying cardiac pathology and there were confounding medications that may have explained the event.
- Diarrhea (possible previous report): 74 year old male with end-stage renal disease (ESRD) on hemodialysis and a MRSA paraspinal abscess initially treated with vancomycin and rifampin, then daptomycin, followed by telavancin. The patient developed diarrhea on Day 11 of telavancin treatment and was treated with oral vancomycin. The patient died (b) (6) later and was noted to have negative *C. difficile* toxin tests.
- ECG QT prolonged, loss of consciousness: A patient being treated with telavancin underwent wound debridement, went outside for a cigarette, and passed out. The patient was noted to have a slightly prolonged QTc interval. Key information regarding the QTc abnormality has not been provided.
- Confusional state: 36 year old female treated with a single dose of telavancin for an unspecified indication who went home after the initial infusion of telavancin and did not return for the next day's infusion. Her caregiver found her confused, obtunded, and was unable to get the patient to her next appointment.
- Convulsion: male patient developed seizures, shaking, or some type of convulsion with the use of telavancin. Additional history or medications were not provided.
- Renal failure, dehydration, rash: the patient had received telavancin for 3-4 weeks and was hospitalized with renal failure, dehydration, and rash while on telavancin therapy. Telavancin was discontinued and the events abated and the patient was discharged from the hospital.
- Chest pain and dyspnea: developed with infusion of telavancin on Day 8 of therapy and required transport to the hospital. Limited documentation limits assessment of causality.

Renal events and leucopenia were the most frequently reported serious events during this period. General disorders (chills and pyrexia), gastrointestinal (nausea and vomiting), and skin disorders (rash) are the most common AE by SOC.

Clinical Trial Mortality Analysis

The Safety Update included with the initial incomplete response submission on December 21, 2009, also contained updated mortality data (primarily vital status and cause of death if known).

In the original NDA, there was a prespecified period of time during which deaths were recorded for the trials. This period included deaths occurring prior to the “test of cure” (TOC) assessment or in patients with no TOC assessment for 28 days following discontinuation of study therapy.

As mortality data for the application was being reviewed for efficacy determination, it became apparent that not all patients had been followed for 28 days post randomization. The Applicant provided updated information to NDA 22407 on March 26, 2010, identifying 17 additional deaths occurring during the 28 day post-randomization and end of therapy + 28 day time periods. On July 22, 2010, the Applicant notified the Division that more deaths had been identified while developing Kaplan-Meier analyses requested by the Agency. The Applicant stated that deaths were identified from clinical and serious adverse event databases and from a pharmaco-economic substudy not analysed by Theravance. Narratives for the additional deaths were reported to NDA 22407 on August 13 and 14, 2010. This updated mortality information was included in Dr. Sorbello’s review and is shown in Table 14 below.

Table 14: Summary of Vital Status at Day 28 – AT Population

| | 0015 | | 0019 | | 0015 + 0019 Total | |
|--|--------------|--------------|--------------|--------------|-------------------|--------------|
| | TLV N=372 | VAN N=374 | TLV N=377 | VAN N=380 | TLV N=749 | VAN N=754 |
| Dead | 92 (25) | 73 (20) | 80 (21) | 88 (23) | 172 (23) | 161 (21) |
| Alive | 280 (75) | 301 (80) | 299 (79) | 290 (77) | 579 (77) | 591 (79) |
| Mortality Difference (T-V) | 5% | | -2% | | 2% | |
| Censored | 126 (34) | 134 (36) | 113 (30) | 193 (27) | 239 (32) | 237 (32) |
| NDA 22407, August 12, 2009, ISE, Response to FDA Information Request July 31, 2009 | | | | | | |

Dr. Sorbello noted in his review, “When the all cause mortality data is analyzed from the safety perspective, the results for Study 0015 suggest that there is a substantially higher risk for death in the telavancin treatment group compared to the vancomycin treatment group. The results for Study 0019 and the results of the pooled vancomycin data do not suggest a similar conclusion.” It was also noted with the large amount of censored data (>30%), the actual number of deaths may be underestimated.

Table 15 summarizes the most frequent causes for death in both treatment groups reported in the Applicant’s original summary of mortality for Study 0015. The most commonly reported cause of death in the telavancin treatment group was multi-organ failure, while in the vancomycin treatment group it was respiratory failure.

Table 15: FDA Medical Officer Summary Table of the Most Frequent Causes (>3%) for Death, Study 0015, AT Population

| | | TLV | VAN |
|---|----------------------------|------------|------------|
| All Treated | N (%) | 372 | 374 |
| Total Subject Deaths | n (%) | 80 (21.5%) | 62 (16.6%) |
| Causes for Death n (% of all deaths) | Not specified | 16 (20.0%) | 10 (16.1%) |
| | Multi-organ failure* | 11 (13.8%) | 6 (9.7%) |
| | Septic shock** | 7 (8.8%) | 6 (9.7%) |
| | Respiratory Arrest | 6 (7.5%) | 10 (16.1%) |
| | Heart Failure [#] | 3 (3.8%) | 2 (3.2%) |
| | Sepsis [†] | 3 (3.8%) | 2 (3.2%) |
| <p>* Includes the following preferred terms (PT): multiple organ failure, multi organ failure, multiorgan system failure, multiple organ failure syndrome, multiple organ failure/cardiogenic shock, multiple organ failure/end stage liver disease/primary biliary cirrhosis</p> <p>** Includes the following PT: septic shock, septic shock/source septicemia, septic shock with multiorgan failure, septicemia shock (<i>A. baumannii</i>), septicemic shock with multiorgan failure, septic shock due to <i>P. aeruginosa</i> bacteremia, septic shock secondary to second episode of VAP, septic shock caused by suspected right sided empyema progressed</p> <p>[#] Includes the following PT: congestive heart failure, heart failure</p> <p>[†] Includes the following PT: sepsis, severe sepsis with burst abdomen, severe sepsis syndrome, worsening sepsis</p> | | | |

This table reflects causes of death for those deaths that occurred within the Applicant’s reporting window. It does not reflect the additional deaths identified by the Applicant in the July 22, August 13 and 14, 2010 submissions. Newly identified deaths occurring during the 28 day post-randomization period were of similar etiologies and included: respiratory failure (1), congestive heart failure (1), sepsis (1), hypotension (1), cardiopulmonary arrest (1), gastrointestinal hemorrhage (1), and unknown (5) in the telavancin treatment group. Causes of death in the vancomycin treatment group during this period included: multi-organ failure (1), metastatic breast cancer (1), sepsis (2), respiratory failure (2), aspiration (1), clinical failure (2), brain hemorrhage (1), and unknown (2).

Table 16 summarizes the most frequent causes for death among patients enrolled in Study 0019 and originally reported to the NDA. Septic shock was the most frequently reported cause of death in the telavancin treatment group and respiratory failure in the vancomycin treatment group.

Table 16: FDA Medical Officer Summary Table of the Most Frequent Causes (>3%) for Death, Study 0019, AT Population

| | | TLV | VAN |
|---|----------------------------------|------------|------------|
| All Treated | N (%) | 379 | 378 |
| Total Subject Deaths | n (%) | 70 (18.6%) | 78 (20.5%) |
| Causes for Death n (% of all deaths) | Septic shock | 11 (15.7%) | 6 (7.7%) |
| | Not specified | 8 (11.4%) | 18 (23%) |
| | Multi-organ failure* | 7 (10%) | 1 (1.3%) |
| | Pulmonary Embolism** | 4 (5.7%) | 1 (1.3%) |
| | Respiratory Failure [†] | 4 (5.7%) | 9 (11.5%) |
| | Heart failure [#] | 1 (1.4%) | 5 (6.4%) |
| * Includes the following PT: multi organ failure, multi-organ failure, multiorgan failure, multiple organ failure, multiple organ failure due to advanced carcinoma of right lung ** Includes the following PT: pulmonary embolism, pulmonary thromboemboli, pulmonary artery thromboemboli, pulmonary embolus suspicion † Includes the following PT: acute respiratory failure, respiratory failure, respiratory failure due to gastric contents aspiration, respiratory failure following removal of life support, acute respiratory failure due to tracheostomy obstruction, respiratory failure Type II, respiratory failure due to respiratory tract block by sputum, respiratory failure due to withdrawal of active therapy, respiratory failures # Includes the following PT: acute heart failure, cardiac failure, CHF, congestive heart failure with MI, heart failure | | | |

This table reflects causes of death for those deaths that occurred within the Applicant’s reporting window. It does not reflect the additional deaths identified by the Applicant in the July 22, August 13 and 14, 2010 submissions. Newly identified deaths occurring during the 28 day post-randomization period were of varying etiologies and included: multi-organ failure (2), congestive heart failure (1), arterial rupture (1), pneumonia (1), sudden death (1), acute myocardial infarction (1), intestinal ischemia (1), and unknown (3) for the telavancin treatment group. Causes of death in the vancomycin treatment group during this period included septic shock (6), ventricular fibrillation (1), aspiration (1), meningitis (1), hospital-acquired pneumonia (1), and unknown (4).

In the incomplete response submitted to the Agency on December 21, 2009, the Applicant had included vital status data (i.e. dead or alive, cause of death if available and the date of death or last day known to be alive if date of death was unknown) for 95% of patients 28 days post-randomization and 90% for 49 days post-randomization. Table 17 shows the vital status for patients at the 28-day timepoint.

Table 17: Summary of Vital Status at Day 28 – AT Population

| | 0015 | | 0019 | | 0015 + 0019 Total | |
|--|--------------|--------------|--------------|--------------|-------------------|--------------|
| | TLV N=372 | VAN N=374 | TLV N=377 | VAN N=380 | TLV N=749 | VAN N=754 |
| Dead | 95 (25.5) | 74 (19.8) | 84 (22.2) | 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) |
| Mortality Difference (T-V) | 5.7% | | -1.7% | | 2.0% | |
| Censored | 19 (5.1) | 28 (7.5) | 17 (4.5) | 20 (5.3) | 36 (4.8) | 48 (6.4) |
| NDA 22407, June 30, 2010, ISE, Table 4.1, pg 51. | | | | | | |

Narratives for each of the additional deaths reported in the 28-day all cause mortality window in the December 21, 2009 submission follow.

Study 0015

- 0015-12006-4123 (telavancin): a 70 year old male with a history of diabetes, hypertension, ischemic cardiomyopathy, and recent hemorrhagic stroke received telavancin for 3 days for HAP. Telavancin was discontinued following isolation of a Gram negative bacterial pathogen. Six days after discontinuing telavancin, the patient had a tracheal hemorrhage and recovered. The patient subsequently died due to a ventricular arrhythmia approximately 10 days after discontinuing telavancin.
- 0015-33016-4457 (telavancin): an 84 year old male with a complicated medical history including complete AV block with pulmonary edema, acute renal failure, congestive heart failure, pacemaker placement, and upper gastrointestinal bleed received 15 days of telavancin for HAP, approximately 1 month after placement of the pacemaker. The patient was reportedly a clinical cure at the test of cure assessment and died 10 days later of unknown cause.
- 0015-38024-4787 (telavancin): an 80 year old male with a history of recent acute renal failure and anemia after being hospitalized for a traumatic motor-bike accident received 10 days of telavancin for HAP. The patient was assessed as a clinical cure at (b) (6) and died 4 days later of unknown cause.
- 0015-18010-4263 (vancomycin): an 84 year old male with a history of vascular disease and hospitalized for a stroke received 11 days of vancomycin for HAP. The patient was assessed as a clinical failure on Day 11 and died of unknown cause on (b) (6)

Study 0019

- 0019-01019-6032 (telavancin): a 68 year old female with a history of severe aortic stenosis, left ventricular hypertrophy, and chronic heart failure was admitted to the hospital for aortic stenosis and respiratory failure and received 9 days of telavancin for HAP. The patient was assessed as a clinical cure on Day 16 and subsequently died of unknown cause on (b) (6) after discharge from the hospital.
- 0019-08001-6261 (telavancin): a 74 year old male with medical history significant for heart failure and renal insufficiency treated with 4 days of telavancin for HAP. On (b) (6) he developed respiratory and multi-organ failure and was “discharged” – the narrative indicates he died the next day.
- 0019-38340-6617 (telavancin): an 84 year old male admitted to the ICU for a subdural hemorrhage received 11 days of telavancin for HAP. On Day 3 of treatment, he developed mild elevation in serum creatinine (1.0 to 1.5) which reportedly resolved while on treatment (although no follow-up laboratory value similar to baseline was recorded). The patient withdrew consent and Cr was noted to be 1.5 on Day 10. He was transferred to another acute care facility and withdrew consent to all non-comfort meds and died on (b) (6)
- 0019-42002-6325 (telavancin): a 95 year old male hospitalized for a COPD exacerbation, hypertension, and stroke received telavancin for 8 days. The patient’s end of therapy assessment was indeterminate due to isolation of a Gram negative bacterial pathogen and the test of cure assessment on Day 15 was also

indeterminate. The patient died secondary to multiorgan failure due to HAP on (b) (6)

- 0019-18004-6717 (vancomycin): a 54 year old male hospitalized with metastatic melanoma was treated with 7 days of vancomycin for HAP. The patient was assessed as a clinical cure on Day 14 and died on (b) (6) secondary to brain metastases.
- 0019-34002-6607 (vancomycin): a 58 year old female was admitted with acute myocardial infarction and treated with 3 days of vancomycin for HAP. The patient died on (b) (6) of study therapy due to heart failure.

Increased risk of mortality with baseline acute renal failure

In attempting to provide justification for its proposed noninferiority margin, the Applicant evaluated relative mortality rates of telavancin versus vancomycin using regression analysis to adjust mortality rates for prognostic factors in both Study 0015 and 0019 and for the two studies combined. The Applicant noted that an imbalance in prognostic factors could skew results for unadjusted treatment comparisons and therefore proposed to base the comparison on an adjusted hazard regression estimate of the log hazard ratio. The purpose of this analysis was to identify patient characteristics which are related to survival to adjust treatment comparisons for imbalances on covariates to minimize random imbalance.

In the multivariate regression model, ARF at baseline was the only variable that showed an interaction with treatment. However, in Studies 0015 and 0019, there was no prespecified definition for acute renal failure and the diagnosis was left to the discretion of the investigator. The diagnosis of ARF was left to the discretion of the investigator and involved checking a box on the CRF. It is unclear whether some of these patients may have had acute on top of chronic renal failure. Tables 18 and 19 show the interaction between treatment and baseline acute renal failure

Table 18: 28-day all-cause mortality (AT population – patients classified as treated)

| History of ARF | 0015 | | 0019 | |
|------------------------|---------------|---------------|---------------|---------------|
| | TLV N=372 | VAN N=374 | TLV N=377 | VAN N=380 |
| YES | 43 | 35 | 30 | 29 |
| Deaths | 22 (51.2) | 8 (22.9) | 19 (63.3) | 13 (44.8) |
| Alive | 21 (48.8) | 26 (74.3) | 9 (30.0) | 16 (55.2) |
| Censored | 0 | 1 (2.9) | 2 (6.7) | 0 |
| NO | 329 | 339 | 349 | 349 |
| Deaths | 73 (22.2) | 66 (19.5) | 65 (18.6) | 76 (21.8) |
| Alive | 237 (72.0) | 246 (72.6) | 269 (77.1) | 253 (72.5) |
| Censored | 19 (5.8) | 27 (8.0) | 15 (4.3) | 20 (5.7) |
| FDA Statistician Table | | | | |

Table 19 shows the estimated difference in 28-day all-cause mortality for both trials.

Table 19: Kaplan-Meier estimates of 28-Day All-Cause Mortality (AT Population)

| ARF at Baseline | 0015 | | | 0019 | | |
|-----------------|--|------|---------------------------|--|------|---------------------------|
| | Estimated K-M Mortality At 28 Days (%) | | Diff (%) (TLV-VANC) 95%CI | Estimated K-M Mortality At 28 Days (%) | | Diff (%) (TLV-VANC) 95%CI |
| | TLV | VAN | | TLV | VAN | |
| YES | 51.2 | 22.9 | 28.3 (7.9, 48.7) | 65.1 | 44.8 | 20.3 (-4.8, 45.3) |
| NO | 22.5 | 19.8 | 2.7 (-3.6, 8.9) | 18.8 | 22.2 | -3.4 (-9.5, 2.6) |

FDA Statistician Table

There is at least a 20% increase in mortality for the telavancin treatment group compared to the vancomycin treatment group in patients with acute renal failure at baseline as compared to minimal effect on mortality in patients who did not have renal failure at baseline.

Based on this analysis, the Applicant proposed the following addition to the Warnings and Precautions Section of the product label:



9. Advisory Committee Meeting

No Advisory Committee meeting was convened for this application.

10. Pediatrics

Not applicable.

11. Other Relevant Regulatory Issues

The draft guidance document “Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment, Revision 1, was

posted to the FDA internet on November 26, 2010. This guidance document may be found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf> (accessed December 1, 2010).

12. Labeling

Not applicable.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this resubmission is issuance of a complete response letter. The Applicant has not provided substantial evidence from adequate and well-controlled trials that telavancin is effective for the treatment of nosocomial pneumonia caused by suspected or confirmed Gram positive pathogens, including MRSA. The trials were designed in accordance with regulatory guidance available at the time (1998 draft guidance document “Nosocomial Pneumonia – Developing Antimicrobial Drugs for Treatment”) with the primary efficacy endpoint of clinical response at a test of cure assessment. However, there is insufficient historical evidence to provide justification for a noninferiority margin for this endpoint, Historical literature identified to date exists only for justification of a noninferiority margin based on an all-cause mortality endpoint.

Although the Applicant has been able to capture a substantial amount of 28-day all-cause mortality data (i.e. for 95% of the trial populations), the results of the two trials (Study 0015 and 0019) are discrepant, with Study 0015 demonstrating increased risk of mortality in telavancin-treated patients that approached statistical significance. The estimated mortality difference (telavancin-vancomycin) was 5.8%, 95% CI (-0.3, 11.9). Study 0019 did demonstrate the non-inferiority of telavancin to vancomycin with a estimated mortality difference of -1.9, 95% CI (-8.0, 4.4). However, both of these analyses were applied to an analysis population of the all-treated population, Since telavancin (and comparator vancomycin) have only Gram positive antibacterial activity, the FDA review team believes that the appropriate primary analysis population should include only patients treated with study medication who have a Gram positive bacterial pathogen (either as a sole pathogen or mixed Gram positive and Gram negative bacterial infection) isolated from baseline culture. Results of the FDA primary analysis for Study 0019 marginally demonstrated that telavancin was noninferior to vancomycin with an estimated mortality difference of 2.0, 95% CI (-6.1, 10) [assuming NI margin of 10%], while analyses of Study 0015 did not demonstrate non-inferiority.

Concerns have been raised by the FDA review team about the suitability of the diagnosis of nosocomial pneumonia in the trial populations. Specifically there are questions about the rigor of the disease definition used, inclusion of chronic care facility patients in the population of patients with nosocomial pneumonia, lack of independent chest radiograph interpretation to establish the diagnosis of pneumonia, reliability of microbiological specimens to identify pathogens due to lack of standardized criteria for evaluability of specimens, and the amount of concomitant Gram negative antibacterial treatment with overlapping Gram positive activity administered.

Therefore, in order to resolve these deficiencies, the Applicant should perform two new adequate and well-controlled trials with design recommendations outlined in the 2010 draft guidance document "Hospital-Acquired Bacterial Pneumonia and Ventilator Associated Bacterial Pneumonia: Developing Drugs for Treatment."

- Risk Benefit Assessment

There has been no benefit demonstrated to date for telavancin for the treatment of nosocomial pneumonia.

However, in the process of evaluating the proportional hazards regression analysis model, the Applicant identified a telavancin treatment related increase in mortality. Telavancin increased the risk of mortality in patients in whom the investigator had made an assessment of ARF at baseline. Unfortunately, there was no standardized definition for ARF, so it unclear if this risk existed for all patients or only patients at risk of renal failure due to the presence of a medical co-morbidity (such as diabetes mellitus or hypertension), concomitant nephrotoxic medication, or with pre-enrollment evidence of chronic renal insufficiency.

At the present time there is no demonstrated benefit for approving telavancin for this indication.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable.

- Recommended Comments to Applicant

CLINICAL

1. The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia. While a substantial amount of missing mortality data has been recovered and provided for analysis, the analysis in the population of interest (i.e. patients with hospital acquired bacterial pneumonia caused by Gram positive bacteria) in Study 0015 does not demonstrate noninferiority of telavancin relative to vancomycin. When the same analysis population is assessed, Study 0019 marginally demonstrated the noninferiority of telavancin to vancomycin with an observed difference in 28-day all-cause mortality rates of 2.0% (telavancin 24.3%; vancomycin 22.3%) and a corresponding 95% CI of (-6.1%, 10.0%).
2. The method of selection of patients did not provide adequate assurance that patients had the disease being studied.
3. Before the application can be approved, it will be necessary for you to perform two adequate and well-controlled trials to demonstrate the efficacy and safety of telavancin in patients with hospital-acquired bacterial pneumonia.
 - The inclusion criteria for enrolled patients should include evidence of a new or progressive infiltrate on chest radiograph with at least two of the following features: fever > 38°C, leukocytosis or leucopenia, and purulent respiratory secretions.
 - Chest radiograph interpretation should be performed by a qualified health care professional (such as a radiologist or pulmonologist) not involved in enrolling patients in the trial.
 - Uniform criteria should be applied to assess the quality of respiratory specimens for culture and subsequent pathogen identification.
 - The use of adjunctive antibacterial therapy should be minimized and rapid de-escalation criteria should be included in the study protocol.

STATISTICAL

1. Your analysis method comparing the telavancin-treated patients from your Phase 3 trials to the historical studies of patients receiving inadequate, inappropriate, and delayed therapy is problematic. Specifically, the baseline comparability of the telavancin patients in the current trials and the historical controls is an outstanding issue.
2. The pooling of patients across the two Phase 3 trials is still problematic because of the differences in potential risk factors for mortality between the two trials, e.g. diabetes mellitus and renal impairment/failure.
3. The inclusion of post-hoc selected prognostic risk factors for mortality in the analyses is data driven and can bias the results.

MICROBIOLOGY [Carried over from Complete Response Letter November 23, 2009]

1. Data from the Phase 3 trials conducted in support of this NDA, do not provide adequate information for the analysis of telavancin activity against penicillin non-susceptible isolates of *Streptococcus pneumoniae*. It is suggested that

additional data from studies enriched to include subjects infected with penicillin non-susceptible isolates of *S. pneumoniae* be submitted.

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/s/

JANICE K POHLMAN
12/20/2010

M E M O R A N D U M**DEPARTMENT OF HEALTH AND HUMAN
SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND
RESEARCH**

DATE: 11-23-09

FROM: Katherine A. Laessig, M.D.
Deputy Director
Division of Anti-infective and Ophthalmology Products

TO: Division File

SUBJECT: Deputy Division Director's Decisional Memo for NDA 22-407,
telavancin for intravenous infusion 10 mg/kg every 24 hours
(Tradename VIBATIV™)

1.0 Background

Telavancin (TLV) is an injectable, lipoglycopeptide antibacterial agent, produced by chemical modification of vancomycin. Its mechanism of action is via inhibition of bacterial wall synthesis by interfering with peptidoglycan synthesis and cross-linking. TLV also causes disruption of the functional integrity of the cell membrane by depolarizing the membrane. It has activity against Gram positive bacteria including *Staphylococcus aureus* and *Streptococcus pneumoniae*, that may cause nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP). TLV was approved for the treatment of complicated skin and skin structure infections (cSSSI) caused by designated, TLV-susceptible, Gram positive organisms including methicillin resistant *S. aureus* on September 11, 2009, after the third review cycle. Previous review cycles had been complicated by problems at a manufacturing facility, data integrity issues which were resolved satisfactorily prior to approval, and the need for implementation of a Risk Evaluation and Mitigation Strategy (REMS), due to the potential risk for teratogenicity, based on animal data.

The applicant, Theravance, Inc., has submitted NDA 22-407 in support of 10 mg/kg of TLV administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to (b) (4) days for the requested indication of the treatment of adults with NP caused by susceptible strains of Gram positive bacteria. The submission contains the data and results from two Phase 3 clinical trials of NP and has been reviewed by multiple disciplines. This memo will summarize elements of all reviews by discipline; for detailed discussion by discipline, please refer to the respective reviews and the cross-discipline team leader memo by Dr. Janice Pohlman.

2.0 Summary of Chemistry, Manufacturing, and Controls

The applicant has cross-referenced NDA 22-110 for CMC information which has been previously reviewed by Dr. Balajee Shanmugam and recommended for approval. Cross-referencing to NDA 22-110 provides adequate information on manufacturing and packaging procedures, in-process controls, methods, and specification. There are no objections to approval from a chemistry/manufacturing perspective.

A product quality microbiology review of NDA 22-110 was completed on June 17, 2007, and the application was recommended for approval. Consequently, the product quality microbiology reviewer finds that NDA 22-407 is adequate with regard to manufacturing processes related to the sterility assurance of TLV. However, the applicant has not provided data to support the proposed maximum post constitution holding times of "stable in the infusion bag for 24 hours at room temperature or 72 hours under refrigeration at 2 to 8 degrees C (36 to 46 degrees F)." Until the applicant provides a risk assessment report summarizing studies that show that adventitious microbial contamination does not grow under storage and infusion conditions, the proposed label should be modified to state that the reconstituted product must be used within 4 hours of preparation when stored at room temperature and within 24 hours when stored under refrigeration.

3.0 Summary of Pharmacology/Toxicology

The pharmacology and toxicology data applicable to this NDA is cross-referenced to NDA 22-110. No new pharmacology or toxicology data is contained in the current NDA. The non-clinical studies are adequate to support the clinical use and sufficient to allow the labeling of TLV for NP. Therefore, the application is recommended for approval by Dr. Wendelyn Schmidt, pharmacology/toxicology supervisor.

4.0 Summary of Clinical Pharmacology

The clinical pharmacology information provided by the applicant has been reviewed by Kevin Krudys, PhD and has been found to be acceptable. Sparse pharmacokinetic (PK) data was collected in the two Phase 3 studies and used to compare the pharmacokinetics of TLV in patients with NP to healthy subjects and to identify major sources of inter-individual variability in TLV PK. The following are the major findings of Dr. Krudys' review:

- The PK of TLV in NP patients is comparable to that in patients with cSSSI.
- Ventilator status does not influence TLV PK in NP patients.
- The linear relationship between creatinine clearance and TLV clearance supports the TLV dosing regimen based on creatinine clearance.

- TLV AUC_{SS(0-48h)} in NP patients with renal impairment receiving the adjusted dose is comparable to that in patients with normal renal function receiving the 10 mg/kg dose.
- No relationship between TLV exposure and clinical cure or death was observed in the Phase 3 studies 0015 and 0019.

5.0 Summary of Clinical Microbiology

The clinical microbiology reviewer, Dr. Kerry Snow, has concluded that due to issues of outstanding mortality data which prevent the assessment of the risk/benefit of TLV for the treatment of NP, no final recommendation can be made. However, he notes that the clinical microbiology in vitro and clinical study data suggest that TLV may have clinical utility in treating NP due to *S. pneumoniae* and *S. aureus*. The applicant has cross-referenced the clinical microbiology data in NDA 22-110, along with some additional new data as well. The major findings of Dr. Snow's review are as follows:

- MIC values for all tested strains of *S. aureus* and *S. pneumoniae*, including isolates resistant to other classes of antimicrobials, were below attainable drug levels.
- The applicant has provided sufficient data to demonstrate a low potential for development of resistance to bacterial species in the proposed indication. Data suggest that TLV is an inducer of the VanA operon, but not the VanB operon. Population analysis profiles have not detected heteroresistance to TLV. No resistance to TLV was noted in isolates collected in clinical trials.
- Data from the Phase 3 clinical trials indicate that TLV is effective against the pathogens in the proposed indication.

6.0 Summary of Efficacy

For the indication of NP, the applicant submitted two pivotal trials: 0015 and 0019. The studies were conducted using identical protocols and were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients with Gram positive NP were randomized 1:1 to receive either TLV 10 mg/kg IV q 24h or vancomycin (VAN) 1 g IV q 12h. Study 0015 enrolled 761 subjects, while study 0019 enrolled 771 subjects. The pre-defined primary endpoint was clinical response at the Test-of-Cure (TOC) visit. However, based on an internal review of the historical literature to justify the treatment effect of antibacterials for NP, there were data to support only an NI margin for an endpoint of all-cause mortality. This issue has been discussed at one meeting of the Anti-infective Drugs Advisory Committee on July 16, 2008, during which the application for doripenem for the treatment of NP was presented, and at a joint workshop of the FDA, Infectious Diseases Society of America, the American Thoracic Society, and the American College of Chest Physicians, held on March 31-April 1, 2009. Therefore, the statistical reviewer, Dr. Scott Komo, and the

medical reviewer, Dr. Alfred Sorbello, have analyzed the Phase 3 data using an endpoint of all-cause mortality with a noninferiority margin of 7%.

Several statistical issues were identified during the course of Dr. Komo and Dr. Sorbello's reviews. Foremost are a large proportion of subjects (approximately 35%) whose survival status is not known throughout the mortality reporting period. In addition, the applicant pooled the study populations for 0015 and 0019 for the purposes of an all-cause mortality analysis, however there were demographic differences in the rates of comorbidities and other baseline characteristics in the study subjects, which may render pooling of the study populations unacceptable. Also, it is unclear at what time the all-cause mortality endpoint should be evaluated, i.e. whether it should be 28 days post-randomization, 28 days post end-of-treatment (EOT), or at some other time. Until the remaining mortality information has been provided by the applicant, a meaningful analysis of the efficacy of TLV in the treatment of NP cannot be undertaken. Therefore, Drs. Komo and Sorbello conclude that a determination of the efficacy of TLV for the treatment of NP cannot be made.

7.0 Summary of Safety

In the absence of the efficacy information necessary to perform a risk/benefit assessment of TLV for the requested indication, Dr. Alfred Sorbello recommends that the application not be approved in its present form. In his review of the safety data, similar to findings from the cSSSI application, Dr. Sorbello noted evidence that TLV is more nephrotoxic than VAN. Specifically, among patients with abnormal baseline Cr (>1.2 mg/dL), more TLV-treated subjects experienced renal treatment emergent adverse events (TEAEs) than VAN-treated patients. In study 0015, serious renal-related TEAEs occurred almost 2.4 times more frequently in the TLV group compared to the VAN group. Although there were no cases of torsades reported in either study, there were more TLV-treated patients than VAN-treated patients who were discontinued from study medication due to having two consecutive EKGs with QTc >500 msec. Other important considerations for the safety assessment of this application include missing clinical laboratory data with $>20\%$ of subjects missing all chemistry, hematology, and urinalysis results at the EOT visit and from 6-17% of subjects with results missing from either chemistry, hematology, or urinalysis labs at the TOC visit.

8.0 Summary of Other Regulatory Issues

The Division of Scientific Investigations (DSI) conducted inspections of selected clinical study sites, the contract research organization retained by Theravance (b) (4) and the applicant, Theravance, Inc. Prior to the inspections, a contractor for the applicant made a complaint to FDA alleging that Theravance had manipulated data submitted in the NDA. Of the six investigative sites that were inspected, one received a final classification of VAI, two received preliminary classifications of VAI, and the remaining three received preliminary

classifications of NAI. The CRO received a final classification of NAI and the applicant's preliminary classification is NAI. Despite the complaint from the contractor, the inspection of Theravance did not reveal any regulatory violations and their documentation of dates of data transfer/data files transferred from (b) (4) is consistent with data transfer dates/data files/file content that were documented by (b) (4) and reviewed during the FDA inspection of the CRO. DSI's overall assessment and recommendation is that, in general, Protocol 0015 and 0019 appear to have been conducted adequately and the data in support of the NDA appear reliable. Upon receipt of and review of the EIRs, an addendum to the clinical summary will be generated should there be a change in the final classifications or additional observations of clinical and regulatory significance discovered.

No pediatric plan was included in the NP submission; thus, the absence of a plan and need for submission of one will be included as a deficiency in the letter.

9.0 Regulatory Action

I concur with the recommendations of the statistical and medical reviewers that the applicant has not provided sufficient evidence to support the efficacy and safety of TLV for the treatment of adults with NP, primarily due to the submission of incomplete mortality data. The applicant will be issued a complete response letter, requesting two new adequate and well-controlled studies for the treatment of adults with NP. It may be possible, once the outstanding mortality data from 0015 and 0019 have been collected, to pool those study results to equate to one study. Also, the pediatric plan deficiency will be included in the letter as well.

Katherine A. Laessig, M.D.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|--------------|
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |

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/s/

KATHERINE A LAESSIG
11/23/2009

Cross-Discipline Team Leader Review

| | |
|--|---|
| Date | |
| From | Janice Pohlman, MD, MPH, Medical Team Leader |
| Subject | Cross-Discipline Team Leader Review |
| NDA/BLA # | 22-407 |
| Supplement# | |
| Applicant | Theravance, Inc. |
| Date of Submission | January 26, 2009 |
| PDUFA Goal Date | November 26, 2009 |
| | |
| Proprietary Name / Established (USAN) names | Vibativ™ |
| Dosage forms / Strength | Intravenous infusion, 10 mg / kg every 24 hrs |
| Proposed Indication(s) | Nosocomial pneumonia |
| Recommended: | Complete Response |

1. Introduction

The Applicant, Theravance, Inc., submitted NDA 22-407 in support of telavancin for treatment for nosocomial pneumonia (NP) on January 23, 2009. The NDA included two Phase 3 clinical trials of identical design, Study 0015 and Study 0019, to support this application. The trials had been originally designed and presented to the Agency at an End of Phase 2 meeting for IND 60,237 on July 12, 2005. Both trials were initiated early in 2005 (Study 0015: 2/8/05, 0019:1/23/05) and completed in 2007 (Study 0015: 7/11/07, 0019: 5/2/07).

Following completion of the trials, two public discussions relevant to clinical trial design in the evaluation of antimicrobial agents for treatment of NP took place and had a direct impact on the review of this application. The first was a meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) on July 16, 2008, during which NDA 22-171 (doripenem) was presented for treatment of NP, including ventilator-associated pneumonia (VAP). The Agency's presentation included a discussion about the non-inferiority design in NP trials and justification for a non-inferiority margin based on all-cause mortality to evaluate efficacy, rather than a clinical endpoint. The second discussion was a public workshop "Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)" (HAP/VAP workshop) co-sponsored by the Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) held on March 31-April 1, 2009 in Silver Spring, MD. Relevant information will be presented in the context of this review.

Two other issues will be more thoroughly discussed in relation to this application. The first issue is related to the quality of data submitted and some concerns about data integrity raised by a consultant on the project. The second issue relates to safety of the drug product, including a mortality imbalance in Study 0015, with more deaths occurring in the telavancin treatment group, nephrotoxicity associated with telavancin, and a requirement for a risk evaluation and mitigation strategy (REMS) due to potential risk for teratogenicity (based on animal data). The REMS was required for approval of NDA 22110, telavancin for treatment of complicated skin and skin structure infections, (cSSSI), which was being reviewed concurrently with review of NDA 22-407.

This application cross-referenced information submitted in NDA 22-110 for chemistry and manufacturing controls (CMC), nonclinical pharmacology and toxicology, clinical pharmacology, and microbiology information. Discipline-specific reviews will be briefly discussed in this memo. New clinical microbiology data and clinical and statistical reports for the two Phase 3 NP trials were the primary source of new data in this application.

2. Background

Telavancin for injection is a lipoglycopeptide antibacterial agent produced by chemical modification of vancomycin. The drug product is a sterilized powder for injection. Telavancin has a dual mechanism of action against Gram positive bacteria; it acts to inhibit bacterial cell wall synthesis by interfering with peptidoglycan synthesis and cross-linking and also causes disruption of the functional integrity of the cell membrane by depolarizing the cell membrane. It has activity against Gram positive pathogens that may cause NP and VAP, including *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant isolates, MRSA and MSSA, respectively) and *Streptococcus pneumoniae*.

Telavancin was approved for the treatment of complicated skin and skin structure infections caused by Gram positive bacteria including MRSA on September 11, 2009 (NDA 22-110) at the end of the application's third review cycle. Approval of this application was complicated initially by problems at a manufacturing facility and concerns regarding nephrotoxicity. During the second review cycle, concerns related to adequacy of study monitoring and data integrity were raised by FDA Division of Scientific Investigation (DSI), resulting in additional DSI inspections and an internal audit of multiple sites conducted by the Applicant. Data integrity and monitoring concerns were resolved based on these efforts. The cSSSI NDA (NDA 22-110) was presented before the AIDAC on November 18 2009 because of concerns regarding the overall benefit to risk assessment of telavancin treatment for this indication. The AIDAC presentation also complied with the Food and Drug Administration Amendments Act (FDAAA) 2007 requirement for presentation of new molecular entities (NME). Although telavancin demonstrated non-inferiority to vancomycin in the treatment of cSSSI, there were concerns regarding potential for teratogenicity based on rare limb defects observed in animal embryo/fetal development studies, nephrotoxicity observed in the clinical trials, and demonstration of prolongation of the

QT interval in a “thorough QT” study. The vote by the committee was 21 to 5 in favor of approval based on a positive benefit to risk assessment for telavancin and perceived public health need. However, the potential for teratogenicity based on rare limb defects in two or three animal species, a REMS (as outlined by FDAAA 2007) was deemed necessary. This required a third cycle of review for development of a Medication Guide and Communication Plan for healthcare providers and design of a pregnancy registry to monitor pregnancy outcomes of women who required treatment with or who had been exposed to telavancin during pregnancy.

The draft guidance document, “Nosocomial Pneumonia – Developing Antimicrobial Drugs for Treatment”, July 1998, allowed for efficacy determination based on a clinical and microbiological response endpoint. Information regarding the statistical evaluation of such studies was not included in this document, but other drug products approved for this indication have utilized a non-inferiority design. Based on a recent comprehensive search of the English language literature, it was determined that a non-inferiority (NI) margin based on a clinical response endpoint could not be justified because the treatment effect of antimicrobial agents relative to placebo for treatment of NP could not be determined. At the July 2008 AIDAC meeting and again at the HAP/VAP public workshop, the FDA presented information based on the historical literature that could be used to justify a NI margin of 7-10% based on all-cause mortality. The Agency is currently in the process of revising the guidance document for developing drugs for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Pneumonia based on this work and discussion at the HAP/VAP public workshop.

3. CMC/Device

For CMC-related information, the Applicant cross-referenced NDA 22110, telavancin for treatment of cSSSI. For more detailed discussion, see the CMC review of NDA 22-110 by Balajee Shanmugam, Ph.D. The cross-reference to NDA 22-110 provides adequate information on manufacturing and packaging procedures, in-process controls, methods, and specifications. Therefore, from a chemistry and manufacturing perspective, the application is recommended for approval by Dr. Shanmugam.

General product quality considerations

The drug substance, telavancin hydrochloride is a semi-synthetic (b) (4) lipoglycopeptide antibacterial agent derived (b) (4) of vancomycin. Telavancin is a sterile, preservative-free, white to slightly colored, lyophilized (b) (4) containing 250 mg or 750 mg of telavancin free base for intravenous use following reconstitution with either (b) (4) 5% dextrose injection or 0.9 % sodium chloride. The inactive ingredients are hydroxypropyl-beta-cyclodextrin (HP-β-CD) in a 10:1 mg ratio with telavancin, mannitol, and sodium hydroxide and hydrochloric acid used in minimal quantities for pH adjustment. The reconstituted solution is clear to slightly colored, with a pH of 4.5 (4.0-5.5). The drug product stability data supports a (b) (4) expiration date when stored refrigerated at 5°±3° C. A letter of authorization

from the DMF holder (b) (4) authorized the Agency to refer to DMF (b) (4) for vancomycin which was previously reviewed and found to be adequate.

The drug substance has been well characterized and along with the drug product, the manufacturing process has been well characterized. All issues regarding drug specifications have been adequately negotiated with the Applicant. The sterility portion of the manufacturing process was reviewed by John Metcalfe, PhD, of Office of Pharmaceutical Science/New Drug Microbiology Staff and was found to be adequate. The post-constitution storage times proposed by the Applicant of 72 hours under refrigeration was supported by microbial studies, however the storage time of (b) (4) at room temperature was not supported by microbial studies. Therefore, 72 hour refrigeration and 4 hour room temperature storage times were recommended for the reconstituted product.

Facilities review/inspection

During the first review cycle for NDA 22-110, the drug manufacturing facility, (b) (4) in (b) (4) was issued a FDA Form 483 (Notice of Observations) for non-compliance with c-GMP prompting a "Withhold" recommendation by the Office of Compliance. Although the issues were not directly related to telavancin, the "Withhold" status factored into the approvable action taken on NDA 22-110 on October 19, 2007. The c-GMP issues with (b) (4) were satisfactorily resolved prior to the first complete response (CR) submission for NDA 22-110 on January 21, 2008 and submission of this NDA (NDA 22-407).

4. Nonclinical Pharmacology/Toxicology

For non-clinical pharmacology and toxicology information, the Applicant cross-referenced NDA 22-110, telavancin for treatment of cSSSI. For more detailed discussion of the issues outlined below, refer to the non-clinical pharmacology/toxicology reviews for NDA 22-110 by Zhou Chen, MD, PhD.

The major findings from the non-clinical pharmacology and toxicology studies include:

- Renal toxicity in rats and dogs, including renal tubular vacuolation, degeneration, and necrosis. Toxicity was related to both dose and duration of treatment. Elevations in blood urea nitrogen (BUN) and serum creatinine (Cr) were observed in studies of 4-weeks or longer duration and were only partially reversible in the 13- and 26-week treatment studies. Some of the renal changes were also noted in animals treated with placebo containing HP- β -CD, but changes were generally more pronounced in those receiving telavancin.
- Liver toxicity in rats and dogs was noted in studies of 13- or 26-week duration in rats and 13-weeks in dogs, with findings of hepatocellular degeneration along with elevated alkaline phosphatase (alk phos), alanine transaminase (ALT), and aspartate aminotransferase (AST) in the 13-week studies in both species and

macrophage accumulation and elevated ALT and AST in the 26-week study in rats. The laboratory changes were partially reversed at recovery. As with the renal changes, similar but less pronounced findings were noted in animals treated with HP- β -CD placebo.

- Macrophage hypertrophy, hyperplasia, and accumulation were seen primarily with more prolonged administration (13- and 26-week studies) and were noted in the reticulo-endothelial cell system (lymph nodes, bone marrow, liver, and spleen) as well as in the kidney and lungs. These changes persisted throughout the 4-week recovery period. As with the previous changes, similar findings were noted in animals treated with HP- β -CD. The clinical significance of these changes is unknown.
- The potential to prolong the QT interval was observed *in vitro*, with inhibition of human ether-a-go-go (hERG) channels in human embryonic kidney (HEK) 293 cells at all doses ≥ 15 $\mu\text{g/mL}$ (although a half maximal inhibitory concentration (IC_{50}) could not be determined) and prolongation of the action potential duration in a canine Purkinje fiber study at 0.5 and 1 Hz at concentrations ≥ 50 $\mu\text{g/mL}$. However, an *in vivo* conscious telemeterized dog study showed no evidence of treatment-related effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters. The study did demonstrate evidence of a histaminergic reaction at high doses (100 mg/kg/day as a single or repeat dose).
- The potential for teratogenicity (limb defects) was demonstrated in embryo-fetal development studies in rats, rabbits, and minipigs, although there were differing interpretations of findings between members of the review team for NDA 22-110 in regard to the number of species with positive findings. The limb defects included brachymelia in rats (two fetuses) and rabbits (one fetus, also with adactyly and absent ulna) and polydactyly and syndactyly in minipigs (seen also in placebo group). There was difficulty in interpreting the minipig study due to poor reproductive performance (small number of litters to examine); one of the control groups had a pregnancy rate to term of only 36%. This made it difficult to draw any conclusions from that study. Additional consultation was provided by the Reproductive and Developmental Toxicity, Pharmacology and Toxicology Coordinating Committee (PTCC) Subcommittee and Maternal Health Team. Subsequent to discussion of NDA 22-110 at an AIDAC meeting in November 2008, a REMS (as required by FDAAA, September 27, 2007) was required to be submitted by the Applicant prior to drug product approval for the cSSSI application.

5. Clinical Pharmacology/Biopharmaceutics

For clinical pharmacology/biometrics information, the Applicant cross-referenced NDA 22-110, telavancin for treatment of cSSSI. For more detailed discussion of the issues outlined below see the review by Jeff Tworanzyski, Pharm.D.

Pharmacokinetics

The clinical pharmacology program for NDA 22-110 included 11 pharmacokinetic (PK) studies to characterize the pharmacokinetic profile in healthy young and elderly adult subjects and subjects with renal and hepatic impairment. Studies were also conducted to examine the effect of telavancin on cardiac repolarization, the degree of penetration of telavancin into skin blister and lung tissue, and the potential for interaction of telavancin with other medications, including aztreonam, piperacillin/tazobactam, and midazolam.

The pharmacokinetics of telavancin are linear and increase relatively proportionately to dose as dose increases from 5 mg/kg to 12.5 mg/kg. Multiple dose infusion with doses ranging from 7.5 mg/kg/day to 15 mg/kg/day demonstrated a half-life of approximately 7-8 hours on Day 1 and 9 hours on Day 7 of dosing. The drug is approximately 90% protein bound and distributes primarily to extracellular water.

The primary metabolite of telavancin is a hydroxylated metabolite, AMI-11352, which has about 10% of the activity of telavancin. The primary route of elimination is through renal excretion (76% of dose).

In vitro assays in human microsomes demonstrated that CYP450 isoforms including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11 did not metabolize telavancin. Telavancin did demonstrate weak inhibitory effects on the major CYP450 enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. An *in vivo* drug interaction study performed with midazolam (substrate for CYP3A4) showed that telavancin has no significant effect on the PK of midazolam. The clinical studies of telavancin allowed the concomitant use of aztreonam (in cSSSI studies and ongoing HAP studies) and piperacillin/tazobactam (ongoing HAP studies). Therefore interaction studies were conducted for each of these drugs with telavancin and the studies did not show evidence of interaction.

An analysis using calculated multiple dosing mean concentration-time profiles for elderly subjects indicated profiles similar to those for young healthy subjects. Plasma clearance may decrease along with decreased renal clearance in the elderly. Mean concentration-time profiles did not differ among male and female subjects. Therefore, there are no specific dose adjustments recommended on the basis of advanced age or gender.

The study of PK parameters in subjects with renal impairment was evaluated in a single 7.5 mg/kg study in subjects with normal renal function (CrCL > 80 mL/min), mild renal impairment (CrCL 51-80 mL/min), moderate renal impairment (CrCL 30-50

mL/min), severe renal impairment (CrCL < 30 mL/min) and patients with end-stage renal disease (ESRD) on hemodialysis. The mean C_{max} was similar among subjects with normal renal function and mild, moderate, and severe renal impairment and lowest in patients with ESRD following hemodialysis. The mean clearance was decreased 11% in those with mild, 19% in those with moderate, and 55% in those with severe renal impairment. End-stage renal disease patients who received hemodialysis after telavancin dosing demonstrated a clearance 40% less than patients with normal renal function (greater than in patients with severe disease). The mean $AUC_{0-\infty}$ increased 13%, 29%, 119%, and 79% in subjects with mild, moderate, severe, and ESRD, respectively, compared to subjects with normal renal function. An average of 5.9% of the telavancin dose was present in the dialysate. Therefore, a dosage adjustment recommended by the Applicant for patients with moderate renal impairment (7.5 mg/kg q 24 hrs) and severe renal impairment (10 mg/kg q 48 hrs) is acceptable. The PK of telavancin has not been evaluated in ESRD subjects who are dosed with telavancin following dialysis.

In general, the mean PK parameters were similar in normal subjects and subjects with hepatic impairment, therefore no dosage adjustment is recommended for patients with hepatic impairment.

Based on non-clinical studies, the Applicant conducted a “thorough ECG trial” as defined by the November 2002 FDA – Health Canada concept paper at the Agency’s request. The results showed that telavancin does have an effect on the QT interval, however the effect on the mean and maximum change from baseline was less than the control (moxifloxacin) in this study.

Pharmacodynamics

The Applicant provided data from *in vivo* animal models of infection that support the use of $AUC_{(0-24)}/MIC$ as the best pharmacokinetic/pharmacodynamic (PK/PD) predictor of antimicrobial efficacy. Additional information about antimicrobial activity and PK/PD modeling for telavancin can be found in the clinical microbiology review for NDA 22-110 by Kerry Snow, MS.

6. Clinical Microbiology

The Applicant cross-referenced NDA 22-110 for clinical microbiology information relevant to telavancin. Additional clinical microbiology information was submitted in this NDA (NDA 22-407). The clinical microbiology sections of both NDAs were reviewed by Kerry Snow, MS, and the information presented below is excerpted from his reviews.

In Vitro Information

Telavancin inhibits bacterial cell wall synthesis by interfering with the synthesis and cross-linking of peptidoglycan. The Applicant also provided data to support a second mechanism of action, depolarization of the microbial cell membrane, leading to disruption of the functional integrity of the membrane.

Telavancin has activity against Gram positive bacteria, including pathogens associated with NP, including *Staphylococcus aureus* (MRSA and MSSA isolates) and *Streptococcus pneumoniae*.

Telavancin has a low potential for development of resistance in bacterial species considered in the proposed indication. Data presented in NDA 22-407 suggest that telavancin is an inducer of the VanA operon, but does not induce activity of the VanB operon. Population analysis profiles have not detected heteroresistance to telavancin in isolates of *S. aureus*.

Telavancin has modest synergy with beta-lactams, rifampin, ciprofloxacin, and gentamicin, against isolates of *S. aureus*, including methicillin-resistant and vancomycin-non-susceptible phenotypes. Telavancin activity is additive with other studied drug combinations. No antagonism has been demonstrated with telavancin and any tested antimicrobial.

Telavancin is approximately 90% protein bound, primarily by albumin. Studies indicate that telavancin retains in vitro activity against the principle respiratory pathogens sought in the proposed indication, in the presence of albumin or human serum. Recent studies also suggest that telavancin activity is not inhibited by pulmonary surfactant. Telavancin is active against isolates of *S. aureus* in stationary growth phase, and has demonstrated activity against isolates of *S. aureus*, *S. epidermidis*, and *E. faecalis* in a biofilm model. The postantibiotic effect of telavancin, against isolates of *S. aureus* (including MSSA and MRSA, as well as vancomycin-non-susceptible isolates) ranges from one to six hours. The antimicrobial activity of the three primary telavancin metabolites (AMI-11352, AMI-11353, and AMI-11355) is \geq 8-fold higher than that of telavancin.

The Applicant has submitted data from time-kill kinetic studies to support that telavancin has bactericidal activity against a variety of strains of *S. aureus*, including methicillin-susceptible (b) (4)

This activity generally occurs at low multiples of the MIC and at concentrations consistent with therapeutic levels, even at trough concentrations.

Human and Animal Studies

The Applicant has submitted data from *in vivo* animal studies that supports the use of $AUC_{(0-24)}/MIC$ as the best PK/PD predictor of antimicrobial efficacy for unbound (free) telavancin.

Monte Carlo simulation, based on the proposed dosage (10 mg/kg) supports a susceptible breakpoint as high as 2 $\mu\text{g/mL}$ (based on $> 99\%$ target attainment at that concentration). Additional information suggests that telavancin is concentrated in human alveolar macrophages (exceeding 10 $\mu\text{g/mL}$) and that the AUC of the antimicrobial in epithelial lining fluid (in uninfected lung tissue) is approximately 75% that of the AUC of plasma.

Clinical Trials

Data from the two Phase 3 clinical trials indicate that telavancin is effective against the pathogens for the proposed indication. The majority of principle pathogens were recovered from non-invasive specimens (sputum and endotracheal aspiration) and a majority of specimens yielded a single Gram-positive pathogen. Methicillin-resistant *S. aureus* was the predominant pathogen isolated. Using breakpoints proposed in this Application, no telavancin-non-susceptible isolates were recovered in the clinical trials. No development of telavancin resistance was observed during the clinical trials.

Susceptibility Test Methods

Telavancin MIC distributions from clinical trials and survey studies are unimodal for *S. aureus* (both MRSA and MSSA isolates) and *S. pneumoniae*. Distributions derived from clinical studies, for these pathogens, are similar to those derived from survey studies, although the percentage of clinical isolates with higher telavancin MIC values appears to trend higher, for isolates of *S. aureus* and *E. faecalis*, compared to survey isolates, particularly at higher MIC values. Since this may imply developing resistance among these pathogens, continued surveillance is warranted. Correlation studies comparing the disk diffusion method of susceptibility testing with the minimum inhibitory concentration method support the zone size recommendations of the Applicant. Data from reference laboratory reports, reviewed in NDA 22110, suggest that susceptibility testing of telavancin using solid media techniques, may result in values that are difficult to reproduce or vary from acceptable quality control ranges. This may be due to the size of the telavancin molecule and its diffusion properties. Susceptibility testing by the agar diffusion method is not recommended. Data presented in this Application suggests that modest alterations in the pH of test media and inoculum size may result in unreliable telavancin susceptibility results for *S. pneumoniae*. Data from quality control studies do not support vancomycin as a class-representative surrogate for telavancin susceptibility testing.

7. Clinical/Statistical- Efficacy

The clinical and statistical review of efficacy was completed by Alfred Sorbello, DO, MPH, and Scott Komo, DrPH. Additional details and discussion of the efficacy analyses are contained within the body of their reviews.

General Design

Two independent Phase 3 clinical trials of identical design, Study 0015 and Study 0019, were conducted in patients with nosocomial pneumonia caused by suspected or confirmed Gram positive bacteria, including MRSA. The trials were randomized, double-blind, active-controlled, multicenter, multinational trials. Patients were randomized 1:1 to receive either telavancin 10 mg/kg IV every 24 hours or vancomycin 1g IV every 12 hours for 7-21 days, with duration decided upon by the investigator based on the patient's clinical status. Randomization was stratified by geographic location, presence or absence of diabetes mellitus, and ventilatory status of the patient. Adjustment of telavancin and vancomycin doses for patients with renal impairment was performed by study personnel not involved in the clinical assessment of the patient (such as an unblinded pharmacist). Patients could receive aztreonam or piperacillin/tazobactam for concomitant Gram negative coverage if necessary, although patients who received piperacillin/tazobactam were not clinically or microbiologically evaluable (Note: prior to a protocol amendment recommended by the Agency, patients could also receive imipenem for Gram negative coverage).

In order to enroll in the trial, patients were to have clinical signs and symptoms consistent with pneumonia after at least 48 hours in an inpatient acute or chronic care facility, or acquired within seven days after being discharged from a hospital stay of ≥ 3 days. At least two of the following signs or symptoms were required: 1) cough, 2) purulent sputum or other deep respiratory specimen, 3) auscultatory findings of pneumonia, 4) dyspnea, tachypnea, or hypoxemia, 5) identification of an organism consistent with a respiratory pathogen isolated from an appropriate respiratory specimen or blood culture. Additionally, at least two of the following conditions must have been present: 1) fever ($>38^{\circ}\text{C}$) or hypothermia (rectal or core temperature $< 35^{\circ}\text{C}$), 2) respiratory rate > 30 breaths/minute, 3) pulse rate ≥ 120 beats/min, 4) altered mental status, 5) need for mechanical ventilation, 6) elevated total peripheral white blood cell (WBC) count $> 10,000$ cells/ mm^3 , $>15\%$ immature neutrophils (band forms) regardless of total peripheral WBC, or leukopenia with total WBC < 4500 cells/ mm^3 . Patients were also required to have a chest radiograph consistent with a diagnosis of pneumonia (progressive infiltrates, consolidation, or pleural effusion) within 48 hours prior to study and an appropriate respiratory specimen for Gram stain and culture.

The predefined primary endpoint was clinical response as assessed by the investigator at the Test-of-Cure (TOC) visit 7-14 days after the End of Therapy (EOT). The primary efficacy analysis was to initially test for the clinical non-inferiority of telavancin using the difference in clinical response rates of telavancin relative to vancomycin at TOC in the all-treated (AT) and clinically evaluable (CE) populations using a non-inferiority margin of 20%. If non-inferiority was demonstrated, 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. If the efficacy analyses of both identically designed trials demonstrated non-inferiority, a key secondary objective was to pool the data from both trials to assess for the superiority of telavancin to vancomycin in patients with MRSA infections.

Dr. Sorbello noted in his clinical efficacy review a number of methodologic problems with the way the study was designed, conducted, and analyzed that may have adversely impacted interpretation of the data and non-inferiority determination. These factors included:

- Reliability of inclusion criteria in selecting a patient population in which patients actually had a diagnosis of NP. Examples of these criteria include:
 - Patients enrolled without any of the three important features of pneumonia: fever, leukocytosis, and/or purulent sputum.
 - The assessment of severity of disease by APACHE II and CPIS scores where measured axillary temperatures were used with one degree added based on method of measurement.
 - The chest radiograph interpretation was not consistently performed by a radiologist.
- Failure of investigators to follow the protocol-specified de-escalation of concomitant Gram negative coverage (with possible overlapping Gram positive anti-bacterial activity).
- Lack of specified criteria to demonstrate adequacy of respiratory specimens for microbiological culture and pathogen determination.
- Use of a non-inferiority design based on clinical response without sufficient evidence for justification of the non-inferiority margin.
- The study was not designed, sized, or powered for a non-inferiority design using all-cause mortality as an endpoint.
- Applicant determinations with potential impact on the patient's clinical evaluability status and/or clinical outcome were made after the medical monitor had been unblinded to treatment assignment.

Additionally, both Dr. Sorbello and Dr. Komo noted the discussions within the past year regarding design of clinical trials for the study of NP at the AIDAC meeting and HAP/VAP workshop. Based on a review of the literature, the Agency outlined the problem with the use of a clinical response endpoint in non-inferiority (NI) trials used to evaluate efficacy of treatment in NP. Based on literature reviewed to date, the lack of historical data for this endpoint does not allow for estimation of the treatment effect of antimicrobial agent over placebo. At the AIDAC meeting in July 2008, the Agency presented historical data from the literature supporting a 7% NI margin for the endpoint of all-cause mortality in clinical trials of NP. Additional information regarding the size of the NI margin which could be justified based on the historical literature was presented at the public workshop on HAP/VAP by the Agency.

While the clearest evidence for treatment effect is based on an all-cause mortality endpoint, it is unclear as to appropriate timing of this assessment. The focus of discussion at the HAP/VAP workshop was based on assessment of all-cause mortality at 28 days post-randomization or initiation of therapy. However, concern regarding use of timepoint after randomization among patients who receive therapy of variable duration arises because of differential follow-up periods. Therefore, Dr. Sorbello's review includes assessments at 28 days post-randomization and 28 days following EOT.

Baseline Demographics

In Study 0015, 746 patients were randomized 1:1 to receive telavancin (n=372) and vancomycin (n=374). In Study 0019, 757 patients were randomized 1:1 to telavancin (n=377) and vancomycin (n=380).

Baseline characteristics including age, gender, race, and ventilatory status were comparable across treatment groups within and across trials. However, there were more patients from the United States enrolled in Study 0015 compared to Study 0019; 31% compared to 14% in Study 0015 and Study 0019, respectively. There was also a difference, as shown in Table 1 (adapted from Table 61 of Dr. Sorbello's review).below, in baseline conditions and co-morbidities associated with mortality across the two study populations.

Table 1: FDA Medical Officer Table: Selected Baseline Demographic and Medical History Characteristics potentially associated with Mortality, Studies 0015 and 0019, AT Population

| Baseline Characteristic | Pooled TLV and VAN Treatment Arms Study 0015 N=746 n (%) | Pooled TLV and VAN Treatment Arms Study 0019 N=757 n (%) | 95% CI for Risk difference (Study 0015 - Study 0019) |
|-------------------------------------|---|---|--|
| Acute renal failure | 78 | 59 | 2.8 (-0.1, 5.7) |
| Chronic renal failure | 67 | 28 | 5.3 (2.8, 7.7)* |
| Baseline CrCl<50 mL/min | 276 | 209 | 9.4 (4.7, 14.1)* |
| Serum creatinine ≤1.2 mg/dL | 531 (71.2) | 596 (78.7) | -7.6 (-11.9, -3.2)* |
| Serum creatinine >1.2 mg/dL | 192 (25.7) | 142 (18.8) | 7.0 (2.8, 11.2)* |
| Hemodialysis | 20 (2.7) | 8 (1.1) | 1.6 (0.3, 3.0)* |
| History of diabetes mellitus | 232 (31.1) | 162 (21.3) | 9.6 (5.3, 14.1)* |
| Any pulmonary co-morbidity | 478 | 517 | -4.2 (-9.0, 0.6) |
| ARDS | 44 | 19 | 3.4 (1.4, 5.4)* |
| Pulmonary edema | 68 | 75 | -0.8 (-3.8, 2.2) |
| VAP | 203 | 224 | -2.4 (-6.9, 2.2) |
| HAP | 500 | 592 | -11.2 (-15.7, -6.7)* |
| HCAP | 243 | 164 | 10.9 (6.4, 15.4)* |
| Baseline signs/symptoms SIRS | 623 | 633 | -0.1 9-3.9, 3.6) |
| Sepsis/septic shock/MOF at any time | 135 | 110 | 3.6 (-0.2, 7.3) |
| Organ failure at baseline | 136 | 183 | -5.9 (-10.1, -1.8)* |
| ICU at baseline | 440 | 431 | 2.0 (-2.9, 7.0) |
| Immunocompromise | 11 | 34 | -3.0 (-4.7, -1.3)* |
| Torsades | 425 | 342 | 11.8 (6.8, 16.8)* |

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

Based on the pooled baseline characteristics shown above, it is apparent that more patients in Study 0015 had chronic renal failure, CrCL < 50 mL/min, serum creatinine > 1.2 mg/dL, were receiving hemodialysis, had health-care associated pneumonia, had torsades, had ARDS, had a history of atrial fibrillation, and/or history of myocardial infarction. In Study 0019 there were more patients with immunocompromise, hospital-acquired pneumonia, organ failure at baseline, and left ventricular hypertrophy. The differences between study populations make the Applicant’s subsequent pooling of studies for mortality analysis problematic and uninterpretable.

There were also differences noted between the telavancin treatment groups across the two trials with the telavancin treatment group in Study 0015 having greater evidence of renal impairment at baseline, diabetes mellitus, health-care associated pneumonia, and torsades.

Efficacy Analyses

Table 2 below shows the results of the Applicant’s analysis of efficacy based on clinical response at TOC.

Table 2: Summary of Clinical Cure Rates at the TOC Visit, Studies 0015 and 0019 (adapted from Applicant’s Summary of Clinical Efficacy, Module 2.7.3, Tables 6 and 12)

| Analysis Population | Study 0015 | | | Study 0019 | | |
|---------------------------------|----------------------------|----------------------------|-----------------------------|----------------------------|----------------------------|----------------------------|
| | Telavancin | Vancomycin | Diff (95%CI) (TLV-VAN) | Telavancin | Vancomycin | Diff (95%CI) (TLV-VAN) |
| AT | 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) |
| [FDA] AT – GN only ¹ | 177/302 (58.6%) | 188/307 (61.2%) | -2.6 (-10.4, 5.2) | 181/298 (60.7%) | 194/304 (63.8%) | -3.1 (-10.8, 4.7) |
| 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) |

TLV=telavancin; VAN=vancomycin
¹ All-treated analysis population excluding patients with baseline Gram negative pathogens only

The Applicant’s CE population excluded patients with Gram negative pathogens only, while these patients were included in the Applicant’s AT population. Since telavancin and vancomycin have only Gram positive antibacterial activity, the results in the Applicant’s AT population are not informative regarding telavancin or vancomycin activity. An analysis was done by FDA excluding patients with Gram negative pathogens only and is included in Table 2 above. The Applicant had prespecified a NI margin of 20%, but based on further analysis had tried to justify an amended NI margin of 14% based on extrapolation of mortality margin to a clinical response margin; an approach that is not statistically valid. The results of the Applicant’s efficacy analysis for both trials, based on clinical response at TOC, demonstrates that telavancin is non-inferior to vancomycin and the lower bound of the 95% CI is > -14%.

Following the discussions at the July 2008 AIDAC meeting and 2009 HAP/VAP workshop, the Applicant provided additional efficacy analyses based on all-cause mortality. The Applicant assessment for all-cause mortality considered only those deaths which occurred prior to the TOC visit (7-14 days after EOT) or within 28 days of last study medication (EOT). Therefore, the initial all-cause mortality analyses presented in the application did not include all patient mortality up to 28 days post randomization or initiation of therapy.

Table 3 below shows the Applicant’s original all-cause mortality analysis from Study 0015 and Table 4, the Applicant’s results from Study 0019.

**Table 3: All-Cause Mortality, AT Population, Study 0015
(adapted from Applicant’s 0015 Clinical Study Report, Table 8-42)**

| | Telavancin N=372 | Vancomycin N=374 | Difference (95% CI) [1] |
|--|---------------------|---------------------|-------------------------|
| Deaths during or after study medication | | | |
| During or after treatment mortality | 80 (21.5%) | 62 (16.6%) | 4.9% (-0.7%, 10.6%) |
| Deaths while receiving study medication | | | |
| Within-treatment mortality | 48 (12.9%) | 45 (12.0%) | 0.9% (-3.9%, 5.6%) |
| [1] Difference in mortality rates (telavancin – vancomycin); 2-sided 95% CI on the difference. ^= Confidence interval uses Agresti-Caffo adjustment | | | |

The all-cause mortality rate in Study 0015 was approximately 5% higher in the telavancin treatment group, with the difference occurring primarily in the post-treatment period. The upper bound of the 95% confidence interval was 10.6 which exceeds the NI margin of 7-10% discussed at the HAP/VAP workshop and suggests that telavancin may be inferior to vancomycin based on an all-cause mortality endpoint.

**Table 4: All-Cause Mortality, AT Population, Study 0019
(adapted from Applicant’s 0019 Clinical Study Report, Table 8-43)**

| | Telavancin N=377 | Vancomycin N=380 | Difference (95% CI) [1] |
|--|---------------------|---------------------|-------------------------|
| Deaths during or after study medication | | | |
| During or after treatment mortality | 69 (18.3%) | 79 (20.8%) | -2.5% (-8.1%, 3.2%) |
| Deaths while receiving study medication | | | |
| Within-treatment mortality | 43 (11.4%) | 36 (9.5%) | 1.9% (-2.4%, 6.3%) |
| [1] Difference in mortality rates (telavancin – vancomycin); 2-sided 95% CI on the difference. ^= Confidence interval uses Agresti-Caffo adjustment | | | |

The all-cause mortality rate in Study 0019 was approximately 2.5% higher in the vancomycin treatment group, with the difference occurring primarily in the post-treatment period. The upper bound of the 95% confidence interval was 3.2% which is within the NI margin of 7-10% discussed at the HAP/VAP workshop.

In response to a February 25, 2009 information request from the Agency, the Applicant provided an updated table with additional mortality data provided so that all patient deaths occurring within a specified period of time could be considered, however the data in this response just included pooled data from Study 0015 and Study 0019. Results are shown in Table 5 below.

Table 5: Applicant's Summary Table of Deaths occurring between Start of Study Drug and EOT Visit + 28 Days, Studies 0015 and 0019, AT Population

| | Number of patients | |
|--|---------------------|---------------------|
| | Telavancin N=749 | Vancomycin N=754 |
| Deaths between Start of Study Drug and EOT Visit + 28 days | 160 (21.4%) | 147 (19.5%) |
| Deaths between EOT Visit and EOT Visit + 28 days | 113 | 104 |
| Deaths between TOC Visit and EOT Visit + 28 days | 11 | 6 |

Following another information request from the Agency on June 6, 2009, the Applicant notified the Agency that additional mortality data had been identified from the clinical database, safety database, and information collected from a 10-week pharmacoeconomic (PE) substudy. As shown in Table 6, with data generated by the statistician, Dr. Komo, there are still a number of patients in whom survival status is not known for the specified time period. This is primarily due to censored data, as well as incomplete information from the PE study which did not explicitly query for the date of death.

Table 6: Statistician's Summary Table of All-Cause Mortality Rates (AT Population excluding patients with Gram negative pathogens only at baseline)

| | 0015 | | 0019 | |
|---|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=302 | Vancomycin N=307 | Telavancin N=298 | Vancomycin N=304 |
| Deaths Between Start of Study Drug and Study Day 28 | 78 (25.8) | 64 (20.8) | 66 (22.2) | 64 (21.1) |
| Alive | 127 (42.1) | 132 (43.0) | 147 (49.3) | 150 (49.3) |
| Missing ¹ | 97 (32.1) | 111 (36.2) | 85 (28.5) | 90 (29.6) |
| Deaths Between Start of Study Drug and EOT+28 Days | 88 (29.1) | 72 (23.5) | 72 (24.2) | 74 (24.3) |
| Alive | 101 (33.4) | 102 (33.2) | 120 (40.3) | 124 (40.8) |
| Missing ¹ | 113 (37.4) | 133 (43.3) | 106 (35.6) | 106 (34.9) |

¹ Incomplete survival information for the mortality reporting period
 Patients are categorized as randomized. Two patients randomized to the vancomycin group received telavancin; in both Start to Study Day 28 and Start to EOT+28 assessments, 1 patient had died and the other was alive at the end of the period.

Conclusions

Incomplete mortality data limits the ability to determine the efficacy of telavancin in the treatment of NP. The Applicant is attempting to collect the outstanding mortality data. However, given the difference in distribution of baseline prognostic factors associated with mortality in Study 0015 (as compared to Study 0019), pooling the two studies for efficacy analysis based on all-cause mortality is problematic and results are uninterpretable. Conversely, addition of new mortality data could also moderate the difference in mortality rates in Study 0015 and pooling of the two studies may be possible.

8. Safety

The safety assessment for NDA 22-407 is based on data from Studies 0015 and 0019 alone. The information was not integrated into the safety summary for the cSSSI application (NDA22-110) due to differences in the natural history and seriousness of the NP indication.

Overall Adverse Events

In Studies 0015 and 0019 combined, there were 751 telavancin-treated patients and 752 vancomycin-treated patients. Table 7 below from Dr. Sorbello’s review shows the number of deaths, serious adverse events (SAEs), treatment emergent adverse events (TEAE), and TEAE thought to be related to study medication.

Table 7. FDA Medical Officer Summary Table of Treatment-Emergent Adverse Events (TEAE), Serious Adverse Events (SAE), and Deaths while on Study, Studies 0015 and 0019, AT Population

| | Study 0015 | | Study 0019 | |
|---|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| Any TEAE | 321 (86%) | 317 (85%) | 295 (78%) | 296 (78%) |
| Drug-related TEAE | 126 (34%) | 93 (25%) [†] | 86 (23%) | 81 (21%) |
| Serious TEAE (SAE) | 127 (34%) | 88 (24%) | 107 (28%) | 109 (29%) |
| Deaths (while on study) | 80 (22%) | 62 (17%) | 70 (18%) | 78 (21%) |
| [†] 95% CI for difference (telavancin – vancomycin) was 9.0 (2.5, 15.5); | | | | |
| *95% CI for difference (telavancin – vancomycin) was 10.6 (4.2, 17.1) | | | | |

Overall, deaths, SAEs, and drug-related TEAEs occurred most frequently in the telavancin treatment group in Study 0015. The number of patients in each category of AEs was more balanced across treatment groups in Study 0019.

Exposure

As shown in Table 8 below, most patients received study medication for 7-11 days.

Table 8: FDA Medical Officer Summary Table of Subject Exposure to Study Drug, Studies 0015 and 0019, AT Safety Population

| Treatment Duration Strata | Study 0015 | | Study 0019 | |
|---------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| 1-2 days | 23 (6.2) | 15 (4.0) | 17 (4.5) | 17 (4.5) |
| 3-6 days | 77 (20.7) | 62 (16.6) | 53 (14.0) | 52 (13.8) |
| 7-11 days | 172 (46.2) | 194 (51.9) | 195 (51.5) | 184 (48.7) |
| 12-14 days | 59 (15.9) | 63 (16.8) | 64 (16.9) | 72 (19.0) |
| 15-23 days | 41 (11.0) | 40 (10.7) | 50 (13.2) | 53 (14.0) |
| missing | 0 | 0 | 0 | 0 |

Deaths

As shown in Table 9 below, there was a notable imbalance in the mortality rates between the two treatment groups in Study 0015 with a higher death rate (by

approximately 5%) in the telavancin group compared to the vancomycin group. In Study 0019, the mortality rates were comparable across the treatment groups.

Table 9: Applicant Summary of Analysis of Deaths for studies 0015 and 0019, AT Safety Population (adapted from Applicant's 2.7.4 Summary of Clinical Safety)

| | Number of patients | | | | | |
|----------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | 0015 | | 0019 | | 0015 + 0019 Total | |
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Total Deaths in window [1] | 80 (21.5%) | 62 (16.6%) | 70 (18.5%) | 78 (20.6%) | 150 (20.0%) | 140 (18.6%) |
| Difference (95% CI) [2] | 4.9% (-0.7%, 10.6%) | | -2.2% (-7.8%, 3.5%) | | 1.4% (-2.6%, 5.3%) | |

[1] Deaths based on patients with treatment-emergent adverse events with death as an outcome and deaths occurred within protocol-specified window.
 [2] Point estimate and 95% confidence interval on the treatment difference (telavancin – vancomycin) in death rate. The pooled analysis is stratified by study.

Table 10 summarizes the most frequent causes for death in both treatment groups in Study 0015. The most commonly reported cause of death in the telavancin treatment group was multi-organ failure, while in the vancomycin treatment group it was respiratory failure.

Table 10: FDA Medical Officer Summary Table of the Most Frequent Causes (>3%) for Death, Study 0015, AT Population

| | | Telavancin | Vancomycin |
|---|----------------------------|------------|------------|
| All Treated | N (%) | 372 | 374 |
| Total Subject Deaths | n (%) | 80 (21.5%) | 62 (16.6%) |
| Causes for Death n (% of all deaths) | Not specified | 16 (20.0%) | 10 (16.1%) |
| | Multi-organ failure* | 11 (13.8%) | 6 (9.7%) |
| | Septic shock** | 7 (8.8%) | 6 (9.7%) |
| | Respiratory Arrest | 6 (7.5%) | 10 (16.1%) |
| | Heart Failure [#] | 3 (3.8%) | 2 (3.2%) |
| | Sepsis [†] | 3 (3.8%) | 2 (3.2%) |

* Includes the following preferred terms (PT): multiple organ failure, multi organ failure, multorgan system failure, multiple organ failure syndrome, multiple organ failure/cardiogenic shock, multiple organ failure/end stage liver disease/primary biliary cirrhosis
 ** Includes the following PT: septic shock, septic shock/source septicemia, septic shock with multiorgan failure, septicemia shock (*A. baumannii*), septicemic shock with multiorgan failure, septic shock due to *P. aeruginosa* bacteremia, septic shock secondary to second episode of VAP, septic shock caused by suspected right sided empyema progressed
 # Includes the following PT: congestive heart failure, heart failure
 † Includes the following PT: sepsis, severe sepsis with burst abdomen, severe sepsis syndrome, worsening sepsis

Table 11 summarizes the most frequent causes for death among patients enrolled in Study 0019. Septic shock was the most frequently reported cause of death in the telavancin treatment group and respiratory failure in the vancomycin treatment group.

Table 11: FDA Medical Officer Summary Table of the Most Frequent Causes (>3%) for Death, Study 0019, AT Population

| | | Telavancin | Vancomycin |
|---|----------------------------------|------------|------------|
| All Treated | N (%) | 379 | 378 |
| Total Subject Deaths | n (%) | 70 (18.6%) | 78 (20.5%) |
| Causes for Death n (% of all deaths) | Septic shock | 11 (15.7%) | 6 (7.7%) |
| | Not specified | 8 (11.4%) | 18 (23%) |
| | Multi-organ failure* | 7 (10%) | 1 (1.3%) |
| | Pulmonary Embolism** | 4 (5.7%) | 1 (1.3%) |
| | Respiratory Failure [†] | 4 (5.7%) | 9 (11.5%) |
| | Heart failure [#] | 1 (1.4%) | 5 (6.4%) |
| * Includes the following PT: multi organ failure, multi-organ failure, multiorgan failure, multiple organ failure, multiple organ failure due to advanced carcinoma of right lung ** Includes the following PT: pulmonary embolism, pulmonary thromboemboly, pulmonary artery thromboemboly, pulmonary embolus suspicion † Includes the following PT: acute respiratory failure, respiratory failure, respiratory failure due to gastric contents aspiration, respiratory failure following removal of life support, acute respiratory failure due to tracheostomy obstruction, respiratory failure Type II, respiratory failure due to respiratory tract block by sputum, respiratory failure due to withdrawal of active therapy, respiratory failures # Includes the following PT: acute heart failure, cardiac failure, CHF, congestive heart failure with MI, heart failure | | | |

Serious Adverse Events

Table 12 below shows the number of patients within each system organ class (SOC) who had an SAE that occurred in > 1% of patients in the telavancin treatment group.

Table 12: FDA Medical Officer Table of Serious TEAE by System Organ Class, Occurring in > 1% of Telavancin-Treated Patients, Study 0015 and Study 0019, AT Safety Population

| System Organ Class | Study 0015 | | Study 0019 | |
|--|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| Respiratory, Thoracic, and Mediastinal Disorders | 33 (8.9%) | 27 (7.2%) | 28 (7.4%) | 30 (8.0%) |
| Infections and Infestations | 32 (8.6%) | 29 (7.8%) | 37 (9.8%) | 32 (8.5%) |
| Cardiac Disorders | 18 (4.8%) | 21 (5.6%) | 12 (3.2%) | 20 (5.3%) |
| Renal and Urinary Disorders | 15 (4.0%) | 7 (1.9%) | 9 (2.4%) | 9 (2.4%) |
| General Disorders and Administration Site Conditions | 13 (3.5%) | 9 (2.4%) | 13 (3.4%) | 6 (1.6%) |
| Nervous System Disorders | 12 (3.2%) | 5 (1.3%) | 9 (2.4%) | 14 (3.7%) |
| Vascular Disorders | 9 (2.4%) | 4 (1.1%) | 6 (1.6%) | 5 (1.3%) |
| Metabolism and Nutrition Disorders | 5 (1.3%) | 0 (0.0%) | | |
| Gastrointestinal Disorders | 5 (1.3%) | 6 (1.6%) | 7 (1.9%) | 5 (1.3%) |

The most frequent serious TEAEs in both the telavancin and vancomycin treatment groups within and across studies were in the respiratory, thoracic, and mediastinal disorders and infections and infestations SOCs. An imbalance in renal and urinary disorders in Study 0015, with more frequent events in the telavancin treatment group, is also noted; this difference is not observed in Study 0019.

Treatment Emergent Adverse Events

Table 13 provides a summary of the number of subjects who discontinued from study medication due to a TEAE.

Table 13: FDA Medical Officer Table of Subject Count with at least one TEAE that resulted in Discontinuation of Study Medication, Studies 0015 and 0019, AT Population

| Study | Treatment | N | n (%) | difference TLV-VAN (95% CI) |
|--|------------|-----|-----------|-----------------------------|
| 15 | Telavancin | 372 | 33 (8.9%) | 4.4 (0.75, 7.90)* |
| | Vancomycin | 374 | 17 (4.5%) | |
| 19 | Telavancin | 379 | 27 (7.1%) | 1.0 (-2.50, 4.58) |
| | Vancomycin | 378 | 23 (6.1%) | |
| Statistically significant difference; TLV=telavancin, VAN=vancomycin; N=total patients (All treated population); n= number of patients | | | | |

The most frequent TEAEs (stratified by SOC) that resulted in discontinuation of study medication in Study 0015 included AEs in the investigations and renal/urinary disorders in the telavancin treatment group compared to blood and lymphatic systems disorders, infections and infestations, and renal/urinary disorders in the vancomycin treatment group. For both the investigations and renal/urinary disorders SOCs, there was an imbalance indicative of a higher frequency of events among telavancin-treated patients. The most frequent TEAEs that resulted in discontinuation of study medication in Study 0019 included infections and infestations in both the telavancin and vancomycin treatment groups. In contrast to Study 0015, there were no striking imbalances in the frequency of specific TEAEs across the treatment groups in Study 0019.

Common Adverse Events

Table 14 summarizes the most common AEs observed with a frequency of $\geq 5\%$ in either treatment group for Studies 0015 and Study 0019.

Table 14: FDA Medical Officer Table of Subject Count for all TEAE with frequency $\geq 5\%$ in telavancin and comparator treatment groups stratified by Preferred Term, Studies 0015 and 0019, AT Population

| Preferred Term | Study 0015 | | Study 0019 | |
|-------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| Diarrhea | 47 (12.6) | 54 (14.4) | 38 (10.0) | 38 (10.1) |
| Constipation | 32 (8.6) | 36 (9.6) | 38 (10.0) | 35 (9.3) |
| Anemia | 30 (8.1) | 49 (13.1) | 34 (9.0) | 36 (9.5) |
| Hypokalemia | 30 (8.1) | 41 (11.0) | 31 (8.2) | 39 (10.3) |
| Nausea | 27 (7.3) | 19 (5.1) | 13 (3.4) | 12 (3.2) |
| Hypotension | 23 (6.2) | 26 (7.0) | 25 (6.6) | 26 (6.9) |
| Decubitus ulcer | 22 (5.9) | 26 (7.0) | 17 (4.5) | 18 (4.8) |
| Vomiting | 21 (5.7) | 19 (5.1) | 15 (4.0) | 12 (3.2) |
| Rash | 21 (5.7) | 10 (2.7) | 12 (3.2) | 16 (4.2) |
| Peripheral edema | 20 (5.4) | 26 (7.0) | 14 (3.7) | 12 (3.2) |
| Urinary tract infection | 19 (5.1) | 21 (5.6) | 14 (3.7) | 9 (2.4) |
| Insomnia | 16 (4.3) | 32 (8.6) | 18 (4.8) | 15 (4.0) |
| Hypertension | 11 (3.0) | 14 (3.7) | 21 (5.5) | 12 (3.2) |
| Anxiety | 10 (2.7) | 20 (5.4) | 12 (3.2) | 12 (3.2) |

n=number of subjects (patients) with the specified TEAE

Safety Laboratory Studies

Evaluation of results of safety laboratory data was hampered due to a large amount of missing data. Overall, the lowest rates for missing all chemistry, hematology, and urinalysis safety laboratory results occurred at baseline. At the end of therapy, >20% of patients in both clinical trials were missing all chemistry, hematology, and urinalysis test results. At TOC (and after accounting for missing laboratory data due to patient deaths), 6-9% were missing results from all chemistry tests, 7-13% were missing results from all hematology tests, and 12-17% were missing results from all urinalysis tests. Thus, the ability to assess the incidence and clinical significance of laboratory-related TEAEs (especially rare events) was hampered due to the substantial amount of missing laboratory data.

Adverse Events of Special Interest

Renal SAEs

Based on the imbalance in renal SAEs observed in Study 0015 and previous findings from the review of NDA 22-110, renal events were examined in detail by Dr. Sorbello.

In the pooled experience from studies 0015 and 0019, a total of 42 patients experienced serious renal-related TEAEs.

- 26 (61%) occurred in patients treated with telavancin across the trials
- 16 (38%) occurred in patients treated with vancomycin across the trials
- Renal failure acute was the most frequently reported renal-related TEAE

When the serious renal-related TEAEs were assessed by individual clinical trial, the PT event “renal failure acute” was reported most frequently in both trials. Serious

renal-related TEAEs occurred with equal frequency in the two treatment groups in study 0019. However, in study 0015, there was a disparity in serious renal-related TEAEs which occurred almost 2.4 times more frequently in the telavancin group, and the difference was statistically significant as shown in Table 15.

Table 15: FDA Medical Officer Table of Subject Count with Serious Renal TEAE stratified by Preferred Term, Study, and Treatment Group, Studies 0015 and 0019, AT Population

| AE Preferred Term | Study 0015 | | Study 0019 | |
|---|--------------------|----------------|---------------------|----------------|
| | TLV N=372 | VANCO N=374 | TLV N=379 | VANCO N=378 |
| | n (%) | n (%) | n (%) | 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) | |

Pulmonary Embolism

There were a total of 10 patients who experienced pulmonary embolism as a TEAE in the two telavancin NP studies, including two patients in Study 0015 and eight patients in Study 0019. Eight of the 10 patients were telavancin-treated patients (two from Study 0015 and six from Study 0019) and two were vancomycin-treated patients (both from Study 0019).

Eight patients experienced a pulmonary embolism (PE) that was assessed as a serious TEAE by investigators; seven were in telavancin-treated patients and one was in a vancomycin-treated patient. Seven of the eight patients who experienced a PE as a SAE subsequently died. In some cases, there was a temporal association between telavancin administration and the development of a PE; in three other cases, the onset of the event was ≥ 8 days post-EOT. There were also important concurrent factors and underlying medical conditions that may have affected the likelihood for this complication to occur and confounded causality assessment in some patients.

See Dr. Sorbello’s safety review for a tabular presentation of these cases, along with narrative descriptions of these events.

QT Prolongation

The Applicant performed a thorough QT/QTc study (designed with guidelines as defined in the 2002 FDA-Health Canada Concept paper), which demonstrated that telavancin prolonged the QTc interval >10 msec. Please refer to the original NDA 22-110 for the report of the Interdisciplinary Review Team for QT Studies for details.

There were 18 telavancin-treated and 21 vancomycin-treated patients in Study 0015 who experienced serious cardiac adverse events. In Study 0019, 12 telavancin-

treated and 20 vancomycin-treated patients experienced such events. Of note, no patients treated with either study medication experienced Torsades de pointes, although there was an imbalance in the number of patients who experienced a cardiac arrest in Study 0019 (five telavancin-treated compared to no vancomycin-treated patients).

Teratogenicity

Based on the teratogenic effects noted in animals, there is a potential risk for teratogenicity in humans. Approval of the telavancin cSSSI application (NDA 22-110) required development of a REMS to ensure that the benefits of the drug in women of childbearing potential outweigh the potential risk of teratogenicity observed in animals. The REMS goal was to minimize unnecessary telavancin exposure in pregnant women. The REMS elements include a Medication Guide to be distributed with all prescriptions and a communication plan in the form of a Dear Healthcare Provider letter to those who would prescribe the drug. Additionally, a pregnancy registry was developed to assess the signal for teratogenicity as a post-marketing requirement (PMR).

9. Advisory Committee Meeting

An anti-infective drugs advisory committee meeting was not scheduled for this application due to the inability to proceed with analysis of efficacy due to the lack of complete data on mortality in the study population.

Upon submission of a complete response, it is likely that an advisory committee meeting would be scheduled due to issues outlined previous. Issues to be discussed would include the efficacy and safety data from the application as well as NP study design issues such as identification and enrollment of patients who are most likely to have the disease, endpoint and timing of endpoint assessment, and appropriate justification of the non-inferiority margin based on the endpoint of interest and population studied.

10. Pediatrics

The Applicant has requested a deferral for all pediatric age groups for this indication until the clinical trials conducted in adults for this indication have been reviewed and approved by the FDA.

11. Other Relevant Regulatory Issues

The Division of Scientific Investigations has concluded that Studies 0015 and 0019 used to support this NDA appear to have been adequately conducted and data appear to be reliable. Results of inspections of (b) (4) (CRO)

and the Applicant were prompted by a complaint received by the Agency alleging that the Applicant improperly manipulated study data to achieve desired outcomes. The inspection of the Applicant did not reveal any regulatory violations, although it was ascertained that data was added/revised after unblinding. Examples included: addition of missing MIC data, reconciliation of number of deaths and SAEs, updating renal AE status, and an internally generated site audit. Portions of the medical review process including decisions impacting patient evaluability and adequacy of Gram negative coverage also occurred after unblinding. The CRO received a final classification of No Action Indicated (NAI) and the Applicant a preliminary classification of NAI.

Three of six investigators received classifications of NAI (one final and two preliminary). The other three investigators received (or were preliminarily classified) as Voluntary Action Indicated (VAI). One of the three investigators (Dr. Lee) received a final classification of VAI for failure to report some protocol deviations including administration of concomitant medications and enrollment of subjects not meeting eligibility criteria. Additionally, clinical outcome assessment appeared to be changed in response to queries from the contract research organization (CRO) that seemed to be inconsistent with the protocol. This became less of an issue when the efficacy endpoint was changed to all-cause mortality. One of the preliminary site VAIs (Dr. Ortiz) was issued for incomplete reporting of safety data (including AEs not reported to the Applicant, missing safety laboratory studies, and missing ECGs); data submitted supporting efficacy and safety appeared to be reliable. The third (potential) VAI (Dr. Rocha) was based on the site's failure to adequately document drug storage temperature; however, safety and efficacy data reported appeared to be reliable.

12. Labeling

Labeling was not addressed during this review cycle due to the application being not approved in its current form.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

This application cannot be approved in its present form. Although the study was designed to assess the non-inferiority of telavancin relative to vancomycin in the treatment of NP based on a clinical response endpoint, recent review of the scientific literature has not provided sufficient information to allow interpretation of such studies. There is no scientific data available to estimate the effect of antimicrobial therapy relative to placebo based on a clinical endpoint. The literature has however, provided some evidence for estimating treatment effect of antimicrobial therapy relative to placebo based on an all-cause mortality endpoint. However, the mortality data submitted with this application is incomplete and therefore the analyses presented in the application cannot be relied upon to yield valid results. The Applicant is attempting to collect the missing mortality data for

both trials. Based on the data originally submitted, there appeared to be an imbalance in mortality in Study 0015, with more deaths noted in the telavancin treatment group. Based on the imbalance of baseline characteristics between the two study populations, it may not be appropriate to pool the results from Study 0015 and Study 0019 for efficacy assessment based on all-cause mortality.

- Risk Benefit Assessment

The risk / benefit assessment for this drug can not be completed due to insufficient information on mortality data upon which the endpoint is base.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

Not applicable at this time based on the complete response recommendation.

- Recommendation for other Postmarketing Requirements and Commitments

Not applicable at this time based on the complete response recommendation.

- Recommended Comments to Applicant\

The results of the two phase 3 clinical trials (Studies 0015 and 0019) submitted in this application do not provide substantial evidence to demonstrate the safety and efficacy of telavancin in the treatment of nosocomial pneumonia. Both trials were designed and powered for a clinical response endpoint. However, as discussed at the FDA Anti-Infective Drugs Advisory Committee meeting for NDA 22-171 on July 16, 2008 and the subsequent public workshop, "Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia" on March 30-April 1, 2009, published scientific literature (identified to date) does not permit interpretation of non-inferiority studies of antibacterial drugs for NP and VAP using clinical response as the primary endpoint due to the lack of scientific data to estimate the treatment benefit of active control antibacterial therapy relative to placebo. Published historical evidence will only permit interpretation of non-inferiority trails for NP and VAP using all-cause mortality as the primary endpoint. In this application, all-cause mortality was a secondary endpoint.

In this application, all-cause mortality was a secondary endpoint and trials were individually of insufficient size and statistical power to identify a difference in all-cause mortality between telavancin and comparator-treated patient groups if such a difference existed. The submitted mortality data was incomplete and at this time, it is unclear whether an analysis of the all-cause mortality data derived by pooling the results of Studies 0015 and 0019 will be sufficient to determine the efficacy and safety of telavancin. Differences in the distribution of baseline prognostic factors for mortality across the two trials may preclude pooling; if, upon further

review, pooling of the mortality data is determined to be acceptable, the collective all-cause mortality data may only be of sufficient size and statistical power to be considered analogous to one adequately sized trial with a mortality endpoint and additional evidence supporting safety and effectiveness would still be required.

In order to resolve these deficiencies:

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

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|--------------|
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |

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/s/

JANICE K POHLMAN
11/12/2009

CLINICAL REVIEW

| | |
|------------------------|---|
| Application Type | NDA |
| Application Number(s) | 22-407 |
| Priority or Standard | Standard |
| Submit Date(s) | January 23, 2009 |
| Received Date(s) | January 26, 2009 |
| PDUFA Goal Date | November 26, 2009 |
| Division / Office | Division of Anti-Infective and Ophthalmology Products/ Office of Antimicrobial Products |
| Reviewer Name(s) | Alfred Sorbello, DO, MPH |
| Review Completion Date | September 25, 2009 |
| Established Name | Telavancin for injection |
| (Proposed) Trade Name | Vibativ™ |
| Therapeutic Class | Systemic antimicrobial |
| Applicant | Theravance, Inc |
| Formulation(s) | Intravenous infusion |
| Dosing Regimen | 10 mg/kg every 24 hours |
| Indication(s) | Nosocomial pneumonia |
| Intended Population(s) | Adults |

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the clinical review of the submitted safety and efficacy data, this FDA Medical Officer recommends that telavancin should not be approved for the treatment of nosocomial pneumonia in adults caused by susceptible strains of Gram-positive pathogens. Studies 0015 and 0019, the two identical phase 3 clinical trials of telavancin compared to vancomycin in the treatment of nosocomial pneumonia (NP), were designed based on a 20% noninferiority margin (14% post hoc margin) for a clinical response efficacy endpoint. However, in view of discussions at the July 16, 2008 meeting of the Anti-infective Drugs Advisory Committee and the 2009 public workshop entitled “Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)” co-sponsored by the Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) held on March 31-April 1, 2009 in Silver Spring, MD, it was evident that published historical evidence will only permit interpretation of non-inferiority efficacy studies for NP and VAP using all-cause mortality as the primary endpoint. As Studies 0015 and 0019 were not independently designed and statistically powered to assess the noninferiority of telavancin compared to vancomycin in a replicative manner based on all-cause mortality, the Applicant planned to pool the study populations for that analysis. Based on a review of the baseline population characteristics for each study as conducted by this FDA Medical Officer, it was evident that the two study populations differed substantially with respect to the frequencies of various baseline characteristics and co-morbid conditions that could potentially affect the risk for mortality making it unsound to combine them. Review of the data provided by the Applicant revealed a mortality imbalance in Study 0015 with more deaths and higher odds ratios for death in the telavancin arm compared to the vancomycin arm that reached statistical significance in some analyses. This finding raised concerns that telavancin was inferior to vancomycin and that the drug may not be safe to administer in some subpopulations. However, on further investigation in response to information requests from the Division regarding study patient deaths for two time periods (initiation of study drug to Study Day 28 day and initiation of study drug to end of study drug therapy + 28 days), the Applicant uncovered additional mortality data that had not been provided previously. On review, it was apparent that the additional data did not provide adequate information about whether the treated patients had either withdrawn alive, died, dropped out, or were lost to follow-up. A large amount of censored information involving approximately one-third of the treated patients in both studies was included for both time periods, which made it untenable to reach any specific conclusions regarding the efficacy and safety of the drug despite the mortality imbalance observed in earlier analyses. After querying all study sites to assess study patient survival, the Applicant is expected to submit additional mortality data to the Division in the future. The updated data will need to be reviewed by the Division to assess whether telavancin is safe and effective for the treatment of NP caused by susceptible Gram-positive pathogens.

1.2 Risk Benefit Assessment

The mortality data provided in the NDA and subsequent responses to various information requests from the Division did not provide complete information to allow an assessment of the potential benefits or risks of telavancin compared to standard treatment with vancomycin for NP in adults. Based on a review of the currently available all-cause mortality data, the risk-benefit assessment is unfavorable and indicative of a mortality imbalance with higher death rates and odds ratios for death in the telavancin arm in one study (Study 0015). However, due to the substantial amount of censored mortality data submitted by the Applicant in response to a recent information request from the Division regarding study patient deaths for two time periods (initiation of study drug to Study Day 28 day and initiation of study drug to end of study drug therapy + 28 days), no definitive conclusions are possible until the survival status of all of the treated patients has been clarified. Additional mortality data is expected from the Applicant in the future following queries of study sites.

Independent of the mortality analysis above, the review of safety conducted by this FDA Medical Officer revealed the following signals suggestive of an unfavorable risk-benefit assessment for telavancin for the NP indication:

- Telavancin nephrotoxicity:
 - Among patients with normal baseline creatinine (≤ 1.2 mg/dL), there were comparable incidences across the two studies of renal treatment-emergent adverse events (TEAE). However, among patients with abnormal baseline creatinine (> 1.2 mg/dL), more telavancin-treated patients experienced renal TEAEs compared to vancomycin-treated patients.
 - Serious renal-related TEAEs occurred with equal frequency in the two treatment groups in study 0019. However, in study 0015, there was a disparity in that serious renal-related TEAEs occurred almost 2.4 times more frequently in the telavancin group compared to the vancomycin group, and the difference was statistically significant.
 - Among the serious TEAEs that were assessed as related to study drug by the investigators in Study 0015, there was a striking imbalance with 14 telavancin-treated compared to 5 vancomycin-treated patients having experienced acute renal failure, blood creatinine increased, and renal insufficiency as serious drug-related TEAEs.
 - For each of the RIFLE severity categories of acute kidney injury (Risk, Injury, and Failure), there was a higher number of patients in the telavancin treatment groups compared to the vancomycin treatment groups of both studies. The imbalances in patient counts raise concern about the potential nephrotoxicity of telavancin, although the differences were not statistically significant.
 - 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 arms of both studies compared to concomitant mean decreases in serum creatinine and mean increases in creatinine clearance in the vancomycin arms of both studies. The median serum creatinine declined in the vancomycin

arms of both studies compared to no change in the telavancin arms. These findings provide additional evidence of the potential for nephrotoxicity from telavancin use.

- There was a markedly greater number of shifts in serum creatinine and BUN from normal and low values at baseline to high values at EOT in the telavancin group compared to the vancomycin group for Study 0015, and the differences were statistically significant. A similar imbalance in shifts in serum creatinine and BUN was not observed in Study 0019.
 - There was a higher frequency of two-grade toxicity increases in creatinine in the telavancin treatment group compared to the vancomycin treatment group of Study 0015, and the difference was statistically significant. In addition, there was a higher frequency of two-grade toxicity increases in serum creatinine in the pooled telavancin group compared to the pooled vancomycin group, and the difference was statistically significant. Telavancin exposure among patients with an abnormal baseline serum creatinine in Study 0015 was associated with a higher risk for a two-grade toxicity increase in creatinine compared to vancomycin-treated patients.
 - Among the mortality narratives provided by the Applicant, there were telavancin and vancomycin-treated patients identified who experienced renal insufficiency or renal failure that were considered to be possibly or probably related to study drug exposure.
 - There were cases in both treatment groups that were confounded by comorbid conditions or concomitant medications.
- Potential for QTc prolongation associated with telavancin administration:
 - There was a higher post-baseline average change (msec) in QTcF interval and a higher maximum post-baseline change (msec) in QTcF interval in the patients in the telavancin group compared to the vancomycin group in Study 0019, and the difference was statistically significant. A similar finding was not observed in Study 0015.
 - There was a higher post-baseline average change (msec) in QTcB interval and a higher maximum post-baseline change (msec) in QTcB interval in the patients in the telavancin group compared to the vancomycin group in Study 0019, and the difference was statistically significant. A similar higher post-baseline average change (msec) in QTcB interval in the patients in telavancin group compared to the vancomycin group was observed in Study 0015, and the difference was statistically significant.
 - There were more telavancin-treated than vancomycin-treated patients in both studies (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.
 - No cases of torsades de pointes were reported in Studies 0015 and 0019.

Other important safety considerations in relation to the overall risk-benefit assessment of telavancin in this NDA include the following:

- The ability to assess the incidence and clinical significance of some TEAEs (especially rare events) was hampered due to the substantial amount of missing clinical laboratory data.
- There was an imbalance in the incidence of pulmonary embolism (PE) as a TEAE across the treatment groups in that eight of the 10 patients who developed PE were telavancin-treated (two from Study 0015 and six from Study 0019) and only two were vancomycin-treated (both from Study 0019). There was a temporal association of telavancin exposure with the development of PE, but some of the narratives provided by the Applicant were not of sufficient detail to assess causality.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

This section is not applicable as the NDA is not approvable for the indication being sought by the Applicant.

1.4 Recommendations for Postmarket Requirements and Commitments

This section is not applicable as the NDA is not approvable for the indication being sought by the Applicant.

2 Introduction and Regulatory Background

2.1 Product Information

Telavancin is an injectable, semisynthetic, lipoglycopeptide antibiotic with rapid, concentration-dependent bactericidal activity against clinically relevant Gram-positive bacterial pathogens, including *S. aureus* (methicillin-susceptible and resistant isolates), *S. pneumoniae*, and vancomycin-resistant *E. faecalis*. Telavancin has a multifunctional mechanism of action that includes inhibition of bacterial cell wall synthesis and disruption of the functional integrity of the bacterial membrane. It also has a longer postantibiotic effect than that of other agents (such as vancomycin) that act upon the cell wall. Telavancin contains hydroxypropyl- β -cyclodextrin as a solubilizing agent.

The proposed indication for telavancin in this NDA is as follows:

Telavancin is indicated for the treatment of nosocomial pneumonia caused by susceptible strains of the following Gram-positive microorganisms:

VIBATIV is indicated for the treatment of patients with nosocomial pneumonia caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* [including methicillin-susceptible and -resistant isolates] or *Streptococcus pneumoniae*.

(b) (4)

The recommended dosing for telavancin is 10 mg/kg administered over a 60-minute period by intravenous infusion once every 24 hours for 7 to 14 days. Doses of telavancin greater than 10 mg/kg and infusion times of less than 60 minutes have not been studied in Phase 3 controlled clinical trials.

2.2 Tables of Currently Available Treatments for Proposed Indications

The choice of therapy for nosocomial pneumonia is frequently based on consideration of the local microbiological susceptibility patterns for each hospital and consideration of the risk for drug-resistant bacterial pathogens, such as *P. aeruginosa*, *Acinetobacter* species, *K. pneumoniae*, *Enterobacter* species, and methicillin-resistant *S. aureus* (MRSA), as depicted in the table below. Antibacterial drugs and drug combinations that are frequently used for the treatment of NP and VAP include cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, levofloxacin, linezolid, vancomycin, and aminoglycosides. Combination regimens have been recommended to aim for synergy in the treatment of multi-drug resistant Gram-negative bacteria, such as *P. aeruginosa*. Treatment durations of 7 to 21 days are frequently employed based on consideration of clinical response and infecting baseline pathogen(s). Most of the antibacterial drugs noted above are not specifically approved for the indication of NP.

Table 1: Antibiotic Treatment of Hospital-acquired Pneumonia (HAP), Ventilator-associated Pneumonia (VAP), and Healthcare-associated Pneumonia (HCAP)*

| | Potential Pathogens | Antibiotic Therapy |
|--|---|--|
| Initial empiric therapy for HAP or VAP in patients with no known risk factors for multi-drug resistant pathogens, early onset, and any disease severity | <i>S. pneumoniae</i> <i>H. influenzae</i> Methicillin susceptible <i>S. aureus</i> Antibiotic-sensitive Gram-negative bacilli <i>E. coli</i> <i>K. pneumoniae</i> <i>Enterobacter species</i> <i>Proteus species</i> <i>S. marcescens</i> | Ceftriaxone OR Levofloxacin, moxifloxacin, or ciprofloxacin OR Ampicillin/sulbactam OR Ertapenem |
| Initial empiric therapy for HAP, VAP, and HCAP in patients with late onset disease or known risk factors for multi-drug resistant pathogens and all disease severity | Pathogens listed above and MDR pathogens <i>P. aeruginosa</i> <i>K. pneumoniae (ESBL)</i> <i>Acinetobacter species</i> Methicillin resistant <i>S. aureus</i> | Antipseudomonal cephalosporin (cefepime or ceftazidime) OR Antipseudomonal carbapenem (imipenem or meropenem) OR β -lactam/ β -lactamase inhibitor (piperacillin-tazobactam) OR aminoglycoside PLUS Linezolid or vancomycin |

MDR = multi-drug resistant

*Adapted from: 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;171:388-416.

At present, linezolid, levofloxacin, ciprofloxacin, and piperacillin-tazobactam are the only antibacterial drugs that have been approved by the US Food and Drug Administration for the treatment of nosocomial pneumonia. Teicoplanin has also been approved for such use in the European Union.

2.3 Availability of Proposed Active Ingredient in the United States

Telavancin was approved for use in the United States (NDA 22-110) for the treatment of complicated skin and skin structure infections (cSSSI) on September 11, 2009 (see Section 2.6 for additional details).

2.4 Important Safety Issues With Consideration to Related Drugs

Renal toxicity, teratogenicity, and potential for QTc prolongation were problematic safety issues identified in the review of NDA 22-110 regarding telavancin in the treatment of cSSSI. Please refer to Section 2.6 of this report for further details.

Related and alternative Gram-positive antibacterial agents include vancomycin and linezolid. Important adverse effects associated with intravenous vancomycin administration include renal failure, ototoxicity, neutropenia, red neck syndrome, anaphylaxis, phlebitis, rash, and Stevens Johnson Syndrome. Important adverse effects associated with linezolid administration include myelosuppression (anemia, thrombocytopenia, pancytopenia), peripheral neuropathy, optic neuropathy, serotonin syndrome (in patients co-administered certain selective serotonin reuptake inhibitors), nausea, *C. difficile*-related diarrhea, and lactic acidosis.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

April 22, 2002: Pre-IND meeting was held to include discussion of the plans for development of Telavancin.

May 23, 2002: Investigational New Drug Application (IND) 60,237 was submitted regarding the initiation of studies of telavancin in the United States.

July 12, 2004: End of Phase 2 meeting: Proposals for Phase 3 studies in HAP (Studies 0015 and 0019) were submitted to the US FDA and discussed.

December 6, 2006: A New Drug Application for the use of telavancin for the treatment of complicated skin and skin structure infections (cSSSI; NDA 22-110) was submitted to FDA and is here after referred to as the cSSSI NDA. A Safety Update to the cSSSI Integrated Summary of Safety Information (ISS) was submitted as an Amendment to NDA 22-110 on April 17, 2007. On October 19, 2007, the Agency issued an approvable letter on the cSSSI NDA. An End of Review Meeting was held on November 11, 2007, and on January 21, 2008, Theravance submitted a Complete Response to the action letter dated October 19, 2007. Appendix 6 of the Complete Response consisted of a further Safety Update to the cSSSI

ISS. The cSSSI NDA, including all of its Safety Updates, are incorporated herein by reference. At the Pre-NDA Meeting for the HAP indication held on March 6, 2008, it was agreed that the Integrated Summary of Safety (ISS) for the current submission only include the data from Studies 0015 and 0019 in hospital-acquired pneumonia.

November 12, 2007: Prior to final closure of the clinical database, the final Statistical Analysis Plan for Studies 0015 and 0019 was submitted to the US FDA on unblinding of treatment assignment and analysis of the data.

March 6, 2008: Pre-New Drug Application (Pre-NDA) Meeting was held with the FDA.

January 23, 2009: NDA 22-407 for the use of telavancin for the treatment of nosocomial pneumonia was submitted to the US FDA. The NDA consisted of two identical Phase 3 randomized, double-blind, parallel-group, multinational clinical trials of intravenous telavancin versus vancomycin for treatment of hospital-acquired pneumonia with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus*.

2.6 Other Relevant Background Information

The Applicant had previously submitted NDA 22-110 regarding telavancin in the treatment of cSSSI. Telavancin demonstrated non-inferiority to vancomycin in two Phase 3 clinical trials of patients with cSSSIs suspected to be caused by Gram-positive bacterial pathogens. However, telavancin did not demonstrate superiority compared to vancomycin in the treatment of patients with MRSA as the baseline pathogen.

The Agency issued an approvable letter for NDA 22-110 on October 17, 2007, citing three deficiencies:

- (1) FDA inspection of the (b) (4) facility in (b) (4) revealed significant deviations from the Current Good Manufacturing Practice Regulations
- (2) Financial disclosure information for three sub-investigators was not included in the application.
- (3) Benefit-risk assessment of the drug product was problematic due to concerns about the decreased efficacy of the drug in patients with baseline renal impairment and advanced age compared to vancomycin-treated patients, an imbalance with respect to rates of serious renal and vascular disorders, evidence of QTc prolongation on the thorough QT/QTc study, potential teratogenicity in at least one and up to three animal species, and insufficient information to provide dosing recommendations for patients with creatinine clearance <10 mL/min including patients on hemodialysis.

The Applicant provided a Complete Response to the approvable action on January 21, 2008.

The telavancin cSSSI NDA was to have been presented at the Anti-Infective Drug Advisory Committee (AIDAC) Meeting on February 27, 2008, but the meeting was cancelled shortly before the scheduled date due to concerns from the Division of Scientific Investigations (DSI)

related to trial conduct monitoring activities by a contract research organization (CRO) that may have impacted data integrity. Additional investigative sites, the Applicant, and the CRO of concern were inspected subsequently by the FDA, and a comprehensive audit was performed by the Applicant. Data from three study sites was excluded from the efficacy analyses, whereas efficacy data from the remainder of the study sites was found to be reliable. The telavancin cSSSI NDA was presented to the AIDAC on November 18, 2008 with the committee voting 21 (yes) and 5 (no) that the data presented demonstrated the safety and effectiveness of telavancin for the treatment of cSSSI due to susceptible Gram-positive bacteria.

A Complete Response letter was issued on February 20, 2009. Deficiencies to be addressed, included development of a Risk Evaluation and Mitigation Strategy (REMS) to include a Medication Guide and Communication Plan related to potential teratogenicity, additional follow-up information on patients with nephrotoxicity, and a post-marketing requirement for a pregnancy registry.

A Complete Response was submitted to the FDA on March 13, 2009.

The telavancin cSSSI NDA was subsequently approved on September 11, 2009. In the approval letter, a REMS consisting of a Medication Guide, communication plan, and a timetable for submission of assessments of the REMS was included. The REMS assessment plan was to include but was not limited to the following:

- a. A survey of healthcare providers and patients' understanding of the serious risks of VIBATIV (telavancin)
- b. A summary and analysis of maternal and fetal outcomes for all reported pregnancies (from any data source) including:
 1. A cumulative number of all fetal exposures and outcomes reported for all reported pregnancies
 2. A root cause analysis to investigate the pregnancies reported with VIBATIV (telavancin) use in the U.S.

In addition, the Applicant was required to conduct a postmarketing study consisting of a pregnancy registry to evaluate the safety of this product in pregnant women and their offspring and to conduct a prospective study over a five-year period after introduction of VIBATIV (telavancin) to the market to determine if decreased susceptibility to VIBATIV (telavancin) is occurring in the target population of bacteria that are in the approved VIBATIV (telavancin) package insert.

Finally, there were two postmarketing study commitments:

1. In order to determine if there may be some effect of renal function on the biological activity of VIBATIV (telavancin) that may explain the decreased efficacy of telavancin in patients with renal impairment to include the following:
 - a. Compare results obtained with the current analytical assay for determining concentrations of telavancin in plasma to results obtained with a bioassay method for

patients with normal renal function, severe renal impairment (creatinine clearance <30 mL/min), and end-stage renal disease receiving hemodialysis.

b. The bioassay is to be reproducible with appropriate controls developed to determine if the test is performing correctly at the time subject specimens are tested.

c. Subjects are to be dosed per the Phase 3 cSSSI clinical trial protocols.

d. Enroll sufficient subjects with normal renal function, severe renal impairment, and end-stage renal disease receiving hemodialysis in the trial to obtain data from 15 evaluable patients for each subject population.

2. to conduct a deferred pediatric study under PREA for the treatment of cSSSI in pediatric patients ages 0 to 17 years.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The FDA review team issued multiple information requests regarding the execution of the two phase 3 clinical trials 0015 and 0019 and requested additional data for analysis. The various issues are described in relevant sections of this report, including Section 5.3.1.2.6 Evaluability and Eligibility.

In response to an information request dated April 30, 2009 regarding the significant amount of missing laboratory safety data, the Applicant reported that there were transit time delays, courier issues (resulting in clotted samples due to the short stability of whole blood), laboratory error, and varying physical conditions of the patients themselves that contributed to missing central laboratory safety data. The Applicant reported that the majority of laboratory values that were missing from the database were hematology tests. The Applicant also reported that the principal safety issue was renal dysfunction based on the safety database provided in the cSSSI submission (NDA 22-110) and the available data in the current NDA submission for NP. As renal dysfunction is measured by serum creatinine and almost 95% of patients had a serum creatinine determination at the TOC visit or within 3 days of the visit, the Applicant considered that these data would be sufficient to characterize the safety profile of telavancin.

3.2 Compliance with Good Clinical Practices

In the 0015 and 0019 clinical study reports, the Applicant stated that each study was conducted in accordance with the principles of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (GCP) and the principles of the World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects (as amended in Tokyo, Japan; Venice, Italy; Hong Kong; Somerset West, Republic of South Africa; and Edinburgh, Scotland; and clarified in Washington and Tokyo) or with the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the

study patient. Each study met the ethical requirements of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

According to the two clinical trial reports, Investigators obtained written informed consent from each individual (or a legally acceptable representative) who participated in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and prior to undertaking any study-related procedures. Patients were informed that they were completely free to refuse to enter the study or to withdraw from it at any time for any reason.

Data Integrity Assessment Report

The Applicant conducted an audit to assess data integrity. A final data integrity assessment report was provided to the Agency in response to an information request dated February 25, 2009, which described an assessment of the integrity of clinical site data documentation from the two phase 3 clinical trials 0015 and 0019 with regards to patient eligibility criteria and the investigators' assessments of clinical response. A second objective was assistance with collection of radiology reports for the chest x-rays (or CT scans) performed as part of the studies. Qunitiles, Inc and QA Partners conducted remonitoring and auditing site visits, respectively. The investigational plan called for visiting 120 sites across 28 countries that collectively accounted for 1,216 patients representing 81% of the total number of patients treated in the pooled studies.

According to the report, site visits were completed for 94% of the targeted sites (113 of the planned 120 sites) and source documents were reviewed for 94% of the targeted patients (1,144 of 1,216 patients). This represented 76% of all patients treated in the pooled studies.

The significant findings as described in the report are summarized below:

- Of the 113 sites, two sites of concern were identified (34003 and 29005). They accounted for a total of 15 patients (11 in site 34003 and 4 in site 29005). Medical records could not be found for the involved patients, such that data integrity could not be assessed at either site. The Applicant conducted a sensitivity analysis in which data from both sites was excluded, and reported that the results supported the conclusion of non-inferiority of telavancin compared to vancomycin based on a 20% NI margin using a clinical response endpoint.
- A total of 27 significant data errors (a discrepancy that may directly impact the validity of efficacy and safety conclusions for a particular patient) were confirmed, resulting in an error rate of 2% (27 of 1,144).
- Six previously unreported serious adverse events were identified, including four deaths that occurred outside of the protocol-specified reporting window. The six patients were as follows:
 - 0015-09008-4406: post-follow-up visit death due to acute respiratory distress syndrome and respiratory arrest
 - 0015-38049-4243: aspiration pneumonia
 - 0019-20019-6605: post-consent withdrawal death due to congestive heart failure and myocardial infarction

- 0019-20019-6609: post-consent withdrawal death with no details (occurred after patient transferred to another hospital)
- 0019-20019-6437: post-consent withdrawal death due to acute coronary syndrome
- 0019-08006-6302: heart failure
- There were 139 other unreported adverse events identified in the data audit.

The overall conclusion stated in the report was that the clinical site documentation relating to patient eligibility and the primary efficacy endpoint for 76% of the patients in the two pooled studies was verified.

Division of Scientific Investigation (DSI)

During the review cycle for this NDA, a site inspection was conducted at Theravance. During the inspection, it was noted that subsequent to treatment unblinding, medical review determinations were made impacting patient population evaluability, assessments of potentially effective non-study antibiotics, and assessments of the adequacy of Gram-negative coverage. Medical Monitor evaluation of such issues following treatment unblinding raises concern about the potential for biased assessments.

3.3 Financial Disclosures

For both phase 3 clinical trials, the Applicant submitted Form FDA 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) stating that the Applicant had not entered into any financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, the Applicant certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in the product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) and none disclosed any such interests. The Applicant also certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f).

The Applicant indicated that despite due diligence, documentation of financial interest (or lack thereof) was not available for 41 sub-investigators participating in Studies 0015 and 0019 (see table below). The reasons for this varied. Some sub-investigators failed to complete the forms prior to departing from the study site due to a change in employment. In these instances the study sites were asked to contact the sub-investigator and request the information. This was not always successful. In other instances the original forms were completed but were not present in the study project files at the close of the study owing to loss or misplacement in the interim. In these cases the responsible CRO has undertaken recontact with the sub-investigator to obtain the information. Again, these efforts have not always been successful.

Table 2: Investigators for whom Financial Information was not obtained (from Module 1, Section 1.3.4 Financial Certification of Applicant's NDA Submission)

| Study | Country | Site# | Subinvestigator Name | No. of Patients Enrolled at the Site* |
|---------------|----------------|---------|----------------------|---------------------------------------|
| 0015 | Argentina | (b) (4) | (b) (4) | (b) (4) |
| | Australia | | | |
| | Brazil | | | |
| | Chile | | | |
| | Czech Republic | | | |
| | France | | | |
| | India | | | |
| | Israel | | | |
| | Malaysia | | | |
| | South Africa | | | |
| | United Kingdom | | | |
| 0019 | Argentina | | | |
| | Australia | | | |
| | Canada | | | |
| | China | | | |
| | Greece | | | |
| | Lebanon | | | |
| | Mexico | | | |
| | Mexico | | | |
| | Mexico | | | |
| | Philippines | | | |
| | Poland | | | |
| Serbia | | | | |
| United States | | | | |

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Balajee Shanmugam, PhD is the chemistry reviewer for this submission. Please refer to his report for complete details.

4.2 Clinical Microbiology

Kerry Snow, MS is the clinical microbiology reviewer for this NDA. Please refer to his report for complete details.

4.3 Preclinical Pharmacology/Toxicology

Wendy Schmidt, PhD is the clinical pharmacology reviewer for this NDA. No new pharmacology/toxicology data was submitted with this NDA. Please refer to her report for complete details.

4.4 Clinical Pharmacology

The clinical pharmacology program for telavancin to characterize the PK profile in healthy young and elderly adults and subjects with renal and hepatic impairment was reviewed as part of the submission of NDA 22-110 regarding telavancin in the treatment of cSSSI.

For the current NDA 22-407, Ryan Owen, PhD is the clinical pharmacology reviewer and Kevin Krudys, PhD is the reviewer for the population PK findings. In brief, there does not appear to be a significant difference between the pharmacokinetics of telavancin as observed in healthy subjects, subjects with cSSSI, and patients with NP. The dose adjustments for telavancin in renally impaired patients that were recommended in NDA 22-110 (cSSSI) were also appropriate for patients with NP who were renally impaired. In addition, ventilation status did not appear to influence the pharmacokinetics of telavancin. Please refer to their reports for complete details.

4.4.1 Mechanism of Action

The mechanism of antibacterial action of telavancin includes inhibition of cell wall synthesis and disruption of bacterial membrane function. Telavancin inhibits cell wall synthesis by binding to late-stage peptidoglycan precursors, including Lipid II. Telavancin also binds to the bacterial membrane and disrupts membrane function. Both the cell wall and membrane mechanisms of telavancin occur *in vitro* at concentrations that are readily achieved in human plasma.

4.4.2 Pharmacodynamics

The following information is derived from the report of the FDA Medical Officer who reviewed NDA 22-110:

- The pharmacokinetics of telavancin are linear and increase relatively proportionately to dose as dose increases from 5 mg/kg to 12.5 mg/kg. Multiple dose infusion with doses ranging from 7.5 mg/kg/day to 15 mg/kg/day demonstrated a half-life of approximately 7-8 hours on Day 1 and 9 hours on Day 7 of dosing. The drug is approximately 90% protein bound and distributes primarily to extracellular water.
- The primary metabolite of telavancin is a hydroxylated metabolite, AMI-11352, which has about 10% of the activity of telavancin. The primary route of elimination is through renal excretion (76% of dose).
- *In vitro* assays in human microsomes demonstrated that CYP450 isoforms including CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP4A11 did not metabolize telavancin. Telavancin did demonstrate weak inhibitory effects on the major CYP450 enzymes including CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5. An *in vivo* drug interaction study performed with midazolam (substrate for CYP3A4) showed that telavancin has no significant effect on the PK of midazolam. The clinical studies of telavancin allow the concomitant use of aztreonam (in cSSSI studies and ongoing HAP studies) and piperacillin/tazobactam (ongoing HAP studies). Therefore interaction studies were conducted for each of these drugs with telavancin and the studies did not show evidence of interaction.
- The study of PK parameters in subjects with renal impairment was evaluated in a single 7.5 mg/kg study in subjects with normal renal function ($CL_{cr} > 80$ mL/min), mild renal impairment (CL_{cr} 51-80 mL/min), moderate renal impairment (CL_{cr} 30-50 mL/min), severe renal impairment ($CL_{cr} < 30$ mL/min) and patients with end-stage renal disease (ESRD) on hemodialysis. The mean C_{max} was similar among subjects with normal renal function and mild, moderate, and severe renal impairment and lowest in patients with ESRD following hemodialysis. The mean clearance was decreased 11% in those with mild and 19% in those with moderate renal impairment, with a decrease of 55% in those with severe renal impairment. ESRD patients who received hemodialysis after telavancin dosing demonstrated clearance 40% less than patients with normal renal function (greater than that in patients with severe disease). The mean $AUC_{0-\infty}$ increased 13%, 29%, 119%, and 79% in subjects with mild, moderate, severe, and ESRD, respectively, compared to subjects with normal renal function. An average of 5.9% of the telavancin dose was present in the dialysate. Therefore, a dosage adjustment recommended by the Applicant for patients with moderate renal impairment (7.5 mg/kg q 24 hrs) and severe renal impairment (10 mg/kg q 48 hrs) is acceptable. The PK of telavancin has not been evaluated in ESRD subjects who are dosed with telavancin following dialysis.

Please refer to the previous review for NDA 22-110 as well as the reports of Ryan Owen, PhD and Kevin Krudys, PhD for further details regarding the clinical pharmacology data submitted in the current NDA.

4.4.3 Pharmacokinetics

In the NP studies, pharmacokinetic (PK) sampling and sampling for coagulation tests (prothrombin time [PT], activated partial thromboplastin time [aPTT], and international normalized ratio [INR]) were to be conducted at selected sites. Blood samples for coagulation testing were to be collected at pretreatment and prior to the infusion (trough blood levels) on the same day that PK samples were to be obtained (Study Day 4). Please refer to the reports of Ryan Owen, PhD and Kevin Krudys, PhD for further information and relevant analyses.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

There were two pivotal phase 3 clinical trials involving telavancin in the treatment of NP, Studies 0015 and 0019. They were identical in design and comparable in size of patient population enrolled. The key aspects of the trials are summarized in the following table:

Table 3: Listing of Clinical Studies (from Applicant's Summary of Clinical Efficacy, Table 1, Section 2.7.3.2.1)

| Study Number | Title | Design / Type of Control | Treatments / Dose / Route of Administration | Efficacy Population | Duration of Treatment | # Centers / Location |
|--------------|--|---|--|---------------------|-----------------------|----------------------|
| 0015 | A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to methicillin-resistant <i>Staphylococcus aureus</i> | Randomized Double-Blind Active-Controlled | Telavancin 10 mg/kg IV q24h; Vancomycin 1 gm IV q12h; no oral switch | 746 | Up to 21 days | Multinational |
| 0019 | A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to methicillin-resistant <i>Staphylococcus aureus</i> | Randomized Double-Blind Active-Controlled | Telavancin 10 mg/kg IV q24h; Vancomycin 1 gm IV q12h; no oral switch | 757 | Up to 21 days | Multinational |

5.2 Review Strategy

This clinical review contains general information about the NDA and detailed reviews of the efficacy and safety of telavancin in the treatment of patients with nosocomial pneumonia (NP). The Applicant's rationale for the selection of the non-inferiority margin is also reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Protocol 0015: A Phase 3, Randomized, Double-blind, Parallel-group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-resistant *Staphylococcus aureus*

5.3.1.1 Protocol Overview

Study 0015 was an active-controlled study designed to compare telavancin with an approved antimicrobial therapy. Since the study was designed to enroll patients with Gram-positive hospital acquired pneumonia (HAP), especially patients with infection due to MRSA, vancomycin was selected as the comparator agent because it is standard empiric therapy for HAP, especially in settings where infections with MRSA are prevalent. Vancomycin was also expected to be effective for the treatment of HAP caused by other Gram-positive pathogens, including MSSA and has been used as the active comparator in other contemporary registration trials. A second Phase 3 study, Study 0019, was conducted under an identical protocol to this study. These two studies were given the acronym ATTAIN (Assessment of Telavancin for Hospital-acquired Pneumonia).

The original protocol was dated August 10, 2004 (see Section 5.3.1.1.1 of this report for details on the protocol). One protocol amendment with the following provisions was enacted on September 28, 2005. Multiple Administrative Letters were also issued by the Applicant between November 16, 2004 and August 27, 2008.

Amendment 1:

Herein is a summary of the important revisions incorporated into Protocol 0015 Amendment 1, dated 28 September 2005.

1. The medical monitor has changed from Dr. Barriere to Dr. Friedland and the Co-principal Investigator has changed from Dr. Fowler to Dr. Rubenstein.
2. Data regarding the Phase 2 complicated skin and skin structure infections study has been removed as this is now covered in the Investigator's Brochure in more detail (Section 2.2).
3. Imipenem for Gram-negative coverage has been removed as a treatment option. Aztreonam is still the preferred antibiotic for Gram-negative coverage. Piperacillin/tazobactam remains an alternative antibiotic for those sites with a high rate of aztreonam resistance (Sections 2.3.1, 4.1, 5.3, 6.3, and original 8.5). This change was made to reduce the number of allowed drugs in the treatment

- comparisons. In addition, recent *in vitro* studies performed at Theravance have indicated potential synergy between imipenem and vancomycin as well as imipenem and telavancin. Removing imipenem will reduce the bias in the study results due to the potential synergy.
4. Exclusion criterion #1: Prior antibiotic use within the previous 24 hours has been clarified. Only antibiotics that are potentially effective against Gram-positive hospital-acquired pneumonia (HAP) cannot be administered for more than 24 hours prior to randomization. In addition, treatment failure has been defined as failure to respond to at least 3 days of therapy (Section 5.3).
 5. Exclusion criterion #8: Sustained shock has been revised to “refractory shock”, which allows the use of low-dose sympathomimetics. Due to changes in medical practice, it was impractical to exclude the use of any sympathomimetics in this patient population (Section 5.3).
 6. Exclusion criterion #9: Uncorrected abnormal K⁺ or Mg⁺⁺ blood levels has been changed to abnormal K⁺ or Mg⁺⁺ blood levels that cannot be corrected. This allows enrollment of those patients who are able to respond to K⁺ or Mg⁺⁺ replacement therapy (Section 5.3).
 7. Exclusion criterion #11: Geodon (ziprasidone) therapy is added to the exclusion list as it is also formulated with cyclodextrin (Sections 5.3 and original 8.5.2).
 8. Exclusion criterion #12a: The time period for effective birth control following completion of study medication has been redefined from one month to one complete menstrual cycle (Section 5.3).
 9. The instructions for reconstitution of telavancin for injection 250 mg have been revised to specify addition of 23 mL of 5% Dextrose Injection USP (D5W) to each vial, rather than 24 mL, to account for changes in the drug product manufacturing. The final concentration remains 10 mg of telavancin per mL of reconstituted solution. In addition, telavancin may be reconstituted with normal saline or 5% Glucose Injection (G5W) (Section 6.1). Further, telavancin can also be administered in normal saline infusion bags (Sections 6.2 and 6.5).
 10. The telavancin stability information has been updated to reflect data from recently completed stability studies indicating that telavancin in reconstituted vials and infusion bags is stable for 72 hours under refrigeration (2-8 °C). Once removed from refrigeration, telavancin in reconstituted vials and infusion bags must be used within (b) (4) hours (Section 6.1).
 11. It has been made clearer that patients with methicillin-sensitive *S. aureus* pneumonia may be treated with an antistaphylococcal penicillin instead of vancomycin (Section 6.2).
 12. Statements regarding the use of cover sleeves for the study medication infusion bags has been removed. The appearances of dilute solutions of telavancin, vancomycin, and antistaphylococcal penicillins are indistinguishable (Sections 6.5 and 6.7).
 13. An instruction that local laboratory values will be used to estimate initial creatinine clearance has been added. Central laboratory data will not be available before administration of the first dose of study medication (Section 6.6).

14. An instruction to call the Physician Helpline for patients requiring continuous renal replacement has been added as this method of dialysis/filtration requires a dosage adjustment of telavancin (Section 6.6).
15. The 12-hour duration between study medication infusions has been clarified. It is permissible to administer two active doses of telavancin in less than 24 hours if necessary. All active doses of telavancin or vancomycin should be separated by at least 8 hours. This will allow flexibility for sites to administer study medications within a reasonable time window (Section 6.7).
16. The requirement for arterial blood gas measurements has been revised. They are strongly encouraged; however, they are only required for patients who are ventilated or who have existing arterial lines (Section 7.1).
17. The magnification for assessment of sputum or endotracheal aspiration specimens has been corrected to 100X (low power field, 10X objective) (Section 7.1).
18. Central laboratory testing has been clarified and an appendix with the list of lab tests has been added.
19. The definitions for clinical response at End-of-Therapy (Section 7.1.6.1 in original protocol) have been more clearly defined. Failure requires continuation of antibiotic therapy while cure requires that no further antibiotics are needed.
20. Instructions regarding the Follow-up visit and Test-of-Cure evaluation have been revised to provide for a Follow-up visit for all patients during which the Test-of-Cure evaluation will be conducted for those patients whose clinical response assessment at End-of-Therapy was determined to be either “Cure” or “Indeterminate” (Section 7.1.6 in original protocol).
21. The definitions for clinical response at Test-of-Cure (Section 7.1.7.1 in original protocol) have been more clearly defined. Indeterminate has been added as a possible outcome. Relapsed infection requires isolation of the same Gram-positive organism.
22. The pharmacokinetic timepoints have been revised to provide better data for the population PK analysis (Section 7.1.8 in original protocol).
23. Pharmacoeconomic objectives and analyses have been added (Sections 7.1.10, 11.2.5, and 11.5.5 in amended protocol).
24. An instruction that investigative sites should use their local laboratories for patient eligibility and for urgent patient management decisions has been added because results from the central laboratory (except for alert and panic values) may not be available for 24-48 hours after specimen collection (Section 8.1).
25. Management of study patients whose pretreatment cultures are subsequently found to grow only Gram-negative organisms has been revised. If these patients still require Gram-positive coverage, they are to remain on study medication and in the study. However, if these patients do not require any further Gram-positive therapy, they are to have study drug discontinued and an End-of-Therapy visit is to be completed. The Follow-up visit (including Test-of-Cure assessment) must be completed 7 to 14 days after ALL antibiotics are stopped instead of after only stopping study medication (Sections 8.2 and 9, and addition of Appendix 5).
26. Patients with persistent *S. aureus* infections are to remain on study medication for as

long as the study protocol allows (i.e., up to 3 weeks). This may make it possible to still assess clinical response of the pneumonia in the all-treated population.

However, if these patients are found to have deep-seated infections, they will not be part of the clinically evaluable population (Removal of Section 8.3 in original protocol and changes to Section 9).

27. Patient discontinuation criteria have been modified to allow for a more complete assessment of clinical outcomes in the All-Treated population (Section 9). These changes have been discussed in Items 25 and 26.
28. As described in Item 25 above, the Follow-up visit must occur 7-14 days after stopping study medication, except for those patients with only Gram-negative organisms cultured from respiratory specimens, where the Follow-up visit must occur 7-14 days after stopping all antibiotics. This allows for a clinical outcome for all patients in the all-treated population (Section 9).
29. Reporting of worsening of hospital-acquired pneumonia as a serious adverse event to the Applicant is not necessary unless it results in death. Worsening of the infection will be captured in the clinical assessment of the infection (Section 10.2).
30. The definition of the clinically evaluable analysis population has been edited to be consistent with other changes in the amendment (Section 11.3).
31. The primary analyses in both the individual study analysis (Section 11.5.3.1) and the pooled-study analysis (Section 11.5.3.6.3) have been made more explicit. In the individual study, the primary analysis will evaluate telavancin's non-inferiority to vancomycin. In the two-study (Protocol 0015 and 0019) pooled analyses, the primary analysis will evaluate telavancin's superiority to vancomycin in the subset of subjects with MRSA pneumonia at baseline.
32. The primary analysis population for the pooled-study MRSA superiority analysis will be the all-treated population, not the clinically evaluable population as indicated in original protocol (Section 11.5.3.6.3). The change has been made because an all treated population is more appropriate for evaluating superiority than is a 'per protocol' population. The power calculation for the MRSA superiority analysis has also been updated to reflect the larger size of the all-treated population (Section 11.6).
33. Grammatical modifications have been made throughout the protocol for the sake of clarity and consistency.

Administrative Letters

A summary of the administrative letters is provided below from the Applicant's 0015 Clinical Study Report.

FDA Requirement for a Confirmatory Study

16 November 2004: Communicated that the ATTAIN studies were being conducted in accordance with advice from the US FDA, which requires that two similar, well-controlled and adequately powered studies be performed to support the application for each indication. The FDA requires a confirmatory study producing results similar to the original study.

Telavancin Shipping and/or Storage

- 01 December 2004: Recent investigations demonstrated telavancin solution stability for (b) (4) hours under refrigeration (2°C–8°C), (b) (4).
- 18 January 2005: (b) (4)
- 01 February 2005: A slight change in manufacturing procedures required (b) (4)
- 19 September 2005: Results of recent investigations demonstrated that telavancin solution must be used within 72 hours and should be stored at 2°C–8°C; once removed from the refrigerator, vials and infusion bags must be used within (b) (4) hours.
- 03 November 2005: Results of recent investigations demonstrated telavancin solution stability for (b) (4) hours at room temperature (15°C–25°C) or under refrigerated conditions; however, it was recommended that reconstituted solutions not intended for immediate use be stored under refrigerated conditions until the time of use, not to exceed 72 hours. In addition to 5% dextrose in water (D5W) (b) (4) telavancin may be diluted using normal saline.

Urinary Antigen Testing

- 13 April 2005: Urinary antigen testing for pneumococci and *Legionella pneumophila* may have been omitted if this testing was not routinely performed at a site (in particular Argentina, Brazil, and Chile) or if rates of Legionella infection at a site did not warrant testing.

Exclusion Criterion 2

- 24 June 2005: This communication clarified a misunderstanding of the protocol Exclusion Criterion 2 with respect to the existence of only Gram-negative bacteria seen on Gram stain or culture. The following patients would be eligible:
 - Gram-positive bacteria only
 - Mixed Gram-positive and Gram-negative bacteria
 - Normal oral flora
 - No bacteria

To clarify, if the above patients were enrolled and the culture result showed one of the options stated above (including no bacteria), then the patient was to continue in the study. The only patients who would be discontinued from study medication would be those whose culture results showed only Gram-negative bacteria.

Exclusion Criterion 8

- 13 July 2005: The wording of the exclusion criterion (concerning sustained shock) was changed in Amendment 1 to take into account the fact that in most ICUs it is common practice to use low-dose sympathomimetic agents to maintain renal perfusion. Revised wording: Refractory shock defined as supine blood pressure <90 mm Hg for >2 hours with evidence of hypoperfusion, despite adequate fluid resuscitation with or without low-dose

sympathomimetic agents. This letter served as a waiver until the amendment was in place for all patients who did not meet the original criterion but did meet the revised criterion.

Data Clarification/Radiology Reports/Re-monitoring Effort

- 02 May 2008: Data clarification forms were sent to sites asking for the following information:
 - Lab results for any serum creatinine values that were obtained within 60 days following the patient's EOT visit, and the outcome of any unresolved renal TEAEs for patients who received at least one dose of study medication and experienced either elevated creatinine levels or an AE signifying decreased renal function that did not fully resolve.
 - Clarification of data for patients whose study medication dosing information on the unblinded Dose Modification CRF appears to be inconsistent with the weight and/or renal status data recorded on blinded CRF page 6.
 - Radiology Reports: Per a request from the FDA, Theravance requested copies of all radiology reports for all patients enrolled in the ATTAIN studies who received at least one dose of study medication. Copies of the radiology reports for each chest X-ray or CT scan obtained during the study were requested to be sent to Theravance.
 - Re-monitoring Effort: A broad re-monitoring effort was initiated to review many of the patients enrolled in the ATTAIN studies. A CRO independent of those who oversaw the conduct of the study was chosen for the re-monitoring effort. Re-monitoring visits were planned for June or July 2008.

Radiology Reports

- 21 May 2008: Follow-up to Theravance's 02 May 2008 letter, which included for each site, a listing of randomized and treated patients with the dates of the X-rays or CT scans reported on the Pulmonary Radiography Log CRF pages. The listing was also to be used as a Radiology Report Transmittal Form to be completed and sent to Theravance with the radiology reports.
- 25 August 2008: Follow-up to Theravance's 21 May 2008 letter. Theravance determined that obtaining copies of radiology reports for radiographic assessments from the Follow-up Visit would provide additional support for the primary endpoint of CR at TOC. The protocol did not require a chest X-ray or CT scan at Follow-up; however, Theravance realized that many study patients may have had these procedures at that visit. Theravance considered this information to be within the context of the protocol because the CR definition included consideration of radiographic results and requested copies of any radiology reports for patients who were assessed as a cure or indeterminate at the Follow-up Visit.
 - 27 August 2008: Follow-up to Theravance's 25 August 2008. Theravance requested copies of any radiology reports (or written investigator source documents if no radiology report is available) for patients who were assessed as a cure or indeterminate at the Followup Visit.

5.3.1.1.1 Population

Inclusion Criteria

Patients who met the following criteria at the time of randomization were eligible for study enrollment.

1. Males and females ≥ 18 years of age
 2. Clinical signs and symptoms consistent with pneumonia acquired after at least 48 hours of continuous stay in an inpatient acute or chronic-care facility, or acquired within 7 days after being discharged from a hospitalization of ≥ 3 days duration. At least two of the following signs and symptoms must have been present:
 - o Cough
 - o Purulent sputum or other deep respiratory specimen
 - o Auscultatory findings of pneumonia
 - o Dyspnea, tachypnea, or hypoxemia
 - o Identification of an organism consistent with a respiratory pathogen isolated from cultures of respiratory tract, sputum, or blood samples
- In addition, at least two of the following must also have been present:
- o Fever ($>38^{\circ}\text{C}$) or hypothermia (rectal/core temperature $<35^{\circ}\text{C}$)
 - o Respiratory rate >30 breaths/min
 - o Pulse rate ≥ 120 beats/min
 - o Altered mental status
 - o Need for mechanical ventilation
 - o Elevated total peripheral white blood cell (WBC) count $>10,000$ cells/ mm^3 , $>15\%$ immature neutrophils (band forms) regardless of total peripheral WBC count, or leukopenia with total WBC count <4500 cells/ mm^3
3. A chest radiograph with findings consistent with a diagnosis of pneumonia (new or progressive infiltrates, consolidation, or pleural effusion) within 48 hours before randomization in the study
 4. Availability of appropriate respiratory or sputum specimens for Gram stain and culture, and venous access for IV dosing
 5. Willing to receive IV therapy for the duration of treatment
 6. Informed consent for participation in this study as defined by the local IRB or EC

FDA Medical Officer Comments: The inclusion criteria do not provide a high probability that all enrolled patients had NP. The inclusion criteria utilized in this clinical trial are not consistent with the recommendations of the 1998 FDA Draft Guidance for Industry: “Nosocomial Pneumonia — Developing Antimicrobial Drugs for Treatment” nor are they consistent with the recommendations in the ATS/IDSA Guidelines for the management of Hospital-acquired Pneumonia. According to the 1998 FDA Draft Guidance on Antibacterial Drugs for Nosocomial Pneumonia, fever (100.4°F), leukocytosis, and two of the following clinical findings are required inclusion criteria for clinical trials: cough, new or change in sputum production, auscultatory change (rales), dyspnea, tachypnea (respiratory rate $\geq 30/\text{min}$), or hypoxemia <60 on room air (1). According to the ATS/IDSA Guidelines, Clinical Strategy for NP should include evidence of a new or progressive chest x-ray infiltrate with at least two of the following three clinical

features: Fever >38 °C (100.4 °F), leukocytosis or leucopenia, and purulent secretions. As described in the guidelines document, “Although sensitivity for the presence of pneumonia is increased if one criterion is used, this occurs at the expense of specificity, leading to significantly more antibiotic treatment”(2).

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

The inclusion criterion regarding radiographic findings “consistent with a diagnosis of pneumonia” was problematic in such patients as they may have other non-infectious illnesses (such as atelectasis, congestive heart failure, pulmonary embolism with infarct, pulmonary contusion, and chemical aspiration) that may produce x-ray findings that may mimic pneumonia (3). Confirmation of the Investigators’ interpretation of chest radiographs by a radiologist was not required. The lack of radiologists’ confirmation of the chest x-ray findings that were reported by Investigators adds to the dilemma of assessing whether enrolled patients actually had the disease being studied.

In addition to concerns about the enrollment of patients with noninfectious disorders as described above, it is likely that some patients enrolled in this clinical trial may have purulent tracheobronchitis rather than NP or VAP as a consequence of the lack of stringent inclusion criteria. Purulent tracheobronchitis may produce clinical signs similar to those associated with HAP and VAP and may require treatment with intravenous antibiotics (2).

Exclusion Criteria

Patients who satisfied any of the following criteria were not eligible for study enrollment:

1. Received more than 24 hours of potentially effective systemic (IV, intramuscular, or by mouth) antibiotic therapy for Gram-positive pneumonia immediately prior to randomization, (unless documented to have not responded to at least 3 days of prior antimicrobial treatment or if the isolated pathogen for the current pneumonia was resistant in vitro to previous antimicrobial treatment; per Protocol Amendment 1). Investigators were to contact the Study Physician Helpline to determine eligibility of patients with renal impairment who had received one or more doses of vancomycin during the last week prior to enrollment.
2. Respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture

FDA Medical Officer Comments: Page 14 of the case report form has check boxes to capture information on the Gram stain, WBC, and epithelial cell quantitation for sputum and

endotracheal aspirate specimens. Overall quality assessments for sputum specimens were captured in the electronic datasets for this NDA. However, a similar electronic dataset containing quality assessments for endotracheal aspirates was not provided.

According to the ATS/IDSA guidelines document, a reliable tracheal Gram stain can be used to direct initial empiric antimicrobial therapy and may increase the diagnostic value of the clinical pulmonary infection score (CPIS) (2). In the absence of interpretive criteria, all bacteria isolated from endotracheal aspirate cultures could be considered potential pathogens, which confounds distinguishing true pathogens from colonizers. Rejection criteria for endotracheal aspirates have been published in the scientific literature (4). Errors in interpretation of endotracheal aspirates could result in incorrect assessments of the number of isolates considered microbiologically evaluable for efficacy assessment, which could increase the probability of erroneously concluding noninferiority between the two treatment arms in the clinical trial.

3. Known infection with MSSA or *S. pneumoniae* that required 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)

FDA Medical Officer Comments: Multiple patients were identified in the review of this NDA who had MSSA as the sole pathogen and who received more than 24 hours of concomitant piperacillin/tazobactam or imipenem. Although not considered clinically evaluable, the patients were considered part of the all treated (AT) population. As the all treated population is used as a co-primary analysis population, inclusion of these patients could increase the probability of erroneously concluding noninferiority between the two treatment arms in the clinical trial.

4. Known or suspected pulmonary disease that precluded evaluation of therapeutic response (e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs), cystic fibrosis, or active tuberculosis
5. Known or suspected *Legionella pneumophila* pneumonia
6. Known or suspected infection with an organism that was not susceptible to medications permitted by the protocol
7. Documented or suspected meningitis, endocarditis, or osteomyelitis
8. Refractory shock (per Protocol Amendment 1) 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 $\mu\text{g}/\text{kg}/\text{min}$ or norepinephrine ≥ 0.1 $\mu\text{g}/\text{kg}/\text{min}$)
9. Baseline QTc >500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K⁺ or Mg⁺⁺ blood levels that could not be corrected (per Protocol Amendment 1)
10. Severely neutropenic (absolute neutrophil count <500/mm³) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or had HIV with CD4⁺ cell count <100/mm³ during the last 6 months
11. Requirement for concomitant administration of intravenous Sporanox® (itraconazole), Vfend® (voriconazole), or any other medication containing a cyclodextrin solubilizer;

Geodon® (ziprasidone) was added to the list of named drugs, per Protocol Amendment 1 (Section 6.4.8.2)

12. a) Female patients of childbearing potential if they were pregnant, nursing, or unable to use a highly effective method of birth control during the study and for at least one complete menstrual cycle (per Protocol Amendment 1) following the last dose of study medication: A negative serum pregnancy result must have been documented prior to treatment. A highly effective method of birth control was defined as one that results in a low failure rate (i.e., <1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence, or a vasectomized partner.
b) Male patients must have agreed to use medically acceptable birth control for at least 3 months following the last dose of study medication. A vasectomy or a condom used with a spermicide was a medically acceptable birth control method for males.
13. Prior enrollment in a clinical trial of telavancin
14. Known hypersensitivity to, or intolerance of, study medications or their formulation excipients
15. Treatment with another investigational medication within 30 days of study entry
16. Considered unlikely to survive at least 7 days due to underlying illness
17. Considered unlikely to comply with the study procedures or to return for scheduled posttreatment evaluations
18. Any other condition that, in the opinion of an Investigator, would confound or interfere with evaluation of safety or efficacy of the investigational medication or prevent compliance with the protocol.

5.3.1.1.2 Study Procedures

Study Treatments

If the patient was randomized to:

- Telavancin, the patient was to receive one 60-minute infusion of telavancin and one 60-minute infusion of D5W (G5W) or normal saline daily, at 12-hour intervals.

OR

- Vancomycin, the patient was to receive two 60-minute infusions of vancomycin daily, at 12-hour intervals.

Protocol Amendment 1 clarified that all active doses of telavancin or vancomycin should be separated by at least 8 hours.

The total duration of study therapy was to be determined by the Investigator, as clinically indicated. The minimum duration of study therapy was to be 7 days and the maximum allowable duration of study therapy was to be 21 days. Note that the total duration of dosing may have extended to Study Day 22 to allow completion of the full study medication regimen (21 days × 24 hours). Patients were to be treated with IV therapy throughout and were not to have been

switched to oral therapy. When appropriate, patients may have been discharged but must have continued to receive IV study medication as an outpatient.

For patients with documented MSSA pneumonia, the Investigator had the choice of changing vancomycin to IV nafcillin or oxacillin as the comparator agent. In these instances, the Blinding Plan Template (Appendix 3 of the protocol) was to be referenced for preparation of blinded doses and dosing instructions.

Randomization

Patients were to be randomized to either telavancin or vancomycin in a 1:1 ratio, using a permuted blocks algorithm. The algorithm used a block size of four per stratum. The randomization was to be stratified on geographic region, the presence or absence of diabetes, and ventilatory status of the patient. The assignment to telavancin or vancomycin was to be blinded to the Investigator and study staff as well as to the patient. As a patient qualified for the study, the Investigator was to notify an unblinded site pharmacist (or other authorized staff member), who was to access a centralized interactive voice response system (IVRS) to obtain a patient number and treatment (Section 6.4.7 [Blinding] and Appendix 9 [Randomization Scheme and Treatment Assignments] of the protocol). The telephone numbers and the instructions on how to use this service were provided in the IVRS Manual.(Appendix 1 of the protocol).

The active treatment for each patient, telavancin or vancomycin, was assigned based on the randomization schedule (Section 6.4.3 of the protocol). The timing of each dose was to be determined in accordance with the procedures described in Section 6.4.1 of the protocol. The total duration of study therapy for each patient was to be determined by the Investigator, as clinically indicated. The minimum duration of study therapy was to be 7 days and the maximum allowable duration of study therapy was to be 21 days. Individual dose adjustments were to be made in accordance with procedures summarized in Section 6.4.6 of the protocol.

Dosage Adjustment

The dosage of telavancin was to be adjusted in patients with moderate to severe renal insufficiency, as follows (from Applicant's Clinical Study Report):

| Creatinine Clearance (mL/min) | Telavancin Dosage (10 mg/kg) |
|----------------------------------|--|
| 30-50 | 7.5 mg/kg q 24 hr |
| <30 | 10 mg/kg q 48 hr |
| Hemodialysis | 10 mg/kg q 48 hr (supplemental telavancin does not need to be administered following dialysis) |

The vancomycin regimen was to be monitored and the dosage was to be adjusted on the basis of weight and/or renal function, according to the institutional policy at the respective investigative site. Required monitoring and dosage adjustments for telavancin and vancomycin were to be managed by study personnel not responsible for clinical assessment of the patients, as described in a Blinding Plan prepared by each investigative site

(Section 6.4.7 of the protocol).

Blinding

The Investigator, patient, and all research staff with responsibility for the assessment of safety and efficacy measures were to be blind to the patient's treatment assignment. A site pharmacist (or other staff member) was designated as the unblinded site staff and charged with communicating patient information to the centralized randomization service via IVRS, receiving treatment assignments, and ensuring that study medication was accurately prepared. Prior to initiation of enrollment, each site was to be required to have an approved Blinding Plan describing the procedures that would assure that the blind would be maintained and identifying the personnel designated to perform any clinical activities that required knowledge of the treatment assignment, such as preparation of doses, completion of study medication accountability logs, receipt of vancomycin serum concentration reports, and management of vancomycin or telavancin dosage adjustments. Patient treatment assignments were to be maintained in a secure manner. Except in the instance of a required unblinding for management of an adverse event, treatment assignments were not to be shared with study personnel during the conduct of the study. Unblinded study staff were responsible for ensuring that the Investigator and blinded study staff remained blinded to the patient's treatment assignment regardless of a change in dosage or dosing frequency.

FDA Medical Officer Comments: The double-blind study design used for this clinical trial is consistent with the recommendations of the 1992 FDA/IDSA General Guidelines for the Evaluation of New Anti-Infective Drugs for the Treatment of Respiratory Tract Infections (5), and serves to minimize the potential for bias by clinical trial investigators, patients, and data analysts. However, it should be noted that two telavancin-treated and four vancomycin-treated patients were unblinded during the study dosing period. One telavancin and five vancomycin-treated patients were unblinded after discontinuation of study drug for various reasons.

Permitted Concomitant Antibacterial Drugs

Since the study was designed to compare the safety and efficacy of two drugs with activity against Gram-positive pathogens, the use of concomitant Gram-negative therapy was left to the discretion of the Investigator. Therefore, in addition to study medication for Gram-positive organisms, aztreonam and/or metronidazole therapy, used in accordance with the manufacturer's prescribing information, could have been added to study therapy for patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. The addition of aztreonam and/or metronidazole was permissible in this study, because neither agent has antibacterial activity against Gram-positive pathogens of interest, such as staphylococci and streptococci.

Piperacillin-tazobactam may have been administered for Gram-negative coverage only if aztreonam was not appropriate due to an unacceptable level of resistance among Gram-negative bacteria at the particular research site. However, as piperacillin-tazobactam has activity against MSSA and *S. pneumoniae*, patients with those organisms, who required more than 24 hours of treatment with this medication, should not have been enrolled. For those patients already

enrolled, wherever possible, piperacillin-tazobactam was to be discontinued or changed to aztreonam as soon as possible. Finally, therapy with metronidazole was considered to be unnecessary if piperacillin-tazobactam, which has activity against anaerobic bacteria, was administered.

The Original Protocol had 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 (Section 6.8.1 of the protocol).

FDA Medical Officer Comments: Although the protocol stipulates that piperacillin-tazobactam and imipenem were to be discontinued or changed to aztreonam “as soon as possible”, there were multiple cases in which such de-escalation in antibiotic coverage did not occur (particularly in patients infected with MSSA as a baseline pathogen without concurrent Gram-negative bacterial pathogens). Errors in de-escalation could result in incorrect assessments of the number of patients considered clinically and microbiologically evaluable for efficacy assessment in the AT population. As a co-primary analysis population, inclusion of such patients in the AT population tends to erroneously support a conclusion of noninferiority between the two treatment arms in the clinical trial.

Prohibited Medications

Nonstudy systemic antibacterials with activity against the baseline pathogen(s), other than piperacillin-tazobactam, metronidazole, aztreonam, and (before Protocol Amendment 1) imipenem, were prohibited.

Agents containing a cyclodextrin-solubilizing agent, such as intravenous Sporanox® (itraconazole), Vfend® (voriconazole), or Geodon® (ziprasidone), were prohibited because telavancin is formulated with a cyclodextrin (hydroxypropyl-beta-dex), and avoiding administration of additional cyclodextrin was considered prudent.

Therapy with other investigational agents was also prohibited.

Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) periodically reviewed and evaluated the study results on an unblinded basis. Theravance’s primary charge to the IDMC was to monitor for unacceptable safety risk associated with telavancin. This is in contrast to other settings in which an IDMC may monitor for evidence of superior efficacy relative to control and subsequent early stopping. Although the IDMC was to review both safety and efficacy data, the purpose of the efficacy review was to enable monitoring for inferior telavancin efficacy and assessment of benefit-to-risk profile.

The IDMC was asked to make recommendations regarding the continuation and/or modification of the study. Review of unblinded data was to be conducted in closed sessions with no participation from Theravance. Unblinded results were not to be disseminated outside the IDMC.

Study Procedures

A flow chart of study procedures (adapted from Amendment 1) is presented in the table below (from the Applicant's Table 6-2, 0015 Clinical Study Report):

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Clinical Review
 Alfred Sorbello, DO, MPH
 NDA 22-407/N-000
 Theravance for injection (VIBATIV™)

Table 4: Study Procedures Flowchart (from Applicant's 0015 Clinical Study Report)

| Event | Prestudy Treatment | Treatment | | | | EOT Visit | Follow-up Visit ^a | Week 10 |
|---|--------------------|----------------|----------------|-------------|-------------------------------|----------------|------------------------------|---------|
| | | Daily | Study Day 4 | Study Day 7 | Study Days 10, 14, 17, and 21 | | | |
| Informed consent | X | | | | | | | |
| Medical history | X | | | | | | | |
| Vital signs | X | | | | | | | |
| Evaluate clinical signs/symptoms of pneumonia | X | X | | | | X | X | |
| Glasgow coma score | X | | | | | | | |
| Chest X-ray or CT scan | X | | X | X | | X | | |
| Oxygenation | X | | X | X | | X | | |
| Pulmonary specimen or sputum Gram stain & culture | X ^b | | X ^c | | | X ^c | X ^c | |
| Blood culture x 2 | X | X ^d | | | | | | |
| Urine for Legionella testing (if applicable) | X ^e | | | | | | | |
| Hematology | X | | X | X | X | X | X | |
| Serum chemistry | X | | X | X | X | X | X | |
| Urinalysis | X | | X | X | X | X | X | |
| Pregnancy test (serum) | X | | | | | X | | |
| Coagulation testing ^f | X | | X | | | | | |
| Pharmacokinetic sample collection | | | X ^g | | | | | |
| 12-lead ECG | X | | X | X | X | X | | |
| Study drug administration | | X | | | | | | |
| Assess AEs | | X | | | | X | X | |
| Concomitant medications | | X | | | | X | X | |
| Clinical response | | | | | | X | X | |
| Pharmacoeconomic contact | | | | | | | | X |

a 7-14 days after last dose

b Collect baseline respiratory specimens for Gram-stain and culture prior to the administration of antibiotics,

- whenever possible. These specimens were to be processed as soon as possible after collection, or refrigerated. All organisms isolated by the local laboratory were to be subcultured and sent to the central microbiology laboratory for identification of genus and species and MIC testing.
- c Obtain respiratory specimen, ONLY if clinically indicated, for Gram stain and culture. Refer to Section 6.5.2 and Section 6.5.3 of the protocol for specimen requirements according to ventilatory status.
 - d Two samples were to be obtained if the baseline blood culture was positive, OR was negative but the patient's condition had deteriorated, leading the Investigator to suspect a bloodstream infection. All pathogens isolated were to be subcultured and sent to the central microbiology laboratory for identification of genus and species and MIC testing.
 - e This testing may have been omitted if it was not routinely performed at the site or if the rates of *Legionella* infection did not warrant testing.
 - f Patients who had blood collected for PK were to have samples collected for coagulation testing on the day that PK samples were obtained and sent to the central laboratory for analysis. The following parameters were assessed: PT, aPTT, and INR. Blood samples for coagulation testing were to be collected prior to the infusion (trough blood levels).
 - g Pharmacokinetic (PK) samples were to be collected from approximately 300 study patients at selected sites. A total of four samples were to be obtained per patient on Study Day 4 of treatment (\pm 1 day) and sent to the central laboratory for analysis (Section 6.5.9 of the protocol).

End-of-therapy Visit

All patients were to have an EOT Visit as soon as possible, but no later than 3 days after the last dose of study medication. The procedures that were to be performed at the EOT Visit are summarized below. Procedures that had already been performed that day did not need to be repeated.

- Evaluation of clinical response: Upon a patient's termination of study medication, the Investigator was to assess the patient's clinical response as cure, failure, or indeterminate, defined as follows:
 - 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 antistaphylococcal medication
 - Death on or after Day 3 attributable to primary infection
 - Cure: Signs and symptoms of pneumonia improved to the point that no further antibiotics for pneumonia were required, and baseline radiographic findings improved or did not progress.
 - Indeterminate: Inability to determine outcome (for example, Gram-positive antibiotic coverage no longer required but Gram-negative antibiotic coverage continuing at EOT)
- Recording of clinical signs and symptoms of pneumonia
- Chest X-ray or computed tomography (CT) scan for evaluation of radiographic lung infiltrates
- Oxygenation status, as measured by arterial blood gas, was to be strongly encouraged for all patients and was to be required for patients who were ventilated and/or had an existing arterial line.
- Respiratory specimens were to be obtained ONLY if clinically indicated, for Gram-stain

and culture. These specimens were to be processed as soon as possible after collection, or they were to be refrigerated. All organisms isolated by the local laboratory were to be subcultured and sent to the central microbiology laboratory for identification of genus and species and MIC testing.

- For patients who required mechanical ventilation, the following techniques were to be considered adequate for collection of respiratory specimens: bronchoalveolar lavage (BAL), mini-BAL, protected specimen brush (PSB), blind bronchial suctioning (BBS), and endotracheal aspirate (ETA).
- For nonventilated patients with HAP, an adequate sputum or ETA specimens were to have >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per field at 100× magnification (low-power, 10× objective; per Amendment No.1; Section 6.8.1 of the protocol). Specimens that were derived by any of the methods listed above were to also be acceptable.

FDA Medical Officer Comments: Although the quantity of polymorphonuclear leukocytes and squamous epithelial cells could be ticked on the CRF, there was no variable that captured the overall assessment of the adequacy of ETA specimens in the case report form or in the electronic datasets as discussed previously. Errors in specimen interpretation introduce uncertainty in assessing the microbiologically evaluable population and could bias erroneously towards a conclusion of noninferiority between the two treatment arms in the clinical trial.

- Blood and urine samples were to be obtained and sent to the central laboratory for the following tests.
 - o Hematology
 - o Serum chemistry
 - o Urinalysis
 - o Serum beta-human chorionic gonadotropin (β hCG) pregnancy test, if the patient was a female of childbearing potential
- Three sequential 12-lead ECGs at 5- to 10-minute intervals (within 1 hour after completing the designated active dose infusion if on the last day of study medication) were to be obtained. If the QTc was >500 msec, an ECG was to be repeated in 15 minutes.
- Recording of all medications, including antimicrobials that the patient had received from the day of the last dose of study medication to the day of the EOT Visit
- Assessment of adverse events

Follow-up Visit/Test-of-cure

For all patients randomized into the study, a Follow-up Visit was to be conducted 7 to 14 days after the last dose of study medication. However, for the specific case of patients in whom study medication was discontinued but other antibiotics were given to treat pneumonia due to Gram-negative organisms only, the Follow-up Visit was to be conducted 7 to 14 days after the last dose of ALL antibiotics administered to treat the pneumonia (per Protocol Amendment 1; Section 6.8.1 of the protocol). Only those patients who were evaluated as a clinical cure or indeterminate at the EOT Visit were to have a TOC evaluation during the

Follow-up Visit.

The following procedures were to be performed on all patients:

- Blood and urine samples to be obtained and sent to central laboratory for the following tests.
 - o Hematology
 - o Serum chemistry
 - o Urinalysis

- Assessment of adverse events.

The following additional procedures were to be performed on patients considered clinically cured or having an indeterminate outcome at the EOT Visit:

- Evaluation of clinical response as cure, failure, or indeterminate as defined below:
 - Failure: At least one of the following:
 - o Relapsed pneumonia with the same Gram-positive organism after termination of study medication
 - o Death after the end of study medication therapy attributable to primary infection (i.e., pneumonia)
 - Cure:
 - o Signs and symptoms of pneumonia resolved, and
 - o Baseline radiographic findings improved or did not progress
 - Indeterminate: Inability to determine outcome
- Clinical signs and symptoms of pneumonia to be recorded.
- Respiratory specimen to be obtained, ONLY if clinically indicated, for Gram stain and culture. These specimens were to be processed as soon as possible after collection, or they were to be refrigerated. All organisms isolated by the local laboratory were to be sub-cultured and sent to the central microbiology laboratory for identification of genus and species and MIC testing.
- For patients who required mechanical ventilation, the following techniques were to be considered adequate for collecting respiratory specimens: BAL, mini-BAL, PSB, BBS, and ETA.
- For nonventilated patients with HAP, an adequate sputum specimen was to be >25 polymorphonuclear leukocytes and <10 squamous epithelial cells per field at $100\times$ magnification (low-power, $10\times$ objective). Specimens that were derived by any of the methods listed above were to also be acceptable.
- All systemic antibiotic medications that the patient had received since the EOT Visit were to be recorded.
- A second posttreatment chest X-ray or computed tomography (CT) scan was not required for the Follow-up Visit since the assessments were only made for patients who had an EOT assessment of cure or indeterminate (had already demonstrated resolution/nonprogression of radiographic findings, and of signs and symptoms). Because clearance of pneumonia as documented by chest radiographs may be slower (weeks to months after treatment) than other, more clinically relevant markers (signs and symptoms), the TOC assessment focused on these measures.

Primary Efficacy Variable

The primary efficacy endpoint was the clinical response at the TOC evaluation. Possible values were cure, failure, and indeterminate.

Per the protocol, patients who were failures at EOT were not to have a TOC evaluation. Consequently, for purpose of analysis, a clinical response of failure at the EOT assessment was extrapolated to the TOC evaluation, even if a value was recorded on the CRF at Follow-up/TOC.

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

FDA Medical Officer Comments: In consideration of the presence of multiple co-morbid conditions that could increase the risk for death, subjective assessments of mortality attributable to the HAP episode under study independent of those conditions could be subject to bias.

Clinical Signs and Symptoms of Pneumonia

The clinical signs and symptoms of pneumonia were to be assessed as listed in the following table. Each of the clinical signs/symptoms of pneumonia was to be assessed daily and at the EOT Visit for all patients and at the TOC evaluation during the Follow-up Visit for those patients who had a clinical response of cure or indeterminate at the EOT Visit.

The following table summarizes the clinical signs and symptoms assessments (as per Table 6-3 of Applicant's 0015 Clinical Study Report):

Table 5: Applicant's Summary Table of Clinical Signs and Symptoms Assessments (as per Table 6-3 of Applicant's 0015 Clinical Study Report)

| Parameter | Evaluation | | | | | |
|--|--------------|---------------|----------|----------|----------|----------|
| | Oral | Rectal | Tympanic | Axillary | Not eval | |
| Body temperature (oral, rectal, tympanic, or axillary) | | | | | | |
| Respiratory rate | Breaths/min | Not evaluated | | | | |
| On ventilation | No | Yes | | | | |
| Sputum characterization | None | Slight | Moderate | Heavy | Not eval | |
| Sputum Quality | Not Purulent | Purulent | | | | |
| Cough characterization | No | Yes | Not eval | | | |
| Rales | 0 | +1 | +2 | +3 | +4 | Not eval |
| Dyspnea | None | Slight | Moderate | Severe | Not eval | |
| Decreased breath sounds | None | Slight | Moderate | Severe | Not eval | |
| Pleuritic chest pain | None | Slight | Moderate | Severe | Not eval | |

FDA Medical Officer Comments:

Axillary temperatures were the most frequently employed modality for body temperature measurement in both Studies 0015 and 0019. In order to assess the magnitude of axillary temperature measurements at various study visits compared to the use of other modes of temperature measurements (oral, rectal, tympanic, nasal, and bladder), the FDA Medical Officer performed a sensitivity analysis as depicted in the table below. It is evident that temperature measurement by the axillary route was employed frequently in 33.1% to 62.5% of patients at various study visits.

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

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

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

The Applicant retained use of axillary temperatures despite recommendations against their use in publications that provide guidelines for evaluating new fever in critically ill adults (6,7). In response to an information request from the Division dated April 30, 2009, the Applicant stated that “during initiation of the studies, it became evident that standard clinical practice at numerous investigative sites was to determine body temperature using the axillary method. However, the protocol inadvertently was not updated to reflect this practice, which Theravance did acknowledge and allow.” In addition, the Applicant cited a publication (8) and indicated that “while axillary temperatures did not correlate well with core temperature, this was because the axillary temperature readings averaged 1°C below the core readings, ranging as much as 4°C below core temperature. Therefore, we chose to conservatively adjust the axillary temperature readings by adding 1°C.” In the opinion of this FDA Medical Officer, the approach described above appears arbitrary, is not supported by scientific evidence from other publications, and is not consistent with current medical practice guidelines. The use of axillary temperatures introduces considerable uncertainty in the evaluation of eligible patients for enrollment and in the reliability of APACHE II scores and CPIS scores used for assessment of severity of illness and likelihood of VAP, respectively.

Nasal and bladder temperatures were reported for some study patients, although there was no specific provision in the protocol permitting such methods of body temperature assessment and no published scientific data was provided by the Applicant to substantiate their use as surrogates for core body temperatures.

Additionally, the response options for the evaluation scales for sputum characterization, dyspnea, decreased breath sounds, and pleuritic chest pain include the subjective descriptors “slight”, “moderate”, and “severe” without providing specific objective criteria to define each response option. This approach can be confusing to distinguish conceptually and may lead to considerable inter-observer variability in assessments. Similar concerns relate to the evaluation scale for rales, which ranges from +1 to +4 without clearly defined objective criteria for each severity strata.

Additional clinical assessments were as follows:

- A modified acute physiology and chronic health evaluation (APACHE II) was to be performed at Baseline. The APACHE II is a severity of disease classification system that combines in one summary measure the risk factors of physiologic derangement, age, and poor chronic health status (9). Derived from the original APACHE system, which provided weightings for 34 potential physiologic measures, the APACHE II system consists of only 12 physiologic measures, including temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH; serum sodium, potassium, and creatinine measurements; hematocrit and WBC count; and Glasgow coma score (GCS).
- The GCS, which is used to assess the level of consciousness, was determined at Baseline. The total GCS is the sum of the individual responses for eye, verbal, and motor function (minimum score of 3, maximum score of 15).
- Measurement of oxygenation status by arterial blood gas (ABG) was strongly encouraged, especially for patients who were ventilated and/or had an existing arterial line.
- Pulmonary Radiographic Assessment by chest X-ray or CT
- The Clinical Pulmonary Infection Score (CPIS) was designed to aid with the clinical diagnosis of ventilator-associated pneumonia (VAP) (10, 11). Seven parameters make up the composite score, which varies from 0 to 12. The CPIS was to be assessed on the basis of the first five parameters (i.e., temperature, blood leukocyte count, tracheal secretions, oxygenation, and pulmonary infiltrate characterization) at the first assessment. The CPIS assessment at other time points was to be calculated algorithmically using all seven parameters, including progression of pulmonary infiltrate and culture results of the tracheal aspirate. The CPIS was considered a tertiary endpoint.

The parameters used in calculating the CPIS are indicated in the table below.

Table 7: Table of parameters included in the calculation of the Clinical Pulmonary Infection Score (CPIS) (from Applicant's 0015 Clinical Study Report, Table 6-4)

| Parameter | Points | | |
|---|--|--|--|
| | 0 | 1 | 2 |
| Temperature, °C | ≥36.5 and ≤38.4 | ≥38.5 and ≤38.9 | ≥39 and ≤36 |
| Blood leukocytes, mm ³ | ≥4000 and ≤11,000 | <4000 and >11,000 | <4000 and >11,000 + band forms ≥50% |
| Tracheal secretions | Absent | Presence of nonpurulent tracheal secretions | Presence of purulent tracheal secretions |
| Oxygenation: PaO ₂ /FiO ₂ , mm Hg | >240 or ARDS* | | ≤240 and no ARDS |
| Pulmonary radiography | No infiltrate | Diffuse (or patchy) infiltrate | Localized infiltrate |
| Progression of pulmonary infiltrate | No radiographic progression | | Radiographic progression (after CHF and ARDS excluded) |
| Culture of tracheal aspirate | Pathogenic bacteria (predominant organism in the culture) cultured in rare or light quantity, or no growth | Pathogenic bacteria cultured in moderate or heavy quantity | Pathogenic bacteria cultured in moderate or heavy quantity and same pathogenic bacteria seen on Gram stain |

For temperatures taken by the axillary method, for purposes of analysis, one degree Celsius was added by the Applicant to the recorded value on the CRF. No adjustments were to be made for temperatures taken by any other method (8).

FDA Medical Officer Comments: Please refer to previous comments about axillary temperatures. The APACHE II algorithm specifically requires rectal temperatures for determination of the temperature component of the score. The CPIS algorithm does not specify the method for temperature measurements. Modifying the axillary temperatures as above and then using the modified value as representative of core/rectal temperature creates substantial uncertainty in the severity of illness as reflected by APACHE II scores and the likelihood of having VAP based on the CPIS scores as reported at baseline and at subsequent study visits. By adding one degree Celsius to axillary temperatures, the magnitude of increase can be as much as 3 points in the APACHE II scores and 2 points in the CPIS scores. Thus, this approach for analysis purposes tends to depict the study population as having a higher severity of illness and a greater likelihood for VAP than is actually true. The reference journal article (8) provided in the Applicant's Clinical Study Report does not specifically support the modification of recorded axillary temperatures for analysis purposes; instead, the article indicates that axillary temperatures are not reliable and should not be used as a measure of core body temperature.

5.3.1.1.3 Statistical Considerations

Efficacy Analysis Populations

Four analysis populations were defined for efficacy-related summaries. These four populations were not mutually exclusive; a patient could belong to more than one population. In all four populations, patients were associated with the treatment group assigned by the randomization:

- All-treated (AT): All patients who received any amount of study medication
- Modified All-treated (MAT): Patients 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, ETA, BBS, BAL, mini-BAL, or PSB; additional details regarding the definition of a baseline pathogen are presented in the text that follows
- Clinically Evaluable (CE): Patients in the AT Population whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication; further detail on the evaluability criteria for determination of the CE Population can be found in Section 6.7.1.3 of the protocol
- Microbiologically Evaluable (ME): Patients in the CE Population who also had a Gram-positive baseline respiratory pathogen, as defined above for the MAT Population. 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 qualified a patient for the MAT Population. If baseline respiratory tract and blood cultures identified different respiratory pathogens, then only those pathogens identified from respiratory tract specimens were deemed baseline respiratory pathogens.

Primary Efficacy Analysis

The primary efficacy endpoint was to be clinical response at the Test-of-Cure evaluation, after extrapolation of failures at End-of-Therapy to Test-of-Cure. Relative treatment effect was to be measured by the arithmetic difference in cure rates between the two treatment arms.

The primary analysis was to first test the hypothesis of telavancin's clinical noninferiority to vancomycin, employing a noninferiority margin (the "Δ") of 20 percentage points on the difference scale. The null hypothesis was to be that telavancin is clinically inferior to vancomycin, where "clinically inferior" was defined as having a population cure rate that is 20 percentage points (or more) lower than that for vancomycin. The alternative hypothesis was to be that telavancin is at least clinically equivalent to vancomycin, where "clinically equivalent" was defined as having population cure rates that differ by less than 20 percentage points. Expressed symbolically, the null hypothesis (H0) and the alternative hypothesis (H1) were as follows:

$$H_0: \pi_{TLV} - \pi_{VANC} \leq -0.20$$

$$H_1: \pi_{TLV} - \pi_{VANC} > -0.20$$

where π_{TLV} and π_{VANC} denote the population cure rates of telavancin and vancomycin,

respectively.

Testing was to be conducted at a one-sided 0.025 significance level. Testing was to be implemented by the construction of a two-sided 95% confidence interval (CI) on the treatment difference, $\pi_{TLV} - \pi_{VANC}$. If the lower confidence limit (CL_{LOWER}) was less than or equal to -0.20, then the null hypothesis of inferiority was not to be rejected. If $CL_{LOWER} > -0.20$, then the null hypothesis of clinical inferiority was to be rejected in favor of the alternative hypothesis of clinical noninferiority.

In the noninferiority analysis, the CE and AT analysis populations were to be considered co-primary.

FDA Medical Officer Comments: The AT population includes patients in which only Gram-negative bacterial pathogens were isolated from their respiratory tract specimens, whereas such patients are excluded from the CE population. Analysis of a clinically modified AT population that also excludes patients having only Gram-negative bacterial pathogens would be more informative as a co-primary analysis population in assessing the efficacy of telavancin compared to vancomycin in NP and VAP, since both of those drugs lack Gram-negative antibacterial activity. Inclusion of patients infected with only Gram-negative bacterial pathogens in the AT population for analysis purposes reflects the efficacy of non-study antibacterial drugs, which can introduce bias in assessing the noninferiority of telavancin compared to vancomycin.

If the above analysis concluded that telavancin was clinically noninferior to telavancin, then a superiority analysis was to be conducted. The superiority analysis was to test the null hypothesis that telavancin is the same as (or worse than) vancomycin, against the alternative hypothesis that telavancin is superior to vancomycin. Expressed symbolically, the null and alternative hypotheses were as follows:

$$\begin{aligned} H_0: \pi_{TLV} - \pi_{VANC} &\leq 0 \\ H_1: \pi_{TLV} - \pi_{VANC} &> 0 \end{aligned}$$

If the lower confidence limit (CL_{LOWER}) of the previously described CI was zero or less, then the null hypothesis was not to be rejected. If CL_{LOWER} was greater than zero, then the null hypothesis was to be rejected in favor of the alternative hypothesis of superiority.

By the closure principle, no multiple-testing α -adjustment was to be necessary for the noninferiority and superiority tests, because the two null hypotheses constitute a closed family, and the hypothesis of clinical inferiority ($H_0: \pi_{TLV} - \pi_{VANC} \leq -0.20$) implies the hypothesis of nonsuperiority ($H_0: \pi_{TLV} - \pi_{VANC} \leq 0$).

The primary analysis population in the superiority analysis was to be the CE Population. A supporting analysis was to be conducted in the AT Population.

FDA Medical Officer Comments: The Applicant has based the primary efficacy analysis of Studies 0015 and 0019 on a prospectively selected 20% noninferiority margin for a clinical response endpoint and a post hoc 14% noninferiority margin for a clinical response endpoint estimated from a mortality data analysis. However, the analysis of noninferiority trials of

antibacterial drugs for NP and VAP using clinical response as the primary endpoint cannot be justified based on published scientific evidence. Interpretation of such noninferiority trials can only be justified using all-cause mortality as the primary endpoint as discussed in Section 6.1.1 of this report.

Secondary Endpoints

The secondary and tertiary endpoints for both studies were:

- Clinical response at EOT
- By-pathogen microbiological response at TOC
- By-patient microbiological response at TOC
- Clinical Pulmonary Infection Score (CPIS)
- Duration of treatment with study medication
- Length of stay in the ICU
- Length of stay in hospital
- All-cause mortality; and mortality attributable to primary infection
- Number of days on mechanical ventilation, for patients on ventilation at randomization
- Potential superinfection
- Time to resolution of fever (defervescence), defined as the first day of the earliest 2-day period during which all temperatures were $\leq 38^{\circ}\text{C}$

5.3.1.2 Study Results

5.3.1.2.1 Demographic and Baseline Characteristics

The All Treated population in Study 0015 consisted of 746 patients, including 372 in the Telvancin arm and 374 in the Vancomycin arm. US sites enrolled 230 patients (30.8%), whereas non-US sites enrolled a total of 516 patients (69.2%) as depicted in the following table:

Table 8: FDA Medical Officer Table of Subject Count by Country, AT Population, Study 0015

| COUNTRY | Subject Count n (%) |
|----------------|----------------------------|
| UNITED STATES | 230 (30.8) |
| INDIA | 85 (11.4) |
| TAIWAN | 63 (8.4) |
| CROATIA | 59 (7.9) |
| ISRAEL | 49 (6.6) |
| ARGENTINA | 48 (6.4) |
| AUSTRALIA | 45 (6.0) |
| FRANCE | 32 (4.3) |
| BRAZIL | 26 (3.5) |
| CANADA | 24 (3.2) |
| MALAYSIA | 20 (2.7) |
| CHILE | 14 (1.9) |
| GREECE | 12 (1.6) |

| COUNTRY | Subject Count n (%) |
|----------------|---------------------|
| BELGIUM | 8 (1.1) |
| ITALY | 7 (0.9) |
| UNITED KINGDOM | 6 (0.8) |
| PERU | 5 (0.7) |
| SOUTH AFRICA | 4 (0.5) |
| MALTA | 3 (0.4) |
| TURKEY | 3 (0.4) |
| POLAND | 2 (0.3) |
| CZECH REPUBLIC | 1 (0.1) |

FDA Medical Officer Comments: Patients were enrolled from 22 countries worldwide. Approximately 31% were enrolled from sites in the United States, which was the country with the highest enrollment percentage. Enrollment at non-US sites was variable with India accounting for approximately 11% of patients, whereas <1% of patients were enrolled from eight other nations.

The Applicant developed groupings of countries (Groups 1, 2 and 3) as a stratification to ensure balanced assignment of patients to the two treatment groups based on medical practice patterns. The following table from the Applicant's 0015 Clinical Study Report (Table 7-2) provides the country groupings used for this study:

Table 9: Applicant's Table of Country Groupings, Study 0015

| | |
|---------|----------------|
| Group 1 | Australia |
| | Belgium |
| | Canada |
| | France |
| | Israel |
| | Italy |
| | United Kingdom |
| | United States |
| Group 2 | Argentina |
| | Brazil |
| | Chile |
| | South Africa |
| | Taiwan |
| Group 3 | Croatia |
| | Czech Republic |
| | Greece |
| | India |
| | Malaysia |
| | Malta |
| | Peru |
| | Poland |
| | Turkey |

The following table depicts patient enrollment by study investigator. No single investigator enrolled 10% or more of study patients. Patrick Lee was the largest single enroller accounting for 6% of subjects in both treatment arms.

Table 10: FDA Medical Officer Summary Table of Subject Enrollment by Study Investigator (only includes sites with enrollment ≥10 subjects/investigator), AT Population, Study 0015

| Investigator | N | TELAVANCIN n (%) | VANCOMYCIN n (%) |
|--------------------------|----|---------------------|---------------------|
| Lee, Patrick | 45 | 21 (6) | 24 (6) |
| Skerk, Visnja | 36 | 16 (4) | 20 (5) |
| Lentnek, Arnold | 27 | 9 (2) | 18 (5) |
| O'Riordan-38271, William | 22 | 13 (3) | 9 (2) |
| Simmons, Grant | 20 | 5 (1) | 15 (4) |
| Shehabi, Yahya | 19 | 12 (3) | 7 (2) |
| Sarubbi, Felix | 18 | 5 (1) | 13 (3) |
| Teglia, Osvaldo | 18 | 9 (2) | 9 (2) |
| Raz, Paul | 17 | 6 (2) | 11 (3) |
| Gudelj, Ivan | 16 | 10 (3) | 6 (2) |
| Orozco, Carlos | 16 | 11 (3) | 5 (1) |
| Clavel, Marc | 15 | 7 (2) | 8 (2) |
| Shitrit, Pnina | 15 | 11 (3) | 4 (1) |
| Kraatz, James | 14 | 8 (2) | 6 (2) |
| Towfigh, Shirin | 13 | 7 (2) | 6 (2) |
| O'Riordan-38101, William | 12 | 5 (1) | 7 (2) |
| Khoja, Amir | 11 | 9 (2) | 2 (0.5) |
| Bhattacharya-41000, Amal | 10 | 4 (1) | 6 (2) |
| Chen-33004, Yao Shen | 10 | 6 (2) | 4 (1) |
| Gupta, Jugal | 10 | 3 (0.8) | 7 (2) |
| Talwar, Deepak | 10 | 7 (3) | 3 (0.8) |
| Tural, Ahmet | 10 | 5 (1) | 5 (1) |
| Witty, Lynn | 10 | 6 (2) | 4 (1) |

Baseline Patient Characteristics

The following table summarizes selected baseline demographic characteristics stratified by treatment group for patients enrolled in Study 15. There were no statistically significant differences across treatment groups for any of the baseline characteristics included in the table. In terms of baseline characteristics, the telavancin and vancomycin treatment groups were comparable with respect to age, gender, race/ethnicity, body mass index, baseline renal function (serum creatinine), hemodialysis, acute renal failure, mechanical ventilation at baseline, and VAP. The mean severity of illness as measured by APACHE II scores was approximately 15-16 in both groups for patients who had all components included in the APACHE II score determination. There were similar numbers of patients with concomitant diabetes mellitus and cardiac co-morbid conditions.

Table 11: FDA Medical Officer Table of Baseline Characteristics, AT Population, Study 0015

| Characteristic | TLV N=372 | VAN N=374 | 95% CI for difference* |
|--|--------------|--------------|---------------------------|
| Age, mean, yrs | 63±19.2 | 64±17.3 | |
| median | 66 | 68 | |
| range | 18-99 | 19-97 | |
| Gender | | | |
| Female | 137 (37%) | 161 (43%) | -6.2 (-13.2, 0.8) |
| Male | 235 (63%) | 213 (57%) | 6.2 (-0.8, 13.2) |
| Race/Ethnicity | | | |
| White/Caucasian | 267 (72%) | 272 (73%) | -0.9 (-7.4, 5.5) |
| All other race/ethnicity groups combined | 105 (28%) | 102 (27%) | 1.0 (-5.5, 7.4) |
| Body Mass Index (BMI) | | | |
| Number of patients having BMI | 369 (99%) | 371 (99%) | -0.004 (-1.3, 1.3) |
| mean BMI (±SD) | 26.6 (±7.90) | 26.1 (±6.51) | |
| median | 25.2 | 24.8 | |
| Baseline Serum Creatinine (Central Lab) | | | |
| Serum Creatinine ≤1.2 mg/dL | 259 (70%) | 272 (71%) | -3.1 (-9.6, 3.4) |
| Serum Creatinine >1.2 mg/dL | 103 (28%) | 89 (24%) | 3.9 (-2.4, 10.2) |
| Missing Serum Creatinine | 10 (3%) | 13 (3%) | -0.8 (-3.3, 1.7) |
| Renal Impairment | | | |
| Acute renal failure | 43 (12%) | 35 (9%) | 2.2 (-2.2, 6.6) |
| Hemodialysis | 11 (3%) | 9 (2%) | 0.6 (-1.8, 2.9) |
| Apache II Scores | | | |
| 0-13 (all patients) | 160 (43%) | 164 (44%) | -0.8 (-7.9, 6.3) |
| 14-19 (all patients) | 125 (34%) | 117 (31%) | 2.3 (-4.4, 9.0) |
| ≥20 (all patients) | 87 (23%) | 93 (25%) | -1.5 (-7.6, 4.7) |
| Mean score ±SD, all patients | 15±6.2 | 15±6.1 | |
| Patients having all APACHE II components | 214 (57.5%) | 206 (55.1%) | 2.4 (-4.7, 9.6) |
| Mean score ±SD, patients with all APACHE II components | 16.2 ±6.2 | 16.6 ±5.8 | |
| Median score, patients with all APACHE II components | 15 | 16 | |
| Mechanical Ventilation | | | |
| Ventilator-associated Pneumonia (VAP) | 103 (28%) | 100 (27%) | 1.0 (-5.4, 7.3) |
| Vented at Baseline | 166 (45%) | 176 (45%) | -2.4 (-9.6, 4.7) |
| Selected Co-morbid Conditions | | | |
| Diabetic status (yes) | 100 (27%) | 100 (27%) | 0.1 (-6.2, 6.5) |
| History of diabetes mellitus | 118 (32%) | 114 (30%) | 1.2 (-5.4, 7.9) |
| History of atrial fibrillation | 72 (19%) | 76 (20%) | -1.0 (-6.7, 4.8) |
| History of congestive heart failure | 71 (19%) | 78 (21%) | -1.8 (-7.5, 4.0) |
| History of myocardial infarction | 47 (13%) | 62 (17%) | -3.9 (-9.0, 1.1) |
| History of left ventricular hypertrophy | 16 (4%) | 12 (3%) | 1.1 (-1.6, 3.8) |
| Other cardiac diseases | 136 (37%) | 159 (43%) | -6.0 (-13.0, 1.0) |
| ≥1 cardiac co-morbidity | 225 (60%) | 241 (64%) | -4.0 (-10.9, 3.0) |

*difference = TLV – VAN; TLV = telavancin; VAN = vancomycin

Baseline Clinical Pulmonary Infection Scores (CPIS) were reported for all patients in the Applicant’s electronic dataset submission, although the CPIS is only relevant to assessing the likelihood for VAP. As depicted in the table below, there was a statistically significant higher percentage of VAP patients having all CPIS components at baseline in the telavancin arm compared to the vancomycin arm. The median CPIS in the patients with VAP was 6, which is considered the minimum threshold for identifying patients at high likelihood for VAP using this scoring system. There was a substantial proportion of VAP patients having all CPIS components at Baseline who had CPIS scores ≤ 6 , suggesting that they were less likely to have had pneumonia.

Table 12: FDA Medical Officer Table of Baseline CPIS Scores, AT Population, Study 0015

| Baseline CPIS (AT population) | TLV N=372 | VANCO N=374 | 95% CI for difference (TLV – VAN) |
|--|----------------------|------------------------|--|
| Mean (SD), all patients | 5.6 (1.61) | 5.6 (1.58) | |
| Median, all patients | 5.5 | 6 | |
| Number of VAP patients | 103 (100%) | 100 (100%) | 1.0 (-5.4, 7.3) |
| Mean CPIS \pm SD, all VAP patients | 5.9 \pm 1.6 | 5.9 \pm 1.6 | |
| Median CPIS, all VAP patients | 6 | 6 | |
| VAP patients having all CPIS components at Baseline | 89 (86%) | 74 (74%) | 12.4 (1.6, 23.3)* |
| Mean CPIS \pm SD for VAP patients having all CPIS components at Baseline | 6 \pm 1.6 | 6 \pm 1.6 | |
| Median CPIS for VAP patients having all CPIS components at Baseline | 6 | 6 | |
| CPIS ≤ 6 , VAP patients having all CPIS components at Baseline | 56 (63%) | 48 (65%) | -1.9 (-16.7, 12.9) |
| CPIS >6 , VAP patients having all CPIS components at Baseline | 33 (37%) | 26 (35%) | 1.9 (-12.9, 16.7) |

*statistically significant difference

FDA Medical Officer Comments: The Applicant’s modification of the recorded axillary temperatures by the addition of one degree Celsius to the recorded value on the CRF for the purposes of analysis created considerable uncertainty in assessing how informative APACHE II and CPIS scores were with respect to severity of illness and likelihood for VAP as described previously in Section 5.3.1.1.2 of this report.

A substantial number of patients had one or more missing components of the APACHE II and CPIS scores at baseline and at subsequent timepoints, which contributed uncertainty as to the patients’ actual severity of illness and likelihood for pneumonia (VAP), respectively. Limiting analysis only to VAP patients who had all CPIS components at baseline revealed a median CPIS score of 6. However, the median CPIS score of 6 for this subgroup did not provide reassurance that all patients had the disease (VAP) being studied. A substantial proportion (63-65%) of enrolled patients with VAP had CPIS ≤ 6 in both treatment arms. Singh and colleagues (12) reported in their published study of empiric antibiotic therapy for patients with pulmonary infiltrates in the ICU that patients with CPIS ≤ 6 were those in whom “pneumonia was considered unlikely”. Considering that approximately 25% of the VAP patients in both treatment

arms who had all CPIS components at baseline had CPIS scores of ≤ 5 , it is evident that there is a substantial proportion of patients enrolled in the study with a preliminary diagnosis of VAP in whom there is a very low likelihood for having bacterial VAP and whose actual diagnosis remains uncertain.

5.3.1.2.2 Analysis Populations

As described in the Applicant's 0015 Clinical Study Report, four analysis populations were defined for efficacy-related summaries. These four populations were not mutually exclusive; a patient could belong to more than one population. In all four populations, patients were associated with the treatment group assigned by the randomization:

- All-treated (AT): All patients who received any amount of study medication
- Modified All-treated (MAT): Patients 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, ETA, BBS, BAL, mini-BAL, or PSB;
- Clinically Evaluable (CE): Patients in the AT Population whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication;
- Microbiologically Evaluable (ME): Patients in the CE Population who also had a Gram-positive baseline respiratory pathogen, as defined above for the MAT Population.

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 qualified a patient for the MAT Population. If baseline respiratory tract and blood cultures identified different respiratory pathogens, then only those pathogens identified from respiratory tract specimens were deemed baseline respiratory pathogens.

The analysis populations as summarized by subject count are provided in the following table. Of note, there was a smaller percentage of telavancin compared to vancomycin-treated patients in the CE population. In the MAT and ME populations, most patients had pathogens recovered from respiratory tract specimens. Only a small proportion had pathogens recovered only from blood cultures. Approximately 26% of patients in the MAT population in both treatment arms had NP due to Gram-negative pathogens only.

Table 13: FDA Medical Officer Table of Subject Count in Efficacy Analysis Populations, Study 0015

| Study Populations | Number of Patients | |
|---|--------------------|------------|
| | Telavancin | Vancomycin |
| All Randomized | 381 | 380 |
| Randomized but not treated | 9 | 6 |
| All Treated (AT) | 372 (100%) | 374 (100%) |
| Enrolled under Original Protocol (permitted imipenem use) | 78 | 77 |
| Enrolled under Amendment 1 (prohibited imipenem) | 294 | 297 |
| Modified AT (MAT) | 257 (69%) | 247 (66%) |
| CE | 141 (38%) | 172 (45%) |
| ME | 108 (29%) | 113 (30%) |
| Gram-negative pathogen only (MAT) | 68 (26%) | 67 (27%) |
| Gram-negative pathogen only (CE) | 0 (0) | 0 (0) |

CE=clinical evaluable; ME=micobiologically evaluable

There were no patients randomized to telavancin who had been treated with vancomycin; similarly, no patients who had been randomized to vancomycin were treated with telavancin in this clinical trial. Nine patients in the vancomycin group were treated with anti-staphylococcal penicillins; such alternative drugs were not an option for patients in the telavancin arm.

5.3.1.2.3 Patient Disposition

The following table summarizes the disposition of patients in terms of discontinuation of study medication in the AT population (from Applicant's Table 7-4, 0015 Clinical Study Report). Among telavancin-treated patients in the AT population, 206 (55%) completed their course of study medication while 166 (45%) did not complete it. Among vancomycin-treated patients in the AT population, 230 (61%) completed their course of study medication while 144 (39%) did not complete it. The most common reasons cited for premature discontinuation of study drug in both treatment groups were death, unsatisfactory therapeutic response, and Gram-positive coverage no longer indicated. Additionally, the number of patients who discontinued study medication prematurely due to an adverse event was 2-fold higher in the telavancin arm than the vancomycin arm, and there were more telavancin-treated patients who discontinued study drug due to having two consecutive ECGs with QTc > 500 msec .

Table 14: Disposition of Patients in terms of Discontinuations of Study Medication in the AT population (from Applicant's 0015 Clinical Study Report, Table 7-4)

| | Study 0015 | | |
|---|---------------------|---------------------|------------------|
| | Telavancin N=372 | Vancomycin N=374 | Overall N=746 |
| Completed course of study medication | 206 (55%) | 230 (61%) | 436 (58%) |
| Resolution of signs and symptoms in ≤21 days | 204 (55%) | 229 (61%) | 433 (58%) |
| Infection not resolved, but patient received maximum allowable 21 days of treatment | 2 (<1%) | 1 (<1%) | 3 (<1%) |
| Premature discontinuation of study medication | 156 (45%) | 144 (39%) | 310 (42%) |
| Unsatisfactory therapeutic response, did not receive maximum allowable 21 days of treatment | 28 (8%) | 35 (10%) | 63 (8%) |
| Death | 38 (10%) | 29 (8%) | 67 (9%) |
| Two consecutive ECGs with QTc > 500 msec [1] | 8 (2%) | 1 (<1%) | 9 (1%) |
| Adverse event | 22 (6%) | 11 (3%) | 33 (4%) |
| Patient withdrew consent | 11 (3%) | 12 (3%) | 23 (3%) |
| Major protocol deviation | 4 (1%) | 0 | 4 (<1%) |
| Infection due to Gram-negative organisms only | 11 (3%) | 9 (2%) | 20 (3%) |
| Infection due to <i>Stenotrophomonas maltophilia</i> or <i>Burkholderia cepacia</i> | 0 | 4 (1%) | 4 (<1%) |
| Gram-positive coverage no longer clinically indicated | 27 (7%) | 18 (5%) | 45 (6%) |
| Required non-study antibiotics | 6 (2%) | 5 (1%) | 11 (1%) |
| Other | 11 (3%) | 19 (5%) | 30 (4%) |

[1] Based on machine-read ECG results versus a manual read.

The Investigator could select “major protocol deviation” as the primary reason for discontinuation of study medication on the drug discontinuation page of the CRF. Four patients in the telavancin group (1%) and none in the vancomycin group were classified by the Investigator as discontinuing study medication because of a major protocol deviation. Patients 0015-01010-4041 and 0015-18001-4058 received more than 24 hours of piperacillin-tazobactam and were discontinued, as the study pathogen was MSSA; this was not considered a true violation of Exclusion Criterion #3 by the Applicant as the identification of MSSA was not

known at study entry. Patient 015-33012-4225 had a diagnosis of tuberculosis, which violated Exclusion Criterion #4. Patient 0015-38271-4220 participated in another investigational study within 30 days of entry, which violated Exclusion Criterion #15. One additional patient, Patient 0015-30905-4035, was discontinued due to Gram-negative infection only. However, this was not considered a true violation of Exclusion Criterion #2 by the Applicant as the identification of the infecting pathogen was not known at enrollment.

The following table summarizes the disposition of patients in terms of study completion in the AT population (from Applicant's Table 7-5, 0015 Clinical Study Report). Among telavancin-treated patients in the AT population, 286 (77%) completed the follow-up visit with the majority of them having the follow-up visit between 7-14 days after end of therapy. Among vancomycin-treated patients in the AT population, 299 (80%) completed the follow-up visit with the majority of them having the follow-up visit between 7-14 days after end of therapy. The most common reason for early termination in both treatment arms was death. Less than 1% were lost to follow-up.

Table 15: Disposition of Patients in terms of Study Completion in the AT Population (from Applicant's 0015 Clinical Study Report, Table 7-5)

| | Study 0015 | | |
|--------------------------------------|------------|------------|-----------|
| | Telavancin | Vancomycin | Overall |
| | N=372 | N=374 | N=746 |
| Completed Follow-up Visit | 286 (77%) | 299 (80%) | 585 (78%) |
| Number of days after last study drug | | | |
| 6 days or less | 7 (2%) | 6 (2%) | 13 (2%) |
| 7-14 days | 249 (67%) | 265 (71%) | 514 (69%) |
| 15 days or more | 30 (8%) | 28 (7%) | 58 (8%) |
| Patients who terminated early | | | |
| Reason for early termination | | | |
| Death | 75 (20%) | 61 (16%) | 136 (18%) |
| Withdrew consent | 9 (2%) | 6 (2%) | 15 (2%) |
| Lost to follow-up | 0 | 3 (<1%) | 3 (<1%) |
| Other | 2 (<1%) | 5 (1%) | 7 (<1%) |

5.3.1.2.4 Potentially Effective Prior and Concomitant Non-Study Antimicrobial Medications

A patient was defined as having received potentially effective antibiotic therapy (PEAT) if he/she was treated on 3 or more calendar days—either prior to and/or concomitantly with study medication—with one or more antibiotics that either (1) had activity against all of the patient's baseline Gram-positive respiratory pathogens or, (2) if no baseline Gram-positive respiratory pathogen had been identified, had activity against any Gram-positive respiratory pathogen. If the baseline Gram-positive pathogen(s) was resistant to the prior antibiotics, then the prior antibiotics were not considered PEAT.

The PEAT classification was used in determining the CE and ME analysis populations. For each patient a determination was made whether the patient had received PEAT in addition to the study treatment. For the determinations, information about systemic and inhaled antimicrobials

administered to the patient, along with other clinical information, was reviewed by Theravance's Medical Monitor on a case-by-case basis. Using these data, the Medical Monitor assessed each systemic or inhaled antimicrobial administered to the patient and determined whether it was potentially active against the Gram-positive respiratory pathogens identified in baseline cultures available for that patient.

Whether a Gram-positive pathogen was identified or not, prior antibiotics were not considered PEAT if either of the following criteria were recorded: (1) the patient received 3 or more days of prior antibiotic treatment and was considered a treatment failure prior to study enrollment, or (2) the patient developed pneumonia despite treatment with antibiotics prior to study enrollment. In either of these two situations, prior antibiotics were ignored with respect to assessment of PEAT.

Three active antibiotics each given for a single day, but on different days, constituted PEAT. In contrast, three active antibiotics given for a single day, on the same day, did not constitute PEAT.

Determination of activity was dependent on the susceptibility pattern of the baseline respiratory pathogen, if a susceptibility pattern was identified, and thus required case-by-case consideration.

Only systemic and inhaled antibiotics were evaluated for potential effectiveness. Aztreonam, metronidazole, and colistin were defined a priori as not potentially effective against Gram-positive pathogens. Piperacillin/tazobactam and carbapenems were defined a priori as potentially effective against MSSA but not potentially effective against MRSA.

FDA Medical Officer Comments: The Applicant defined PEAT based on a minimum of 3 calendar days of antibacterial drugs, but did not provide scientific evidence to corroborate that that choice of time interval was appropriate compared to a shorter period of less than 3 days.

In addition, PEAT has been defined by the Applicant in relation to activity against the patient's baseline Gram-positive respiratory pathogens only. However, for patients with mixed infections involving Gram-positive and Gram-negative pathogens who were considered evaluable for efficacy analysis in the AT population, PEAT must also be assessed with respect to activity against baseline Gram-negative organisms. This becomes important in the Applicant's assessments of the adequacy of Gram-negative therapy and the potential impact of inadequate Gram-negative coverage on clinical response and mortality outcomes.

The most frequent indication for PEAT was pneumonia/HAP. In assessing the use of PEAT from randomization through TOC, it is evident that there was comparable use of PEAT across both treatment arms in this study as depicted in the table below.

Table 16: FDA Medical Officer Table of Subject Count Receiving Potentially Effective Non-study Antibiotics (PEAT) from Randomization through the TOC Visit, AT efficacy population, Study 0015

| Study | Treatment | N (AT) | n (%), PEAT Subject count | 95% CI for difference (TLV-VAN) |
|-------|------------|--------|---------------------------|---------------------------------|
| 0015 | Telavancin | 372 | 108 (29.0%) | 3.1 (-3.3, 9.5) |
| | Vancomycin | 374 | 97 (25.9%) | |

N (AT) = subject count in AT population; TLV=telavancin; VAN=vancomycin

5.3.1.2.5 Adequacy of Concomitant Gram-negative Therapy

Because the study was designed to compare the efficacy of two drugs with activity against Gram-positive pathogens only, the use of concomitant Gram-negative therapy was left to the Investigators' discretion as described in Section 5.3.1.1.2 of this report. For patients with Gram-negative pathogens only or mixed Gram-positive and Gram-negative baseline pathogens, the study medical monitors determined whether Gram-negative therapy was adequate or inadequate. This determination was to have made while the monitors were blinded to study treatment assignment and outcome. Gram-negative therapy was considered adequate if concomitant antibiotic(s) with *in vitro* activity covering all Gram-negative pathogens isolated at Baseline was administered from Study Day 1 through EOT. Patients were considered to have received inadequate therapy if they (a) never received antibiotic(s) with *in vitro* activity covering all Gram-negative pathogens isolated at Baseline (i.e., never received adequate therapy) or (b) did not receive concomitant antibiotic(s) with *in vitro* activity covering all Gram-negative pathogens isolated at Baseline until Study Day 3 or later (i.e., inadequate initial therapy). For purposes of these determinations, in the absence of *in vitro* susceptibility data, a concomitant antibiotic with known Gram-negative activity was deemed active against the baseline Gram-negative pathogen unless the antibiotic was known to routinely not have activity against the baseline pathogen. Patients with no baseline pathogens were considered to have received inadequate Gram-negative therapy if they (a) never received at least one antibiotic with known Gram-negative activity (i.e., never received adequate therapy) or (b) did not receive at least one antibiotic with known Gram-negative activity until Study Day 3 or later (i.e., inadequate initial therapy).

The adequacy of Gram-negative therapy is summarized for the AT Population in the following table. Of those patients in the AT Population with infections due to Gram-negative pathogens only, a total of 70 patients (38 of 70 telavancin-treated and 32 of 67 vancomycin-treated) received inadequate Gram-negative therapy, with the majority of these patients never having received adequate therapy. Of those patients in the AT Population with mixed infections of both Gram-positive and Gram-negative pathogens, a total of 52 patients (29 of 50 telavancin-treated and 23 of 45 vancomycin-treated patients) received inadequate Gram-negative therapy. The majority of these patients received Gram-negative therapy that was considered inadequate to treat the organisms present. Among the patients with no baseline pathogen, 46 of 115 telavancin-treated patients and 44 of 127 vancomycin-treated patients were assessed as having received inadequate Gram-negative therapy. Overall, in the AT Population, a

greater proportion of patients in the telavancin group (48%) received inadequate Gram-negative therapy than patients in the vancomycin group (41%). In the CE Population, the overall proportion of patients who received inadequate Gram-negative coverage was comparable between treatment groups.

Table 17: Adequacy of Gram-negative Therapy, AT Population, Study 0015 (from Applicant's 0015 Clinical Study Report, Table 8-26)

| | Number of patients | |
|--|--------------------|------------|
| | Telavancin | Vancomycin |
| Gram-negative pathogen only | | |
| Adequate Gram-negative therapy | 32 (46%) | 35 (52%) |
| Inadequate Gram-negative therapy | 38 (54%) | 32 (48%) |
| Initial Inadequate Therapy | 7 (10%) | 5 (7%) |
| Never received adequate therapy | 31 (44%) | 27 (40%) |
| Total | 70 (100%) | 67 (100%) |
| Mixed Gram-positive and Gram-negative pathogens | | |
| Adequate Gram-negative therapy | 21 (42%) | 22 (49%) |
| Inadequate Gram-negative therapy | 29 (58%) | 23 (51%) |
| Initial Inadequate Therapy | 9 (18%) | 5 (11%) |
| Never received adequate therapy | 20 (40%) | 18 (40%) |
| Total | 50 (100%) | 45 (100%) |
| No Baseline Pathogen [1] | | |
| Adequate Gram-negative therapy | 69 (60%) | 83 (65%) |
| Inadequate Gram-negative therapy | 46 (40%) | 44 (35%) |
| Initial Inadequate Therapy | 9 (8%) | 4 (3%) |
| Never received adequate therapy | 37 (32%) | 40 (31%) |
| Total | 115 (100%) | 127 (100%) |
| Total-Inadequate Gram-negative Therapy [2] | 113 (48%) | 99 (41%) |

[1] Patients with no baseline pathogen were considered to have inadequate therapy if they did not receive at least one antibiotic with Gram-negative activity during study Days 1 and 2 (ie, initial inadequate therapy) or if they never received at least one antibiotic with Gram-negative activity (ie, never received adequate therapy)

[2] Percentages are calculated based on the total number of patients with Gram-negative pathogens only, mixed Gram-positive and Gram-negative pathogens, or No baseline pathogen.

FDA Medical Officer Comments: Although the use of concomitant Gram-negative therapy was not required and was left to the discretion of the Investigators (Section 6.4.8.1 of the protocol), the Applicant's algorithm for the assessment of the adequacy of such therapy tended to penalize Investigators who did not administer any Gram-negative coverage to patients with no baseline pathogen(s) by considering such treatment management to be inadequate even if Gram-negative therapy was not clinically indicated at the pre-treatment visit. In the response to an information request dated June 17, 2009 from the Division, the Applicant stated that "patients with negative baseline cultures were included in the assessment of concomitant Gram-negative therapy for completeness...the inclusive approach towards assessment was performed in line with ATS/IDSA Guidance on the management of patients with HAP/VAP (AM J Respir Crit Care Med, Vol 171, pp 388-416, 2005) wherein it is recommended that all patients receive empiric therapy that provides coverage for both Gram-positive and Gram-negative pathogens...The investigators' clinical opinion regarding the need for Gram-negative therapy was not considered for these

assessments... This was exploratory in nature.” However, of note, no rationale was provided by the Applicant to explain why the assessment of the adequacy of Gram-negative therapy was considered to be a necessary post-hoc exploratory analysis even though the two NP study protocols were not designed to be consistent with the ATS/IDSA Guidance cited above in terms of empiric Gram-negative therapy. A site inspection conducted at Theravance revealed that Medical Monitor determinations of the adequacy of Gram-negative coverage were conducted subsequent to treatment unblinding, raising concerns about the potential for biased assessments. As Studies 0015 and 0019 were not designed to be consistent with ATS/IDSA Guidance on the management of patients with HAP/VAP in terms of empiric Gram-negative therapy and the Medical Monitors’ assessments were made post-unblinding, this FDA Medical Officer does not consider the Applicant’s post-hoc exploratory analysis of the adequacy of Gram-negative therapy to be appropriate or relevant for the evaluation of the efficacy data for this NDA.

It is this FDA Medical Officer’s view that patients whose pre-treatment respiratory tract and blood cultures were no growth and whose subsequent respiratory tract cultures grew Gram-negative bacteria should not be classified as having received inadequate initial Gram-negative therapy if the bacterial isolates were colonizers and did not require treatment with antibacterial agents. The designation of inadequate Gram-negative therapy derived from the Applicant’s algorithm potentially increases the number of patients assessed as having been treated with inadequate Gram-negative coverage, biases toward attributing some clinical failures and deaths to such treatment, and biases toward a conclusion of noninferiority.

5.3.1.2.6 Evaluability and Eligibility

Eligibility Deviations:

The following table summarizes the eligibility deviations for enrolled patients in the AT population. In some situations, helpline physicians could grant a waiver of approval to enroll a patient overriding one or more exclusion criteria if it was believed that there would be no adverse effect on patient safety or efficacy assessment. Overall, comparable percentages of the study population in each treatment arm did not meet the Inclusion and Exclusion Criteria. The most frequently violated Inclusion Criteria were #2b (signs and symptoms) and #4 (appropriate respiratory specimens). The most frequently violated Exclusion Criterion was #1 (>24 hour prior antibiotics).

Table 18: Summary of Eligibility Deviations, AT Population, Study 0015 (from Applicant's 0015 Clinical Study Report, Table 7-6)

| | Number of patients | | | | | |
|--|---------------------|-------------|---------------------|-------------|------------------|-------------|
| | Telavancin N=372 | | Vancomycin N=374 | | Overall N=746 | |
| Did not meet all Inclusion/Exclusion Criteria | 47 (13%) | | 44 (12%) | | 91 (12%) | |
| Enrollment approval not obtained | 15 (4%) | | 15 (4%) | | 30 (4%) | |
| Enrollment approval obtained | 32 (9%) | | 28 (8%) | | 61 (8%) | |
| | Approval | No Approval | Approval | No Approval | Approval | No Approval |
| Inclusion criteria violated [1] | | | | | | |
| Inclusion 2b: signs and symptoms | 9 (2%) | 2 (<1%) | 7 (2%) | 4 (1%) | 16 (2%) | 6 (<1%) |
| Inclusion 3: chest radiograph | 0 | 0 | 0 | 1 (<1%) | 0 | 1 (<1%) |
| Inclusion 4: appropriate respiratory specimens | 6 (2%) | 9 (2%) | 5 (1%) | 4 (1%) | 11 (1%) | 13 (2%) |
| Exclusion criteria violated [1] | | | | | | |
| Exclusion 1: >24 h prior antibiotic | 12 (3%) | 2 (<1%) | 10 (3%) | 2 (<1%) | 22 (3%) | 4 (<1%) |
| Exclusion 2: only Gram-negative bacteria | 0 | 2 (<1%) | 1 (<1%) | 2 (<1%) | 1 (<1%) | 4 (<1%) |
| Exclusion 3: Requirement for potentially effective antibiotics | 1 (<1%) | 1 (<1%) | 2 (<1%) | 0 | 3 (<1%) | 1 (<1%) |
| Exclusion 7: meningitis, endocarditis, osteomyelitis | 1 (<1%) | 0 | 1 (<1%) | 0 | 2 (<1%) | 0 |
| Exclusion 8: refractory shock | 2 (<1%) | 0 | 1 (<1%) | 2 (<1%) | 3 (<1%) | 2 (<1%) |
| Exclusion 9: QT issues | 1 (<1%) | 0 | 4 (1%) | 0 | 5 (<1%) | 0 |
| Exclusion 10: Neutropenia | 1 (<1%) | 0 | 0 | 0 | 1 (<1%) | 0 |
| Exclusion 12: birth control | 0 | 0 | 1 (<1%) | 1 (<1%) | 1 (<1%) | 1 (<1%) |
| Exclusion 15: other investigational medication | 0 | 2 (<1%) | 0 | 0 | 0 | 2 (<1%) |

[1] Patients could have violated more than one criterion.

One patient (0015-38049-4243) in the telavancin group who is not included in the table above as having violated any inclusion/exclusion criteria, had chronic fibrosis without new infiltrates or effusion and was, therefore, in violation of Inclusion Criterion 1 and Exclusion Criterion 4. In addition to the patients summarized in the preceding table as having violated Exclusion Criterion 1 (received >24 hours of prior antimicrobial therapy), there were an additional two patients (both in the vancomycin group) who received >24 hours of prior antimicrobial therapy but were not recorded on the CRF by the Investigator as having violated Exclusion Criterion 1 and did not receive approval for enrollment. Therefore, enrollment for these two patients, described as follows, constituted protocol deviations.

- Patient 0015-05017-4560 received >24 hours of prior antimicrobial therapy for HAP but did not meet definition of prior treatment failure. In addition, the patient was infected with MSSA and was going to receive >24 hours of piperacillin-tazobactam,

therefore violating Exclusion Criterion 3. No approval was granted for either violation.

- Patient 0015-38348-4251 received >24 hours of prior antimicrobial therapy for fever and HAP, but did not meet definition of prior treatment failure. No approval was granted for enrollment.

Unblinding of Treatment Assignment

Table 19: Unblinding of Treatment Assignment, Study 0015, AT Population (from Applicant's 0015 Clinical Study Report, Table 7-8)

| | Number of patients | | |
|---|---------------------|---------------------|------------------|
| | Telavancin N=372 | Vancomycin N=374 | Overall N=746 |
| Treatment not unblinded | 369 (99%) | 365 (99%) | 734 (98%) |
| Treatment unblinded | 3 (<1%) | 9 (2%) | 12 (2%) |
| During study medication dosing period [1] | 2 (<1%) | 4 (1%) | 6 (<1%) |
| After discontinuation of study medication [2] | 1 (<1%) | 5 (1%) | 6 (<1%) |
| Total | 372 (100%) | 374 (100%) | 746 (100%) |

[1] On or before last day of study medication

[2] After last day of study medication

The table above summarizes the number of patients who were unblinded for any reason either during or after study medication dosing. Study medication was unblinded in six patients on or before the last day of study medication as discussed briefly below.

- Patient 0015-02011-4096 (telavancin): The actual study drug name was mistakenly written on the ICU flow chart by nursing staff on Study Day 3.
- Patient 0015-14002-4195 (telavancin) experienced an AE of a moderate rash on the face and chest, which led to early discontinuation of study medication and subsequent unblinding of treatment assignment on Study Day 3. A patient narrative can be found in Supporting Table 202.
- Patient 0015-02012-4348 (vancomycin): Vancomycin concentration reports were inadvertently made available to staff on Study Day 4.
- Patient 0015-02024-4785 (vancomycin): A change in antibiotic therapy following the report of inadequate concentrations of vancomycin on Study Day 5 inadvertently revealed the treatment assignment. Last day of study medication dosing was on Study Day 5.
- Patient 0015-14002-4194 (vancomycin): The patient was unblinded on Study Day 1 because the study treatment identity was mistakenly recorded in the medical record.
- Patient 0015-14002-4197 (vancomycin): The patient was inadvertently unblinded on Study Day 1.

Of the six patients whose treatment assignment was unblinded after discontinuation of study medication, one patient was in the telavancin group and five patients were in the vancomycin group. An SAE of acute renal failure that led to discontinuation of study medication was reported for Patient 0015-38350-4307 (telavancin) on Study Day 3, which

prompted unblinding on Study Day 4. Of the five vancomycin-treated patients, the name of the study medication was accidentally recorded in two patient study files; in the third, the patient's legal representative demanded unblinding; in the fourth, unblinding was required to construct a new regimen for a patient with deterioration following septic shock and multi-organ failure (Patient 0015-18000-4117); and in the fifth, a reason was not documented.

FDA Medical Officer Comments: During the review cycle for this NDA, a site inspection was conducted at Theravance. During the inspection, it was noted that subsequent to treatment unblinding, medical review determinations were made impacting patient population evaluability, assessments of potentially effective non-study antibiotics, and assessments of the adequacy of Gram-negative coverage. Medical Monitor evaluation of such issues following treatment unblinding raises concern about the potential for biased assessments.

Clinical Evaluability Criteria:

To have been deemed to have adhered to protocol expectations, and on that basis to have been included in the CE Population, a patient must have met the following criteria:

- Patient met the following protocol inclusion criteria (IC) (Section 6.3.1 of protocol), or else was approved for enrollment by the Study Hotline Monitor:
 - o IC 2, which required certain signs and symptoms consistent with pneumonia
 - o IC 3, which required a chest radiograph consistent with a diagnosis of pneumonia
 - o IC 4, which required the availability of appropriate specimens for Gram stain and culture and venous access for dosing
- Patient did not violate the following protocol exclusion criteria (EC) (Section 6.3.2 of protocol), or else was approved for enrollment by the Study Hotline Monitor:
 - o EC 1, which excluded patients who had received more than a specified amount of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization
 - o EC 2, which excluded patients with respiratory tract specimens or sputum with only Gram-negative bacteria
 - o EC 3, which excluded patients with MSSA or *S. pneumoniae* who also required more than a specified amount of concomitant antibiotic therapy for Gram-negative coverage that had activity versus MSSA or *S pneumoniae*
 - o EC 4, which excluded patients with known or suspected pulmonary disease that precluded evaluation of therapeutic response, cystic fibrosis, or active tuberculosis
 - o EC 5, which excluded patients with known or suspected *Legionella pneumophila* pneumonia
 - o EC 6, which excluded patients who were known or suspected to be infected with an organism that is not susceptible to medications permitted by the protocol
 - o EC 7, which excluded patients with documented or suspected meningitis, endocarditis, or osteomyelitis
- The patient's identified analysis pathogen(s) were not solely Gram-negative pathogens. That is, either the patient had a Gram-positive analysis pathogen, or no analysis pathogen was identified.

- The patient did not have pneumonia due to *Stenotrophomonas maltophilia* or *Burkholderia cepacia* at Baseline.
- The patient did not have a persistent *S. aureus* bacteremia, defined as two or more *S. aureus*-positive blood cultures on different days between Study Day 1 and TOC, inclusive.
- The patient did not receive more than 2 days of vancomycin or teicoplanin between Study Day -4 and Study Day 1, inclusive. The rationale for excluding patients who had received prior treatment with vancomycin was to exclude prior treatment failures to vancomycin. Only IV vancomycin was to be considered as a potential basis for exclusion from the CE Population; oral administration was not to be a basis for exclusion.
- The patient was treated with the study medication assigned by the randomization.
- The patient received at least 80% of intended doses of active study medication.
- The patient did not receive potentially effective concomitant systemic antibiotic therapy for more than 2 calendar days any time before the TOC assessment. The day of the TOC assessment was not counted for this criterion.
- The patient was a failure at EOT, or else was either a cure or a failure at TOC.
- If the patient was not a failure at EOT, then the TOC assessment was made between Study Day 6P (i.e., 6 days after EOT) and Study Day 28P inclusive.
- If the patient was a cure, the patient received at least 5 days of active study medication.
- If the patient was a failure, the patient received active study medication daily through Study Day 3.

Additionally, for patients who died on or after Study Day 3, where the death was attributable to the HAP episode under study, the receipt of potentially effective antibiotic therapy (PEAT) was not to exclude them from the CE Population.

FDA Medical Officer Comments: In view of multiple co-morbid medical illnesses, assessment of attribution for mortality due to NP under study is difficult and potentially biased due to the absence of pre-specified objective criteria.

The following table summarizes the reasons for exclusion from the CE and ME populations. The most common reasons for exclusion from the CE Population were “Received Potentially Effective Systemic Antibiotics” and “Clinical Response at TOC was Neither ‘Cure’ nor ‘Failure’” (i.e., clinical response at TOC was indeterminate or missing). Both reasons occurred in a greater percentage of patients in the telavancin group than in the vancomycin group.

It should be noted that seven patients who were algorithmically excluded from the CE Population because of violation of inclusion or exclusion criteria were subsequently included based on the Medical Monitor’s override of the algorithmic determination of clinical evaluability. Refer to the following section for additional details.

Table 20: Reasons for Exclusion from the CE and ME Analysis Populations, Study 0015, AT Population (from Applicant's 0015 Clinical Study Report, Table 8-2)

| | Number of patients | | |
|---|---------------------|---------------------|------------------|
| | Telavancin N=372 | Vancomycin N=374 | Overall N=746 |
| Not Clinically Evaluable [1] | 231 (62%) | 202 (54%) | 433 (58%) |
| TOC Clinical Response is neither cure nor failure | 112 (30%) | 85 (23%) | 197 (26%) |
| Did not meet Exclusion criteria | 6 (2%) | 4 (1%) | 10 (1%) |
| Did not meet Inclusion criteria | 2 (<1%) | 3 (<1%) | 5 (<1%) |
| Did not receive minimum days of treatment | 21 (6%) | 6 (2%) | 27 (4%) |
| Isolation of only Gram-negative pathogens | 70 (19%) | 67 (18%) | 137 (18%) |
| TOC visit outside window | 3 (<1%) | 0 | 3 (<1%) |
| Received potentially effective systemic antibiotics | 109 (29%) | 97 (26%) | 206 (28%) |
| Persistently positive <i>S. aureus</i> bacteremia | 2 (<1%) | 4 (1%) | 6 (<1%) |
| Pneumonia due to <i>S. maltophilia</i> or <i>B. cepacia</i> | 8 (2%) | 8 (2%) | 16 (2%) |
| Did not receive at least 80% of intended dose | 1 (<1%) | 0 | 1 (<1%) |
| Excessive prior vancomycin or teichoplanin use | 2 (<1%) | 1 (<1%) | 3 (<1%) |
| | | | |
| Not Microbiologically Evaluable [1] | 264 (71%) | 261 (70%) | 525 (70%) |
| Not clinically evaluable | 231 (62%) | 202 (54%) | 433 (58%) |
| No Gram-positive pathogen isolated at baseline | 184 (49%) | 189 (51%) | 373 (50%) |

[1] Patients could have more than one reason for exclusion.

Applicant's Determination of Patient Evaluability

Determinations of patient evaluability were made after all the data had been entered into the database, after the data had been cleaned, and before the release of the treatment randomization code (i.e., prior to breaking of the treatment blind for the study).

On a patient-by-patient basis, Theravance's Medical Monitor reviewed the patient's qualification for, or disqualification from, the various analysis populations resulting from a computer-aided algorithmic classification. (Note that the algorithmic classification required some intermediate input from the Medical Monitor, such as classification of organisms and assessment of potentially effective antimicrobials.) The Medical Monitor may have overridden the algorithmic classification according to clinical judgment. Any such overrides were documented, including the rationale for the override.

FDA Medical Officer Comments: During the review cycle for this NDA, a site inspection was conducted at Theravance. During the inspection, it was noted that subsequent to treatment unblinding, medical review determinations were made impacting patient population evaluability, assessments of potentially effective non-study antibiotics, and assessments of the adequacy of Gram-negative coverage. Medical Monitor evaluation of such issues following treatment unblinding raises concern about the potential for biased assessments.

The Medical Monitor identified seven patients who violated inclusion or exclusion criteria but were considered suitable for inclusion in the CE population as depicted in the following table:

Table 21: Patients included in the CE Population that violated study entry criteria and did not receive approval to enter the study, Study 0015, AT Population (from Applicant's 0015 Clinical Study Report, Table 19)

| Patient ID | Treatment | CRF Documentation | Inclusion/Exclusion criteria not met | Reason for CE exclusion |
|-----------------|------------|---|--|---|
| 0015-05002-4043 | Vancomycin | The respiratory specimen was obtained 72h prior to first dose | Inclusion 4: appropriate respiratory specimen | Specimen from Day -3 and did not receive adequate antibiotics for the MRSA so did not violate inclusion criteria 4 in reality |
| 0015-05002-4048 | Vancomycin | Since June 3, 2006, the blood pressure <90 mmHg but not more than 2 hours and dopamine was started more than 10 mcg/kg/min | Exclusion 8: refractory shock | Inclusion/Exclusion criteria not met is not one of the CE requirements |
| 0015-06026-4420 | Telavancin | Inclusion criteria 2b only has 1 criteria present – rectal temperature is 38 degrees C. | Inclusion 2b: Signs and symptoms | Patient on high percentage oxygen, many other signs and CXR consistent with pneumonia |
| 0015-14003-4410 | Vancomycin | WBCs in sputum 10-12 | Inclusion 4: appropriate respiratory specimens | Sputum had <10 epithelial cells |
| 0015-37009-4489 | Telavancin | Subsequently was found to have been involved in another investigational study within the exclusion period although this information was not known prior to enrollment | Exclusion 15: other investigational medication | Inclusion/Exclusion criteria not met is not one of the CE requirements |
| 0015-38024-4591 | Vancomycin | At least 2 symptoms not checked for Inclusion 2b, patient not eligible; no waiver granted | Inclusion 2b: Signs and symptoms | Temperature was 0.1F below cutoff. |
| 0015-38024-4781 | Vancomycin | PI believed Gram stain report erroneous | Exclusion 2: Only Gram-negative bacteria | Culture did not grow only Gram-negative pathogens |

FDA Medical Officer Review of Case Report Forms and Electronic Datasets:

This FDA Medical Officer conducted a review of a random sample of approximately 80 case report forms (CRFs) to verify the accuracy of the information compared to the electronic datasets and to provide an independent assessment of the patient's eligibility, evaluability, and outcome. Multiple deficiencies were uncovered that adversely impact the ability to evaluate the efficacy and safety of telavancin compared to vancomycin in this clinical trial. The deficiencies are summarized as follows:

1. Chest x-ray reports

- Radiologists' reports for chest x-rays performed at various study visits were missing for many patients. In response to an information request from the Division dated June 17, 2009, the Applicant stated that radiologists' assessments of chest x-rays were not required in the protocol. Following a separate request from the Division, the Applicant attempted to obtain copies of radiology reports for all patients enrolled in the ATTAIN trials. The initial request was made approximately one year after the studies were completed. Documentation, including radiologists' reports/notes or physician progress notes of

- radiologic assessments, were obtained for 1,334 patients. No documentation was received for 169 of the 1,503 treated patients in the combined ATTAIN trials.
- Some radiologists reports described chest x-ray abnormalities that were not consistent with pneumonia and did not corroborate the Investigators' chest x-ray interpretations
 - Patient 0015-02024-4785: Pre-treatment chest x-ray reported as “atelectasis at bases” by radiologist. The Day 4 chest x-ray was reported as “lung bases seem slightly clearer on this expiratory film”, and the EOT chest x-ray was reported by the radiologist as “increased markings with atelectasis at least at right base. Suboptimal inspiratory effort.”
 - Patient 0015-12016-4241: The Pre-treatment, Day 4, and Day 7 chest x-rays were reported by the radiologist as “compatible with cardiogenic pulmonary edema”.
 - There were patients assessed as clinical cure at the EOT visit who were are missing EOT chest x-rays, which were required as per the protocol-specified definition of clinical cure at EOT in order to assess for evidence of improvement or lack of progression of radiographic findings.
 - Patient 0015-38020-4342 was treated for 13 days with study medication but had no chest x-ray performed beyond Study Day 7. Additionally, none of the chest x-ray reports described a pneumonia or lung infiltrate.
 - There were chest x-ray reports that were signed by a radiologist beyond the study visit window without explanation for the delay.
 - Patient 0015-12006-4523 had an EOT chest x-ray that was signed and dated by the radiologist approximately one year after the radiograph was actually performed.
 - In response to an information request from the Division dated February 25, 2009, the Applicant was unable to provide an electronic dataset that included a flag to indicate whether the radiological assessments for each patient were provided by the radiologist or by the investigator (or investigator's designate). The Applicant reported that this information was requested during the study, and that radiologic assessments were captured in the CRF. However, the identity of the individual making the assessment (investigator or radiologist) was not captured. The assessment reported “may reflect that of the investigator or may be transcribed from a radiologist's report” according to the Applicant.
 - In response to an information request from the Division dated June 17, 2009, the Applicant noted that the following patients did not have a chest x-ray within 48 hours prior to randomization: Patient #s 0015-23004-4357, 0015-38356-4394, and 0019-38108-6074. In addition, Patient # 0015-38049-4243 had an abnormal chest x-ray at pretreatment which was assessed by the investigator as not having a new infiltrate or pleural effusion.
2. Clinical response assessments at EOT and TOC were confounded in some patients by prolonged administration of piperacillin/tazobactam and imipenem. According to the protocol, piperacillin-tazobactam and mipenem were to be discontinued or changed to aztreonam as soon as possible unless aztreonam was not appropriate due to an unacceptable level of resistance among Gram-negative bacteria at the particular investigation site.

However, there were multiple cases in which such de-escalation in antibiotic coverage did not occur in patients infected with MSSA as the sole baseline pathogen. This FDA Medical Officer recommends that the clinical outcome for these patients should be changed from cure to indeterminate at EOT and clinical failure at TOC:

- Patients 0015-01028-4717, 0015-01010-4041, 0015-05004-4044, 0015-33008-4321, 0015-38348-4251, and 0015-14011-4696.
3. Clinical response assessments of cure at TOC for some patients having evidence of chest x-ray progression at the EOT visit or whose TOC clinical response was not supported by clinical and microbiological data recorded in the CRF
 - Patient 0015-01028-4718 received only four doses of study drug (vancomycin) when septic shock developed. The patient was assessed as indeterminate at the EOT visit due to septic shock and then was placed on three intravenous antibacterial drugs. After receiving approximately two weeks of vancomycin and meropenem prior to the TOC visit (and only four doses of study medication), the patient was assessed as a cure at TOC. There was no information provided on the CRF regarding the suspected source of septic shock or of a diagnostic evaluation to identify a source other than the lung. This patient was not considered clinically evaluable, because the minimum duration of study drug (7 days) had not been administered. However, the patient may not have been evaluable for inclusion in the AT population due to the few number of doses of study drug administered, such that the indeterminate clinical response assessment at EOT may not have been valid.
 4. Inconsistencies with respect to Pulmonary Radiology Logs and Oxygenation Status on CRF
 - Patient 0015-01028-4718 was described as having ARDS (requires bilateral lung infiltrates per definition on CRF) in terms of Oxygenation Status at the pre-treatment visit, but the Pulmonary Radiology Log described a unilateral infiltrate only.
 - Patient 0015-02024-4215 was described as having “Overall Radiographic Progression – Yes due to CHF or ARDS” at the Day 7 and EOT visits, although the extent of lung involvement ticked on the Pulmonary Radiology Log was identical for both visits. The chest-x-rays at both of those visits were improved compared to the previous Day 4 x-ray, which is inconsistent with the designation of “Overall Radiographic Progression – Yes”.
 5. Discrepancies between microbiology data recorded on the CRF and reported in the electronic datasets
 - Patient 0015-01010-4041 had no positive blood cultures according to the CRF log (dated in 2005), growth of MSSA and *Proteus* was reported on the data clarification form (dated 2006), and another data clarification form (dated 2007 and signed in 2008) reported no positive blood cultures for the same day. The electronic dataset reported that both bacteria had been isolated from the blood cultures.
 - Patient 0015-02024-4215 had *Serratia* and *Klebsiella* isolated from Day 4 respiratory cultures, which were not treated specifically with antibacterial drugs by the investigator but were identified as both colonizers and superinfections in the electronic datasets.

6. Gram stain quality and Microbiologic evaluability
 - There were patients whose sputum quality was listed as “inappropriate” or “unknown” in the electronic dataset who were included in the ME population despite the lack of evidence from cultures of other respiratory specimens or blood to corroborate the bacterial isolates identified from the baseline sputum specimens as pathogens. This issue is discussed further in Section 5.3.2.2.6 of this report.
7. Quality of endotracheal aspirates (ETA) and Microbiologic evaluability
 - There were patients in which bacteria isolated from ETA were considered pathogens without an overall assessment of the adequacy of the specimen’s quality, and the patients were subsequently being included in the ME population without corroborative evidence from other respiratory specimens or blood. This issue is discussed further in Section 5.3.2.2.6 of this report.
8. Inability to corroborate some enrollment eligibility data based on information recorded in the CRF
 - Patient 0015-23004-4358: Inclusion criterion #2 “Fever (>38°C) or hypothermia” was ticked on the CRF, but the recorded temperature at pre-treatment was not >38°C. The data clarification form indicated that the use of that Inclusion Criterion was “correct as is since value used to qualify patient was different than described at pre-treatment”. However, in the absence of a recorded qualifying temperature, it is not possible to corroborate the applicability of that Inclusion Criterion to qualify the patient for study entry.
 - In response to an information request dated April 30, 2009, the Applicant stated that “regarding the apparent discrepancy between eligibility criteria and clinical signs and symptoms of pneumonia within 24 hours before initiation of treatment, the clinical data used to inform these two assessments were not necessarily recorded at the same time. Many patients with hospital-acquired pneumonia were under intensive care and would have multiple assessments made of signs and symptoms of pneumonia in the 24-hour period prior to initiation of treatment. Given the variability of these parameters and the acuity of illness, it is not surprising that clinical signs and symptoms data might vary during this timeframe. The protocol did not stipulate that the data recorded on the signs and symptoms within 24 hours of treatment page be the data used to assess eligibility. When a discrepancy was noted during data entry, the investigator was asked to verify that the data at variance were accurate by specifying it was ‘correct as is since value used to qualify patient was different than described at pre-treatment’ The eligibility criteria qualifying each patient for enrollment in the study (CRF page 1) were verified against source documentation at the clinical site as were the data recorded on CRF page 12.”
9. Granting of Waivers for Inclusion/Exclusion Criteria when there was inadequate documentation to justify the waiver

- Patient 0015-07002-4069 was granted a waiver for Inclusion Criterion #4 regarding an adequate respiratory specimen for Gram stain and culture. However, no adequate respiratory tract specimens were recorded on the CRF for the patient at pre-treatment, Day 4, and EOT visits. Thus, this patient should not have been granted the waiver and should have been considered not evaluable due to the lack of any adequate respiratory tract specimens.
- Patient 0015-14011-4696 was granted a waiver for Exclusion Criterion #1 regarding treatment for >24 hours with Tazocin (piperacillin/tazobactam). The data clarification form cited “pathogen was resistant to prior treatment” as the reason for the prolonged Tazocin use. The pathogen was identified as MSSA. However, no susceptibility data was provided in the CRF or in the electronic datasets to substantiate that the MSSA isolate was actually resistant to Tazocin.

10. Errors in identification and classification of adverse events

- Patient 0015-02024-4215 developed oral thrush during the course of study drug administration that required treatment with Nistat, but the event was not classified as a treatment-emergent adverse event.
- Patient 0015-05001-4066 developed a urinary fungal infection during the course of study drug administration that required treatment with fluconazole, but the event was not classified as a treatment-emergent adverse event.
- Patient 0015-02009-4054 developed a cavitating lung abscess at the site of resolving pneumonia, which was assessed by the investigator as a mild adverse event not related to study drug. The patient was assessed as a cure at EOT and TOC by the investigator despite having developed the lung abscess. This FDA Medical Officer believes that the event should have been classified as a serious adverse event that was possibly related to study drug (no bacteria were identified from any of the respiratory or blood cultures obtained during study participation to suggest a pathogen resistant to study drug). The patient should have been assessed as a failure at TOC, since there was failure to resolve clinically and there were progressive radiographic findings of abscess development at the site of the original pneumonia under study.

5.3.1.2.7 Efficacy

Clinical and Microbiological Outcomes

The primary endpoint for this clinical trial was clinical response at the Follow-up/TOC visit, which was conducted 7 to 14 days after the last dose of study medication. For specific patients in whom study medication was discontinued but other antibiotics were given to treat pneumonia due to Gram-negative organisms only, the Follow-up visit was conducted 7 to 14 days after the last dose of all antibiotics administered to treat pneumonia. Only those patients evaluated as clinical cure or indeterminate at the EOT visit were to have a TOC evaluation during the Follow-up visit.

The following table provides the Applicant’s summary of clinical outcomes at the TOC visit:

Table 22: Clinical Response at TOC in the AT and CE Populations, Study 0015 (from Applicant's 0015 Clinical Study Report, Table 8-32)

| | Number of Patients | | Difference (95% CI) [1] |
|----------------------|--------------------|--------------|-------------------------|
| | Telavancin | Vancomycin | |
| All-treated | | | |
| Cure | 214 (57.5%) | 221 (59.1%) | -1.6% (-8.6%, 5.5%) |
| Failure | 46 (12.4%) | 68 (18.2%) | |
| Indeterminate | 56 (15.1%) | 41 (11.0%) | |
| Missing | 56 (15.1%) | 44 (11.8%) | |
| -Total- | 372 (100.0%) | 374 (100.0%) | |
| Clinically Evaluable | | | |
| Cure | 118 (83.7%) | 138 (80.2%) | 3.5% (-5.1%, 12.0%) |
| Failure | 23 (16.3%) | 34 (19.8%) | |
| -Total- | 141 (100.0%) | 172 (100.0%) | |

[1] Point estimate and 95% confidence interval on the treatment difference (telavancin – vancomycin) in cure rate. ^= Confidence interval uses Agresti-Caffo adjustment

Based on the clinical response outcome data reported for the AT and CE Populations, the co-primary analysis populations, the Applicant concluded that telavancin was clinically noninferior to vancomycin. The lower bound of the 95% CI around the difference (telavancin - vancomycin) in cure rates was greater than the Applicant’s prospectively defined -20% noninferiority margin for clinical response. Telavancin was also demonstrated to be clinically noninferior to vancomycin based on the post hoc noninferiority margin for clinical response, as evidenced by the lower bound of the 95% CI around the difference (telavancin - vancomycin) in cure rates being greater than -14% in the AT and CE Populations. In both populations, the lower bound of the 95% CI around the difference between treatments in cure rates exceeded -10%. The 95% CI also included zero.

FDA Medical Officer Comments: The inclusion criteria for the study do not provide adequate assurance that all patients enrolled in the clinical trial have a high likelihood of having NP or VAP as previously described. Since the clinical response analyses depicted in the table above are not limited to patients with the greatest likelihood of pneumonia, there is a bias towards a conclusion of noninferiority. The AT population includes patients in which only Gram-negative bacteria were isolated from their respiratory tract specimens, whereas such patients are excluded from the CE population. Inclusion of patients infected with only Gram-negative pathogens in the AT population for analysis purposes reflects the efficacy of non-study antibacterial drugs rather than the two study medications being compared, which does not add useful information in distinguishing ineffective from effective treatments and may increase the probability of bias in assessing the noninferiority of telavancin compared to vancomycin.

The analysis of noninferiority trials of antibacterial drugs for the treatment of NP and VAP using clinical response as the primary endpoint cannot be justified based on published data in the English-language scientific literature. Similarly, the Applicant’s proposed NI margin for a clinical response endpoint cannot be justified. Interpretation of such noninferiority trials can

only be justified using all-cause mortality as the primary endpoint as discussed in Section 6.1.1 of this report.

The reasons for failure are summarized in the following table. In the AT and CE populations, the most common reason for failure at the EOT was persistence or progression of pneumonia. Relapses at TOC were slightly more frequent among vancomycin-treated patients.

Table 23: Reasons for Failure at TOC, AT and CE Populations, Study 0015 (from Applicant's 0015 Clinical Study Report, Table 8-33)

| Population | Number of Patients | | |
|---|--------------------|------------|-------------|
| | Telavancin | Vancomycin | Overall |
| All-treated | 372 | 374 | 746 |
| Clinically evaluable | 141 | 172 | 313 |
| Reason for Failure: All-treated population | | | |
| Failure at End-of-therapy | 37 (9.9%) | 57 (15.2%) | 94 (12.6%) |
| Persistence or progression of pneumonia | 29 (7.8%) | 42 (11.2%) | 71 (9.5%) |
| Lack of efficacy/Initiation of antistaphylococcal antibiotics | 5 (1.3%) | 9 (2.4%) | 14 (1.9%) |
| Death on or after Study Day 3 attributable to HAP | 8 (2.2%) | 10 (2.7%) | 18 (2.4%) |
| Relapsed pneumonia (TOC) | 4 (1.1%) | 10 (2.7%) | 14 (1.9%) |
| Death on or after Study Day 3 attributable to HAP [1] | 0 | 1 (0.3%) | 1 (0.1%) |
| Death after End-of-therapy attributable to HAP [1] | 5 (1.3%) | 0 | 5 (0.7%) |
| -Total- | 46 (12.4%) | 68 (18.2%) | 114 (15.3%) |
| Reason for Failure: Clinically evaluable population | | | |
| Failure at End-of-therapy | 21 (14.9%) | 30 (17.4%) | 51 (16.3%) |
| Persistence or progression of pneumonia | 15 (10.6%) | 19 (11.0%) | 34 (10.9%) |
| Lack of efficacy/Initiation of antistaphylococcal antibiotics | 3 (2.1%) | 4 (2.3%) | 7 (2.2%) |
| Death on or after Study Day 3 attributable to HAP | 6 (4.3%) | 8 (4.7%) | 14 (4.5%) |
| Relapsed pneumonia (TOC) | 1 (0.7%) | 4 (2.3%) | 5 (1.6%) |
| Death after End-of-therapy attributable to HAP [1] | 1 (0.7%) | 0 | 1 (0.3%) |
| -Total- | 23 (16.3%) | 34 (19.8%) | 57 (18.2%) |

[1] Includes patients whose clinical response at TOC was set to failure due to death on or after study day 3 and the cause of death was due to HAP.

The following table from the Applicant's synopsis of Study 0015 provides a summary of various efficacy parameters stratified by Gram-positive bacterial pathogens:

Table 24: Key Efficacy Parameters at TOC, Study 0015, (from Applicant's Summary of Clinical Efficacy, Table 6, Module 2.7.3)

| Efficacy Parameter | Analysis Population | Number (%) of Patients | | Diff (95% CI) [1] |
|--|---------------------|------------------------|-----------------|--|
| | | Telavancin | Vancomycin | |
| Clinical cure rate | AT | 214/372 (57.5%) | 221/374 (59.1%) | -1.6% (-8.6%, 5.5%) |
| | CE | 118/141 (83.7%) | 138/172 (80.2%) | 3.5% (-5.1%, 12.0%) |
| Clinical Cure Rates for Patients with Single Gram-positive Pathogen Only | ME | 68/82 (82.9%) | 66/88 (75.0%) | 7.9% (-4.3%, 20.1%) |
| MRSA | ME | 42/50 (84.0%) | 54/70 (77.1%) | 6.9% (-7.9% [^] , 20.5% [^]) |
| MSSA | ME | 20/24 (83.3%) | 11/17 (64.7%) | 18.6% (-8.8% [^] , 44.1% [^]) |
| Clinical Cure Rate by Pathogen | | | | |
| <i>S. aureus</i> | ME | 80/98 (81.6%) | 81/109 (74.3%) | 7.3% (-3.9%, 18.5%) |
| MRSA | ME | 57/70 (81.4%) | 63/84 (75.0%) | 6.4% (-6.6%, 19.4%) |
| MSSA | ME | 26/32 (81.3%) | 18/25 (72.0%) | 9.3% (-12.9%, 31.0% [^]) |
| By-Patient Microbiological Eradication Rate | MAT | 146/257 (56.8%) | 143/247 (57.9%) | -1.1% (-9.7%, 7.6%) |
| | ME | 86/108 (79.6%) | 85/113 (75.2%) | 4.4% (-6.6%, 15.4%) |

[1] Difference (telavancin – vancomycin); 2-sided 95% CI.

[^]= Confidence interval uses Agresti-Caffo adjustment

Microbiological Data

In the MAT population, 8% of telavancin–treated and 7% of vancomycin-treated patients were bacteremic at baseline. Bacterial pathogens were isolated from blood cultures in only 3% of telavancin–treated and 1% of vancomycin-treated patients. There were comparable numbers of patients in each treatment arm who had Gram-positive bacteria at baseline as primary pathogens. The following table summarizes data related to baseline Gram-positive pathogens.

Table 25: FDA Medical Officer Summary Table of Baseline Gram-positive Pathogens, MAT Population, Study 0015

| | TLV | VAN |
|-------------------------------------|-----------|-----------|
| Baseline Gram-positive Pathogens | 181 (70%) | 178 (72%) |
| MRSA | 111 (43%) | 113 (46%) |
| MSSA | 61 (24%) | 57 (23%) |
| PVL (-) <i>S. aureus</i> (combined) | 83% | 85% |
| <i>Streptococcus pneumoniae</i> | 15 (6%) | 7 (3%) |
| <i>Enterococcus faecalis</i> | 3 (1%) | 6 (2%) |
| <i>Enterococcus faecium</i> | 1 (<1%) | 0 (0%) |
| VAP | | |
| MRSA VAP | 35 (42%) | 28 (38%) |
| MSSA VAP | 23 (28%) | 23 (32%) |

TLV=telavancin, VAN=vancomycin, PVL (-)=absence of Panton-Valentine Leukocidin gene, VAP=ventilator-associated pneumonia, MRSA=methicillin-resistant *S. aureus*, MSSA=methicillin-susceptible *S. aureus*

According to the Applicant’s synopsis of Study 0015, for patients in the ME Population who had a single Gram-positive pathogen and no Gram negative pathogens isolated at Baseline, cure rates were numerically higher in the telavancin group compared with the vancomycin group (82.9%

vs. 75.0%). The 95% CI around the treatment difference included zero. In patients who had only MRSA or only MSSA, clinical cure rates were numerically higher in the telavancin group compared with the vancomycin group (84.0% vs. 77.1% and 83.3% vs. 64.7%, respectively). For these patients, the 95% CI around the treatment difference included zero. In patients with mixed Gram positive and Gram negative pathogens at Baseline, cure rates were numerically lower in the telavancin group than in the vancomycin group (75.0% vs. 82.6%) and the 95% CI around the treatment difference included zero.

According to the Applicant's analysis, for patients in the ME Population, the most common pathogen isolated at Baseline (without regard to whether patients had one or multiple baseline pathogens) was *S. aureus*. Clinical cure rates were numerically higher in the telavancin group compared with the vancomycin group for this pathogen. Cure rates were also evaluated by methicillin susceptibility of the *S. aureus* isolated at Baseline. The clinical cure rates were numerically higher in the telavancin group compared with the vancomycin group for both MRSA and MSSA (81% vs. 75% and 81% vs. 72%, respectively).

Microbiological eradication rates in the MAT and ME Populations were similar to the clinical cure rates in these populations.

Quality of Respiratory Tract Specimens

In assessing the various sources of respiratory tract specimens obtained from patients enrolled in Study 0015, sputum and endotracheal aspirates were obtained from approximately 80% of the total patients as depicted in the table below. Sputum samples were the most common respiratory tract specimens collected from approximately 45% of all patients enrolled in this trial across both treatment arms. Approximately 35% of the patients in both treatment groups had ETA as the primary respiratory tract specimen and approximately 3-4% had the primary respiratory tract specimen listed as missing. Nares cultures were employed in four patients (one in the telavancin treatment group and three in the vancomycin treatment group.) However, the Applicant did not provide any justification to support the use of bacterial isolates obtained from nares cultures as being valid indicators of lower respiratory tract bacterial pathogens in patients with NP and VAP.

Table 26: FDA Medical Officer Summary Table of Respiratory Specimen Source by Subject Count* for Study 0015, AT Population

| RESPIRATORY SPECIMEN SOURCE | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
|---|------------------------------|------------------------------|
| SPUTUM | 169 (45.4) | 174 (46.5) |
| ENDOTRACHEAL ASPIRATION | 132 (35.5) | 134 (35.8) |
| MINI-BRONCHOALVEOLAR LAVAGE | 27 (7.3) | 21 (5.6) |
| BRONCHOALVEOLAR LAVAGE | 20 (5.4) | 22 (5.9) |
| MISSING | 14 (3.8) | 13 (3.5) |
| BLIND BRONCHIAL SUCTIONING | 12 (3.2) | 9 (2.4) |
| OTHER: QUANTITATIVE TRACHEAL LAVAGE | 4 (1.1) | 2 (0.5) |
| PROTECTED SPECIMEN BRUSH | 2 (0.5) | 2 (0.5) |
| OTHER: NARES | 1 (0.3) | 3 (0.8) |
| OTHER: QUANTATIVE TRACHEAL LAVAGE > 10 | 1 (0.3) | 1 (0.3) |
| OTHER: QUANTATIVE TRACHEAL LAVAGE >10 POLYS | 1 (0.3) | 0 (0.0) |
| OTHER: PROTECTED ENDOTRACHEAL SPECIMEN | 0 (0.0) | 1 (0.3) |
| OTHER: QTL WBC >10 QUANTITATIVE TRACHEAL LAVAGE | 0 (0.0) | 1 (0.3) |
| OTHER: QUANTATIVE TRACHEAL LAVAGE >10 | 0 (0.0) | 2 (0.5) |
| OTHER: BRONCHIAL SUCTION VIA FIBROBRONCHOSCOPY | 0 (0.0) | 0 (0.0) |
| OTHER: PLEURAL EFFUSION | 0 (0.0) | 0 (0.0) |
| OTHER: PLEURAL FLUID | 0 (0.0) | 0 (0.0) |
| OTHER: TRACHEOSTOMY ASPIRATE | 0 (0.0) | 0 (0.0) |
| OTHER: QUANTATIVE TRACHEAL LAVAGE <5 | 0 (0.0) | 1 (0.3) |

* Some subjects had specimens from multiple respiratory sources.

The Applicant provided overall quality assessments for sputum specimens in the electronic dataset submission as summarized in the table below:

Table 27: Quality and Culture Positivity of Baseline Sputum Specimens, Study 0015, AT Population (from Applicant's 0015 Clinical Study Report, Supporting Table 64)

| | Telavancin n (%) | Vancomycin n (%) | Overall |
|---|---------------------|---------------------|---------|
| Any Sputum Specimen Quality | 278 (100) | 275 (100) | 553 |
| Culture positive | 155 (55.8) | 144 (52.4) | 299 |
| Culture negative | 123 (44.2) | 131 (47.6) | 254 |
| Appropriate Sputum Specimen Quality | 164 (59.0) | 158 (57.5) | 322 |
| Culture positive | 104 (37.4) | 85 (30.9) | 189 |
| Culture negative | 60 (21.6) | 73 (26.5) | 133 |
| Potentially Appropriate Sputum Specimen Quality | 53 (19.1) | 63 (22.9) | 116 |
| Culture positive | 27 (9.7) | 29 (10.5) | 56 |
| Culture negative | 26 (9.4) | 34 (12.4) | 60 |
| Inappropriate Sputum Specimen Quality | 50 (18.0) | 45 (16.4) | 95 |
| Culture positive | 20 (7.2) | 24 (8.7) | 44 |
| Culture negative | 30 (10.8) | 21 (7.6) | 51 |
| Quality Unknown | 11 (4.0) | 9 (3.3) | 20 |
| Culture positive | 4 (1.4) | 6 (2.2) | 10 |
| Culture negative | 7 (2.5) | 3 (1.1) | 10 |

n (%)=number of sputum specimens (% of any sputum specimen quality)

FDA Medical Officer Comments: The FDA Medical Officer conducted a sensitivity analysis of the microbiological evaluability of all patients who had sputum specimens of inappropriate or unknown quality, as their specimens were considered inadequate for the identification of true pathogens. Of the 169 telavancin-treated patients with sputum specimens at baseline, 12 (7.1%) patients had specimens assessed as inappropriate or unknown sputum quality. Four (33.3%) of the 12 patients were assessed as clinically and microbiologically evaluable by the Applicant. However, only one of the four patients had a confirmatory positive blood culture for the identical pathogen from the sputum culture, and the remaining three patients did not have other confirmatory respiratory tract or blood cultures for the bacterial isolate (all MRSA) originally identified from the sputum specimens. Thus, it is this FDA Medical Officer's opinion that those three patients (0015-38271-4112, 0015-38271-4119, and 0015-38271-4589) should be considered non-evaluable for the ME population.

*Similarly, of the 174 vancomycin-treated patients with sputum specimens at baseline, 16 (9.2%) patients had specimens assessed as inappropriate or unknown sputum quality. Nine (56.3%) of the 16 patients were assessed as clinically and microbiologically evaluable by the Applicant. However, only one of the nine patients had a confirmatory positive blood culture for the identical pathogen from the sputum culture, one patient had the sputum pathogen confirmed based on cultures of another respiratory tract specimen, and the remaining seven patients did not have other confirmatory respiratory tract or blood cultures for the bacterial isolates (5 MRSA, 1 MSSA, and 1 MRSA with *Achromobacter xylosoxidans*) originally identified from the sputum specimens. Thus, it is this FDA Medical Officer's opinion that those seven patients (0015-19019-4665, 0015-33017-4643, 0015-33018-4536, 0015-38148-4147, 0015-38270-4421, 0015-38271-4754, and 0015-41010-4445) should be considered non-evaluable for the ME population.*

The FDA Medical Officer conducted an exploratory analysis of all endotracheal aspirate (ETA) specimens using published rejection criteria (4). The authors of that publication recommended that ETA specimens that show no organisms by Gram Stain and those with > 10 squamous epithelial cells per LPF should be rejected. As depicted in the tables below, a total of 22 subjects had ETA with ≥ 10 Epithelial Cells/HPF and a total of 46 patients had ETA with negative Gram stains; those ETA specimens should have been rejected, the specimens classified as inadequate, and any identified bacterial isolates should not have been considered as pathogens.

Table 28: FDA Medical Officer Table of Subject Count with inadequate Endotracheal aspirate specimens based on published rejection criteria

| Rejection criteria | Telavancin | Vancomycin | Total |
|--------------------------------|------------|------------|-------|
| Negative Gram stain | 23 | 23 | 46 |
| ≥ 10 Epithelial Cells/HPF | 13 | 9 | 22 |

This FDA Medical Officer contends that all patients for which the bacterial pathogens identified from ETA specimens meeting the above rejection criteria that cannot be confirmed based on another acceptable respiratory tract culture or blood culture should be considered non-evaluable for the ME population.

All-cause Mortality

The Applicant’s original summary of all-cause mortality during the study period is presented for the AT Population in the following table. Only those deaths that occurred before the Follow-up/TOC Visit or within 28 days after last study medication if no Follow-up/TOC Visit occurred were included. As depicted in the table, there was a mortality imbalance with more deaths recorded in the telavancin arm compared to the vancomycin arm during or after treatment for Study 0015 .

Table 29: All-Cause Mortality, AT Population, Study 0015 (from Applicant's 0015 Clinical Study Report, Table 8-42)

| | Telavancin | Vancomycin | Difference (95% CI) [1] |
|---|------------|------------|-------------------------|
| Deaths while receiving study medication | | | |
| Within-treatment mortality | 48 (12.9%) | 45 (12.0%) | 0.9% (-3.9%, 5.6%) |
| Deaths during or after study medication | | | |
| During or after treatment mortality | 80 (21.5%) | 62 (16.6%) | 4.9% (-0.7%, 10.6%) |

[1] Difference in mortality rates (telavancin – vancomycin); 2-sided 95% CI on the difference.

^= Confidence interval uses Agresti-Caffo adjustment

The all-cause mortality rate was approximately 5% higher in the telavancin arm, although it did not reach statistical significance. However, the upper bound of the 95% CI was 10.6%, which exceeds the NI margin range of 7-10% based on the all-cause mortality endpoint discussion at the AIDAC Meeting in 2008 and at the 2009 public workshop for issues in clinical trial design for NP and VAP conducted earlier this year. This is a worrisome finding that suggests that telavancin is inferior to vancomycin for the treatment of NP. Additional information requests were issued by the Agency to obtain further mortality data as described in other sections of this report.

The applicant’s time window for mortality primarily included deaths that occurred before and up to the Follow-up visit. This window choice raised concern that some deaths that occurred between the Follow-up visit and Day 28 post-treatment may have been missed. Thus, in an information request dated February 25, 2009, the Agency requested additional data delineating the deaths that occurred up to 28 days post-treatment. The Applicant provided the following table to summarize the requested mortality information. Note that the data is not presented by individual study; instead, only pooled data is provided. Please refer to Section 6.1.5 of this report for further discussion of the new mortality data.

Table 30: Applicant's Summary Table of Deaths occurring between Start of Study Drug and EOT Visit + 28 Days, Studies 0015 and 0019, AT Population

| | Number of patients | |
|--|---------------------|---------------------|
| | Telavancin N=749 | Vancomycin N=754 |
| Deaths between Start of Study Drug and EOT Visit + 28 days | 160 (21.4%) | 147 (19.5%) |
| Deaths between EOT Visit and EOT Visit + 28 days | 113 | 104 |
| Deaths between TOC Visit and EOT Visit + 28 days | 11 | 6 |

Subsequent to providing the mortality data above, the Applicant notified the Division of additional mortality data identified from the clinical database, safety database, and data collected in a 10-week pharmacoeconomic (PE) study and provided the additional data in response to an information request from the Division dated June 9, 2009.

The Applicant noted in the response to that information request that the CRFs for the PE study did not explicitly prompt for date of death. The Applicant inferred death date by algorithmic consideration of multiple data fields collected on the substudy CRF. The algorithm was unable to infer death dates for 43 patients and, following a manual review in a blinded fashion, death dates were inferred for 10 patients. Thus, there were 33 patients with no date of death. According to the Applicant's analysis, 391 deaths occurred on Study Day 49 (which encompasses the maximum protocol-specified treatment period of 21 days plus 28 days post end-of therapy), 33 deaths occurred on Study Day 50 or later, and 33 deaths have an unknown date of death.

In response to an information request from the Division dated July 31, 2009, the Applicant provided summary tables for the study deaths, a list of patients for which mortality status is unknown up to Study Day 28, a list of patients for whom mortality status is unknown up to last study day + 28 days, and an electronic dataset. The Applicant also provided narratives for the deaths. The two summary tables are provided below:

Table 31: Applicant's Summary of Deaths Occurring between Start of Study Drug and Start of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 92 (25%) | 73 (20%) | 80 (21%) | 88 (23%) | 172 (23%) | 161 (21%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 70 (19%) | 51 (14%) | 54 (14%) | 68 (18%) | 124 (17%) | 119 (16%) |
| Alive or censored | 280 (75%) | 301 (80%) | 299 (79%) | 290 (77%) | 579 (77%) | 591 (79%) |
| Censored* | 126 (34%) | 134 (36%) | 113 (30%) | 103 (27%) | 239 (32%) | 237 (32%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

Table 32: Applicant's Summary of Deaths Occurring between Start of Study Drug and End of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 102 (27%) | 82 (22%) | 88 (23%) | 99 (26%) | 190 (25%) | 181 (24%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 80 (22%) | 60 (16%) | 62 (16%) | 79 (21%) | 142 (19%) | 139 (18%) |
| After follow-up visit | 22 (6%) | 19 (5%) | 18 (5%) | 21 (6%) | 40 (5%) | 40 (5%) |
| Alive or censored | 270 (73%) | 292 (78%) | 291 (77%) | 279 (74%) | 561 (75%) | 571 (76%) |
| Censored* | 145 (39%) | 159 (43%) | 139 (37%) | 126 (33%) | 284 (38%) | 285 (38%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

FDA Medical Officer Comments: The risk difference for deaths occurring between start of study drug and start of study drug + 28 Days for the telavancin and the vancomycin arms in Study 0015 was 5.2% with 95% confidence interval of (-0.7%, 11.2%). Similarly, the risk difference for deaths occurring between start of study drug and end of study drug + 28 Days was 5.5% (-0.7%, 11.7%). This is a worrisome finding, since the size of the risk difference for death could be negligible or it could be quite large (>11%) for patients treated with telavancin, which is indicative of a critical efficacy and safety signal and suggests that telavancin is inferior to vancomycin in the treatment of NP.

Of additional concern is the large percentage of censored events among the submitted mortality data. In the analysis of mortality for deaths occurring between start of study drug and start of study drug + 28 Days in Study 0015, censored data was provided for 126 patients (33.9%) treated with telavancin and 134 (35.8%) treated with vancomycin. Similarly, in the deaths occurring between start of study drug and end of study drug + 28 Days, censored data was provided for 145 patients (39%) treated with telavancin and 159 (42.5%) treated with vancomycin. The high percentage of censored data is unacceptable, raising concern that the actual number of deaths is underestimated in both treatment arms. Thus, unless additional mortality data is provided for the patients currently reported with censored events, the all-cause mortality data provided by the Applicant in response to this information request is considered to be uninterpretable.

5.3.2 Protocol 0019: A Phase 3, Randomized, Double-blind, Parallel-group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-acquired Pneumonia with a Focus on Patients with Infections Due to Methicillin-resistant *Staphylococcus aureus*

5.3.2.1 Protocol Overview

The current study was one of two Phase 3 investigations (with Study 0015) conducted under an identical protocol to assess the safety and efficacy of telavancin in adult patients with HAP due to Gram-positive bacteria with an emphasis on patients with infections due to MRSA. As Study 0019 was conducted under an identical protocol to Study 0015, please refer to Section 5.3.1.1 above regarding on the Protocol overview, Inclusion and Exclusion Criteria, Study Procedures, and Statistical Considerations with comments from the FDA Medical Officer.

The primary objective of this study was to compare the efficacy and safety of telavancin with vancomycin in the treatment of adults with Gram-positive hospital-acquired pneumonia (HAP) with an emphasis on patients with infections due to MRSA. A key secondary objective of this study was to pool the data from this study with those from a second study of identical design (Study 0015) and to assess the superiority of telavancin to vancomycin in patients with MRSA infections.

5.3.2.2 Study Results

5.3.2.2.1 Demographic and Baseline Characteristics

The All Treated population consisted of 757 patients, including 377 in the telvancin treatment group and 380 in the vancomycin treatment group. Of note, two patients originally randomized to vancomycin were actually treated with telavancin. US sites enrolled 106 patients (14%), whereas non-US sites enrolled a total of 651 patients (86%) as depicted in the following table:

Table 33: FDA Medical Officer Summary Table of Subject Count by Country, Study 0019, AT Population

| COUNTRY | Subject Count n (%) |
|-------------------|---------------------|
| UNITED STATES | 106 (14.0) |
| ISRAEL | 76 (10.0) |
| CHINA | 64 (8.5) |
| MEXICO | 60 (7.9) |
| KOREA | 53 (7.0) |
| RUSSIA | 50 (6.6) |
| BULGARIA | 40 (5.3) |
| ARGENTINA | 39 (5.2) |
| BRAZIL | 33 (4.4) |
| THAILAND | 33 (4.4) |
| GEORGIA | 30 (4.0) |
| AUSTRALIA | 23 (3.0) |
| UKRAINE | 18 (2.4) |
| LITHUANIA | 17 (2.2) |
| PHILIPPINES | 17 (2.2) |
| SERBIA/MONTENEGRO | 17 (2.2) |
| CANADA | 13 (1.7) |
| SLOVAKIA | 12 (1.6) |
| POLAND | 10 (1.3) |
| SOUTH AFRICA | 10 (1.3) |
| LEBANON | 9 (1.2) |
| ROMANIA | 7 (0.9) |
| CHILE | 5 (0.7) |
| CROATIA | 4 (0.5) |
| CZECH REPUBLIC | 4 (0.5) |
| FRANCE | 2 (0.3) |
| GREECE | 2 (0.3) |
| SPAIN | 2 (0.3) |
| ESTONIA | 1 (0.1) |

FDA Medical Officer Comments: Patients were enrolled from 29 countries worldwide. Approximately 14% were enrolled from sites in the United States, which was the country with the highest enrollment percentage. Enrollment at non-US sites was variable with Israel accounting for approximately 10% of patients, whereas <1% of patients were enrolled from eight other nations.

The Applicant developed country groupings (Groups 1, 2 and 3) as a stratification to ensure balanced assignment of patients to the two treatment groups based on medical practice patterns. The following table from the Applicant’s 0019 Clinical Study Report (Table 7-2) provides the country groupings used for this study:

Table 34: Country Groupings (from Applicant's 0019 Clinical Study Report, Table 7-2)

| | |
|----------|-------------------|
| Group 1 | Australia |
| | Belgium |
| | Canada |
| | France |
| | Israel |
| | Spain |
| | United States |
| Group 2 | Argentina |
| | Brazil |
| | Chile |
| | South Africa |
| Group 3 | Bulgaria |
| | China |
| | Croatia |
| | Czech Republic |
| | Estonia |
| | Georgia |
| | Greece |
| | Korea |
| | Lebanon |
| | Lithuania |
| | Mexico |
| | Philippines |
| | Poland |
| | Romania |
| | Russia |
| | Serbia/Montenegro |
| | Slovakia |
| Thailand | |
| Ukraine | |

The following table depicts the subject enrollment by study investigator. No single investigator enrolled 10% or more of study patients. Forty-one investigators enrolled only one patient in the clinical trial. Galia Rahav was the largest single enroller accounting for 7% of subjects in both treatment arms.

Table 35: FDA Medical Officer Summary of Subject Enrollment by Study Investigator (only includes study sites with enrollment ≥10 subjects per Investigator, Study 0019, AT Population)

| Investigator | Total subject count | TELAVAN CIN N=377 n (%) | VANCOMY CIN N=380 n (%) |
|-----------------------|---------------------|-------------------------------|-------------------------------|
| Rahav, Galia | 54 | 27 (7) | 27 (7) |
| Ortiz, Alejandro | 24 | 13 (3) | 11 (3) |
| Rocha, Marcello | 24 | 12 (3) | 12 (3) |
| Mootsikapun, Piroon | 21 | 12 (3) | 9 (2) |
| Magana, Martin | 18 | 8 (2) | 10 (3) |
| Stock, Kent | 17 | 9 (2) | 8 (2) |
| Luna, Carlos | 15 | 8 (2) | 7 (2) |
| Steinecker, R. Scott | 14 | 7 (2) | 7 (2) |
| Flynn, Jr., William | 13 | 8 (2) | 5 (1) |
| Tamariz, Antonio | 13 | 7 (2) | 6 (2) |
| Park-20019, Myung Jae | 12 | 2 (<1) | 10 (3) |
| Shmelev, Evgeniy | 12 | 3 (<1) | 9 (2) |
| Shpagina, Lyubov | 12 | 6 (2) | 6 (2) |
| Intalaporn, Poj | 11 | 9 (2) | 2 (<1) |
| Kavtaradze, George | 11 | 5 (1) | 6 (2) |
| Koura, Firas | 11 | 8 (2) | 3 (<1) |
| Oren, Ilana | 11 | 5 (1) | 6 (2) |
| Brodnan, John | 10 | 6 (2) | 4 (1) |
| Dretler, Robin Henry | 10 | 7 (2) | 3 (<1) |
| Simanenkov, V. | 10 | 5 (1) | 5 (1) |
| Sun, Sheng Hua | 10 | 4 (1) | 6 (2) |
| Wang, Guang Fa | 10 | 5 (1) | 5 (1) |

Baseline Patient Characteristics

In terms of baseline characteristics, the telavancin and vancomycin treatment groups were comparable with respect to age, gender, race/ethnicity, body mass index, baseline renal function (serum creatinine), hemodialysis, acute renal failure, mechanical ventilation at baseline, and incidence of VAP. The mean severity of illness as measured by APACHE II scores was approximately 16-17 in both groups for patients that had all components included in the APACHE II score determination. There were similar numbers of patients with concomitant diabetes mellitus and cardiac co-morbid conditions. The following table provides a summary of selected baseline demographic characteristics stratified by treatment group for Study 19. There were no statistically significant differences across treatment groups for any of the baseline characteristics included in the table.

Table 36: FDA Medical Officer Summary Table of Baseline Demographic Characteristics, Study 0019, AT Population

| Characteristic | TLV N=377 | VAN N=380 | 95% CI for difference* |
|--|--------------|--------------|---------------------------|
| Age, mean, yrs | 61±17.8 | 62±18 | |
| median | 65 | 65 | |
| range | 18-100 | 18-97 | |
| Gender | | | |
| Female | 125 (33%) | 124 (33%) | 0.5 (-6.2, 7.2) |
| Male | 252 (67%) | 256 (67%) | -0.5 (-7.2, 6.2) |
| Race/Ethnicity | | | |
| White/Caucasian | 248 (66%) | 254 (67%) | -1.1 (-7.8, 5.7) |
| All others (combined) | 129 (34%) | 126 (33%) | 1.1 (-5.7, 7.8) |
| Body Mass Index (BMI) | | | |
| Number of patients having BMI | 377 (100%) | 380 (100%) | 0 (0,0) |
| mean BMI (±SD) | 24.8 (±5.69) | 24.7 (±5.35) | |
| median | 24.2 | 24.1 | |
| Baseline Serum Creatinine (Central Lab) | | | |
| Serum Creatinine ≤1.2 mg/dL | 301 (80%) | 295 (78%) | 2.2 (-3.6, 8.0) |
| Serum Creatinine >1.2 mg/dL | 68 (18%) | 74 (19%) | -1.4 (-7.0, 4.1) |
| Missing Serum Creatinine | 8 (2%) | 11 (3%) | -0.8 (-3.0, 1.5) |
| Renal Impairment | | | |
| Acute renal failure | 30 (8%) | 29 (8%) | 0.3 (-3.5, 4.1) |
| Hemodialysis | 3 (<1%) | 5 (1%) | -0.5 (-2.0, 0.9) |
| Apache II Scores | | | |
| 0-13 | 162 (43%) | 153 (40%) | 2.7 (-4.3, 9.7) |
| 14-19 | 135 (36%) | 129 (34%) | 1.9 (-4.9, 8.7) |
| ≥20 | 80 (21%) | 98 (26%) | -4.6 (-10.6, 1.5) |
| Mean score ± SD, all patients | 15±5.9 | 16±6.3 | |
| Patients having all APACHE II components | 182 (48.3%) | 200 (52.6%) | -4.4 (-11.5, 2.8) |
| Mean score ±SD, patients with all APACHE II components | 16.5 ±5.7 | 17.1± 6.2 | |
| Median score, patients with all APACHE II components | 16 | 17 | |
| Mechanical Ventilation | | | |
| Ventilator-associated Pneumonia (VAP) (AT) | 113 (30%) | 111 (29.2%) | 0.8 (-5.7, 7.3) |
| Vented at Baseline | 175 (46%) | 175 (46%) | 0.4 (-6.7, 7.5) |
| Selected Co-morbid Conditions | | | |
| Diabetic status (yes) | 69 (18%) | 65 (17%) | 1.2 (-4.2, 6.6) |
| History of diabetes mellitus | 85 (23%) | 77 (20%) | 2.3 (-3.6, 8.1) |
| History of atrial fibrillation | 65 (17%) | 48 (13%) | 4.6 (-0.5, 9.7) |
| History of congestive heart failure | 59 (16%) | 63 (17%) | -0.9 (-6.2, 4.3) |
| History of myocardial infarction | 36 (10%) | 44 (12%) | -2.0 (-6.4, 2.3) |
| History of left ventricular hypertrophy | 24 (6%) | 32 (8%) | -2.1 (-5.8, 1.7) |
| Other cardiac diseases | 159 (42%) | 153 (40%) | 1.9 (-5.1, 8.9) |
| ≥1 cardiac co-morbidity | 219 (58%) | 212 (58%) | 2.3 (-4.8, 9.4) |

*difference = TLV – VAN; TLV = telavancin; VAN = vancomycin

Baseline CPIS were reported for all patients in the Applicant’s electronic dataset submission, although the CPIS is only relevant to assessing the likelihood for VAP. As depicted in the table below, there were no statistically significant differences in the number of VAP patients having all CPIS components at baseline in the telavancin arm compared to the vancomycin arm. The median CPIS in the patients with VAP was 6, which is considered the minimum threshold for identifying patients at high likelihood for VAP using this scoring system. There was a substantial proportion of VAP patients having all CPIS components at Baseline who had CPIS scores ≤ 6 , suggesting that they were less likely to have had pneumonia.

Table 37: FDA Medical Officer Summary Table of Baseline Clinical Pulmonary Infection Scores (CPIS), Study 0019, AT Population

| Baseline CPIS (AT population) | TLV N=377 | VANCO N=380 | 95% CI for difference (TLV – VAN) |
|--|----------------------|------------------------|--|
| Mean (SD), all patients | 5.7 (1.55) | 5.9 (1.44) | |
| Median, all patients | 6.0 | 6.0 | |
| Number of VAP patients (total) | 113 (100%) | 111 (100%) | 0.8 (-5.7, 7.3) |
| Mean CPIS \pm SD, all VAP patients | 6.2 \pm 1.5 | 6.0 \pm 1.5 | |
| Median CPIS, all VAP patients | 6.0 | 6.0 | |
| VAP patients having all CPIS components at Baseline | 95 (84%) | 95 (86%) | -1.5 (-10.9, 7.9) |
| Mean CPIS \pm SD for VAP patients having all CPIS components at Baseline | 6.4 \pm 1.5 | 6.0 \pm 1.5 | |
| Median CPIS for VAP patients having all CPIS components at Baseline | 6.0 | 6.0 | |
| CPIS ≤ 6 , VAP patients having all CPIS components at Baseline | 49 (52%) | 57 (60%) | -8.4 (-22.5, 5.7) |
| CPIS >6 , VAP patients having all CPIS components at Baseline | 46 (48%) | 38 (40%) | 8.4 (-5.7, 22.5) |

FDA Medical Officer Comments: The Applicant’s modification of the recorded axillary temperatures by the addition of one degree Celsius to the recorded value on the CRF for the purposes of analysis created considerable uncertainty in assessing how informative APACHE II and CPIS scores were with respect to severity of illness and likelihood for VAP at baseline as described previously in Section 5.3.1.1.2 of this report.

A substantial number of patients had one or more missing components of the APACHE II and CPIS scores at baseline and at subsequent timepoints, which contributed uncertainty as to the patients’ actual severity of illness and likelihood for pneumonia (VAP), respectively. Limiting analysis only to VAP patients who had all CPIS components at baseline revealed a median CPIS score of 6. However, the median CPIS score of 6 for this subgroup did not provide reassurance that all patients had the disease (VAP) being studied. A substantial proportion of patients with VAP had CPIS ≤ 6 in both treatment arms (52% in the telavancin group and 60% in the vancomycin group). Singh and colleagues (12) reported in their published study of empiric antibiotic therapy for patients with pulmonary infiltrates in the ICU that patients with CPIS ≤ 6 were those in whom “pneumonia was considered unlikely”. Thus, there is a substantial

proportion of patients enrolled in the study with a preliminary diagnosis of VAP in whom there is a low likelihood for having bacterial VAP and whose actual diagnosis remains uncertain.

5.3.1.2.3 Analysis Populations

As described in the Applicant's 0019 Clinical Study Report, four analysis populations were defined for efficacy-related summaries similar to those described previously for Study 0015. These four populations were not mutually exclusive; a patient could belong to more than one population. In all four populations, patients were associated with the treatment group assigned by the randomization:

- All-treated (AT): All patients who received any amount of study medication
- Modified All-treated (MAT): Patients 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, ETA, BBS, BAL, mini-BAL, or PSB;
- Clinically Evaluable (CE): Patients in the AT Population whose adherence to protocol expectations made it reasonable to infer that his/her clinical outcome reflected the effect of study medication;
- Microbiologically Evaluable (ME): Patients in the CE Population who also had a Gram-positive baseline respiratory pathogen, as defined above for the MAT Population.

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 qualified a patient for the MAT Population. If baseline respiratory tract and blood cultures identified different respiratory pathogens, then only those pathogens identified from respiratory tract specimens were deemed baseline respiratory pathogens.

The analysis populations as summarized by subject count are provided in the following table. Of note, there was a similar percentage of telavancin-treated and vancomycin-treated patients in the CE population. In the MAT and ME populations, most patients had pathogens recovered from respiratory tract specimens. Only a small proportion had pathogens recovered only from blood cultures. Approximately 25% of patients in the MAT population in both treatment arms had NP due to Gram-negative pathogens only. Additionally, two patients were randomized to vancomycin, but were treated with telavancin in this study. Eleven patients in the vancomycin arm were treated with anti-staphylococcal penicillins.

Table 38: FDA Medical Officer Table of Subject Counts in the Efficacy Analysis Populations, Study 0019

| Study Populations | Telavancin | Vancomycin |
|---|------------|------------|
| All Randomized | 386 | 385 |
| Randomized but no treated | 9 | 5 |
| Randomized to VANCO, but treated with TLV | 0 | 2 |
| All Treated (AT) | | |
| Efficacy | 377 (100%) | 380 (100%) |
| Safety | 379 | 378 |
| Enrolled under Original Protocol (permitted imipenem use) | 60 | 55 |
| Enrolled under Amendment 1 (prohibited imipenem) | 317 | 325 |
| Modified AT (MAT) | 303 (80%) | 282 (74%) |
| CE | 171 (45%) | 170 (45%) |
| ME | 135 (36%) | 124 (33%) |
| Gram-negative pathogen only (MAT) | 77 (25%) | 74 (26%) |
| Gram-negative pathogen only (CE) | 0 (0) | 0 (0) |
| Patients in VANCO group who received anti-staph penicillins | NA | 11 |

CE=clinically evaluable; ME=microbiologic evaluable; NA=not applicable; TLV=telavancin; VANCO=vancomycin

5.3.1.2.4 Patient Disposition

The following table summarizes the disposition of patients in terms of discontinuation of study medication in the AT population. Among telavancin-treated patients in the AT population, 228 (60%) completed their course of study medication while 149 (40%) did not complete it. Among vancomycin-treated patients in the AT population, 224 (59%) completed their course of study medication while 156 (41%) did not complete it. The most common reasons cited for premature discontinuation of study drug in both treatment groups were death, unsatisfactory therapeutic response, and Gram-positive coverage no longer indicated. Additionally, approximately 4% of patients in both treatment arms discontinued study medication prematurely due to an adverse event, and a few more telavancin-treated patients discontinued study drug due to having two consecutive ECGs with QTc > 500 msec compared to vancomycin-treated patients. Two vancomycin-treated patients discontinued study medication prematurely due to persistent *S. aureus* bacteremia, and <1% of patients in both treatment arms prematurely discontinued study medication due to meningitis, endocarditis, or osteomyelitis.

Table 39: Disposition of Patients: Discontinuation of Study Medication, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 7-4)

| | Study 0019 | | |
|---|---------------------|---------------------|------------------|
| | Telavancin N=377 | Vancomycin N=380 | Overall N=757 |
| Completed course of study medication | 228 (60%) | 224 (59%) | 452 (60%) |
| Resolution of signs and symptoms in ≤21 days | 224 (59%) | 216 (57%) | 440 (58%) |
| Infection not resolved, but patient received maximum allowable 21 days of treatment | 4 (1%) | 8 (2%) | 12 (2%) |
| Premature discontinuation of study medication | 149 (40%) | 156 (41%) | 305 (40%) |
| Unsatisfactory therapeutic response, did not receive maximum allowable 21 days of treatment | 25 (7%) | 24 (6%) | 49 (6%) |
| Death | 33 (9%) | 31 (8%) | 64 (8%) |
| Two consecutive ECGs with QTc > 500 msec [1] | 5 (1%) | 2 (<1%) | 7 (<1%) |
| Adverse event | 16 (4%) | 15 (4%) | 31 (4%) |
| Patient withdrew consent | 15 (4%) | 15 (4%) | 30 (4%) |
| Major protocol deviation | 2 (<1%) | 4 (1%) | 6 (<1%) |
| Infection due to Gram-negative organisms only | 5 (1%) | 2 (<1%) | 7 (<1%) |
| Infection due to <i>Stenotrophomonas maltophilia</i> or <i>Burkholderia cepacia</i> | 1 (<1%) | 1 (<1%) | 2 (<1%) |
| Persistent <i>S. aureus</i> bacteremia | 0 | 2 (<1%) | 2 (<1%) |
| Gram-positive coverage no longer clinically indicated | 42 (11%) | 45 (12%) | 87 (11%) |
| Documented endocarditis, osteomyelitis, or meningitis | 1 (<1%) | 2 (<1%) | 3 (<1%) |
| Required non-study antibiotics | 2 (<1%) | 6 (2%) | 8 (1%) |
| Other | 2 (<1%) | 7 (2%) | 9 (1%) |

[1] Based on machine-read ECG results versus a manual read.

The Investigator could select “major protocol deviation” as the primary reason for discontinuation of study medication on the drug discontinuation page of the CRF. Overall, six patients (<1%) were classified by the Investigator as discontinuing study medication due to a major protocol deviation: two patients (<1%) were in the telavancin group and four patients (1%) were in the vancomycin group. Of these six patients, one patient (0019-08002-6181) received the wrong study medication (see below). One additional patient (0019-44010-6452), who was not captured in Table 7-4 as a major protocol deviation, also received the wrong study medication. All seven patients are discussed briefly below:

- Patient 0019-18005-6035 (telavancin) was treated with colistimethate (nonstudy medication) on Study Day 3. This was not a true protocol deviation, as patients were allowed to be treated with nonstudy antibiotics if a resistant Gram-negative pathogen was identified.
- Patient 0019-50000-6424 (telavancin) had planocellular lung cancer reported on Study Day 8, which was recorded as a major protocol deviation by the Investigator. This was not a true protocol deviation as the diagnosis was not known at Baseline.
- Patient 0019-08002-6181 (vancomycin) was randomized to vancomycin and treated with telavancin.
- Patient 0019-18008-6080 (vancomycin): By the study site’s policy, *S. pneumoniae* should not have been treated with glycopeptides; therefore, study medication was

stopped early and antibiotic coverage for pneumonia continued with IV ceftriaxone after EOT. Patient was responding to study medication.

- Patient 0019-25029-6663 (vancomycin) received study medication up to Study Day 4 when a nonstudy physician decided to discontinue study medication because of nonmedical reasons. Patient continued to receive antibiotic coverage for pneumonia with IV Augmentin and amikacin.
- Patient 0019-36003-6642 (vancomycin) was discontinued from the study on Study Day 8 due to the primary diagnosis of community-acquired pneumonia, evident at study entry, which was inconsistent with the protocol.
- Patient 0019-44010-6452 (vancomycin) was randomized to vancomycin and treated with telavancin.

The following table summarizes the disposition of patients in terms of study completion in the AT population (from Applicant’s Table 7-5, 0019 Clinical Study Report). Among telavancin-treated patients in the AT population, 289 (77%) completed the follow-up visit with the majority of them having the follow-up visit between 7-14 days after end of therapy. Among vancomycin-treated patients in the AT population, 289 (76%) completed the follow-up visit with the majority of them having the follow-up visit between 7-14 days after the end of therapy. The most common reason for early termination in both treatment groups was death. Approximately 1-2% were lost to follow-up.

Table 40: Disposition of Patients: Study Completion Data, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 7-5)

| | Study 0019 | | |
|--------------------------------------|------------|------------|-----------|
| | Telavancin | Vancomycin | Overall |
| | N=377 | N=380 | N=757 |
| Completed Follow-up Visit | 289 (77%) | 289 (76%) | 578 (76%) |
| Number of days after last study drug | | | |
| 6 days or less | 7 (2%) | 7 (2%) | 14 (2%) |
| 7-14 days | 248 (66%) | 249 (66%) | 497 (66%) |
| 15 days or more | 34 (9%) | 33 (9%) | 67 (9%) |
| Patients who terminated early | 88 (23%) | 91 (24%) | 179 (24%) |
| Reason for early termination | | | |
| Death | 67 (18%) | 71 (19%) | 138 (18%) |
| Withdrew consent | 13 (3%) | 11 (3%) | 24 (3%) |
| Lost to follow-up | 5 (1%) | 8 (2%) | 13 (2%) |
| Transfer to another hospital | 2 (<1%) | 0 | 2 (<1%) |
| Other | 1 (<1%) | 1 (<1%) | 2 (<1%) |

5.3.2.2.4 Potentially Effective Prior and Concomitant Non-Study Antimicrobial Medications (PEAT)

A patient was defined as having received potentially effective antibiotic therapy (PEAT) if he/she was treated on 3 or more calendar days—either prior to and/or concomitantly with study medication—with one or more antibiotics that either (1) had activity against all of the patient’s baseline Gram-positive respiratory pathogens or, (2) if no baseline Gram-positive

respiratory pathogen had been identified, had activity against any Gram-positive respiratory pathogen. If the baseline Gram-positive pathogen(s) was resistant to the prior antibiotics, then the prior antibiotics were not considered PEAT. The PEAT classification was used in the determining the CE and ME analysis populations. Please refer to Section 5.3.1.2.4 of this report for further details and FDA Medical Officer Comments about PEAT.

The most frequent indication for PEAT across clinical trials 0015 and 0019 was pneumonia/HAP. In assessing the use of potentially effective non-study antibiotics from randomization through TOC Visit, there was a substantially greater use of PEAT in the vancomycin arm compared to the telavancin arm in Study 0019, and the difference was statistically significant as depicted in the table below:

Table 41: FDA Medical Officer Table of Subject Count who received Potentially Effective Non-Study Antibiotics (PEAT) from randomization through the TOC visit, Study 0019, AT Efficacy Population

| Study | Treatment | N (AT) | n, PEAT Subject count | 95% CI for difference (TLV-VAN) |
|-------|------------|--------|-----------------------|---------------------------------|
| 0019 | Telavancin | 377 | 61 | -6.7 (-12.3, -1.1)* |
| | Vancomycin | 380 | 87 | |

*statistically significant difference; N (AT) = subject count in AT population; TLV=telavancin; VAN=vancomycin

5.3.2.2.5 Adequacy of Concomitant Gram-negative Therapy

The adequacy of Gram-negative therapy in Study 0019 is summarized for the AT Population in the following table. Of those patients in the AT Population with infections due to Gram-negative pathogens only, a total of 99 patients (49 of 79 telavancin-treated and 50 of 76 vancomycin-treated) received inadequate Gram-negative therapy, with the majority of these patients never having received adequate therapy. Of those patients in the AT Population with mixed infections of both Gram-positive and Gram-negative pathogens, a total of 109 patients (61 of 94 telavancin-treated and 48 of 81 vancomycin-treated patients) received inadequate Gram-negative therapy. The majority of these patients received Gram-negative therapy that was considered inadequate to treat the organisms present. Among the patients with no baseline pathogen, 40 of 74 telavancin-treated patients and 41 of 98 vancomycin-treated patients were assessed as having received inadequate Gram-negative therapy. Overall, a greater proportion of patients in the telavancin group (61%) received inadequate Gram-negative therapy than patients in the vancomycin group (55%).

Table 42: Adequacy of Gram-negative Therapy, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 8-26)

| | Number of patients | |
|---|--------------------|------------|
| | Telavancin | Vancomycin |
| Gram-negative pathogen only | | |
| Adequate Gram-negative therapy | 30 (38%) | 26 (34%) |
| Inadequate Gram-negative therapy | 49 (62%) | 50 (66%) |
| Initial Inadequate Therapy | 17 (22%) | 7 (9%) |
| Never received adequate therapy | 32 (41%) | 43 (57%) |
| Total | 79 (100%) | 76 (100%) |
| Mixed Gram-positive and Gram-negative pathogens | | |
| Adequate Gram-negative therapy | 33 (35%) | 33 (41%) |
| Inadequate Gram-negative therapy | 61 (65%) | 48 (59%) |
| Initial Inadequate Therapy | 9 (10%) | 15 (19%) |
| Never received adequate therapy | 52 (55%) | 33 (41%) |
| Total | 94 (100%) | 81 (100%) |
| No Baseline Pathogen [1] | | |
| Adequate Gram-negative therapy | 34 (46%) | 57 (58%) |
| Inadequate Gram-negative therapy | 40 (54%) | 41 (42%) |
| Initial Inadequate Therapy | 4 (5%) | 6 (6%) |
| Never received adequate therapy | 36 (49%) | 35 (36%) |
| Total | 74 (100%) | 98 (100%) |
| Total-Inadequate Gram-negative Therapy [2] | 150 (61%) | 139 (55%) |

[1] Patients with no baseline pathogen were considered to have inadequate therapy if they did not receive at least one antibiotic with Gram-negative activity during study Days 1 and 2 (ie, initial inadequate therapy) or if they never received at least one antibiotic with Gram-negative activity (ie, never received adequate therapy)

[2] Percentages are calculated based on the total number of patients with Gram-negative pathogens only, mixed Gram-positive and Gram-negative pathogens, or No baseline pathogen.

Please refer to Section 5.3.1.2.5 of this report for further details about the Applicant's approach to the assessment of the adequacy of Gram-negative therapy and the FDA Medical Officer's Comments on the assessments.

Section 5.3.2.2.6 Evaluability and Eligibility

Eligibility Deviations

The following table summarizes the eligibility deviations for enrolled patients in the AT population. In some situations, helpline physicians could grant a waiver of approval to enroll a patient overriding one or more exclusion criteria if it was believed that there would be no adverse effect on patient safety or efficacy assessment. Overall, a slightly higher percentage of telavancin-treated patients did not meet all of the Inclusion and Exclusion Criteria. The most frequently violated Inclusion Criteria were #2b (signs and symptoms) and #4 (appropriate respiratory specimens). The most frequently violated Exclusion Criterion was #1 (>24 hour prior antibiotics).

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Table 43: Summary of Eligibility Deviations, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 7-6)

| | Number of patients | | | | | |
|--|---------------------|-------------|---------------------|-------------|------------------|-------------|
| | Telavancin N=377 | | Vancomycin N=380 | | Overall N=757 | |
| Did not meet all Inclusion/Exclusion Criteria | 35 (9%) | | 20 (5%) | | 55 (7%) | |
| Enrollment approval not obtained | 22 (6%) | | 12 (3%) | | 34 (4%) | |
| Enrollment approval obtained | 15 (4%) | | 8 (2%) | | 23 (3%) | |
| | Approval | No Approval | Approval | No Approval | Approval | No Approval |
| Inclusion criteria violated [1] | | | | | | |
| Inclusion 2a: signs and symptoms | 1 (<1%) | 0 | 0 | 0 | 1 (<1%) | 0 |
| Inclusion 2b: signs and symptoms | 4 (<1%) | 7 (2%) | 2 (<1%) | 3 (<1%) | 6 (<1%) | 10 (1%) |
| Inclusion 3: chest radiograph | 0 | 1 (<1%) | 0 | 0 | 0 | 1 (<1%) |
| Inclusion 4: appropriate respiratory specimens | 5 (1%) | 2 (<1%) | 0 | 3 (<1%) | 5 (<1%) | 5 (<1%) |
| Exclusion criteria violated [1] | | | | | | |
| Exclusion 1: >24 h prior antibiotic | 5 (1%) | 3 (<1%) | 4 (1%) | 4 (1%) | 9 (1%) | 7 (<1%) |
| Exclusion 2: only Gram -negative bacteria | 0 | 2 (<1%) | 0 | 0 | 0 | 2 (<1%) |
| Exclusion 6: infection due to resistant organism | 1 (<1%) | 1 (<1%) | 0 | 1 (<1%) | 1 (<1%) | 2 (<1%) |
| Exclusion 7: meningitis, endocarditis, osteomyelitis | 0 | 1 (<1%) | 0 | 0 | 0 | 1 (<1%) |
| Exclusion 8: refractory shock | 0 | 0 | 2 (<1%) | 0 | 2 (<1%) | 0 |
| Exclusion 9: QT issues | 0 | 4 (1%) | 0 | 1 (<1%) | 0 | 5 (<1%) |
| Exclusion 12: birth control | 0 | 0 | 0 | 1 (<1%) | 0 | 1 (<1%) |
| Exclusion 15: other investigational medication | 1 (<1%) | 0 | 0 | 0 | 1 (<1%) | 0 |

[1] Patients could have violated more than one criterion.

Note: Two telavancin-treated patients each did not meet two criteria, one of whom had approval obtained and one of whom did not have approval obtained.

Unblinding of Treatment Assignment

Table 44: Unblinding of Treatment Assignment, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 7-8)

| | Number of patients | | |
|---|---------------------|---------------------|------------------|
| | Telavancin N=377 | Vancomycin N=380 | Overall N=757 |
| Treatment not unblinded | 375 (99%) | 374 (98%) | 749 (99%) |
| Treatment unblinded | 2 (<1%) | 6 (2%) | 8 (1%) |
| During study medication dosing period [1] | 1 (<1%) | 4 (1%) | 5 (<1%) |
| After discontinuation of study medication [2] | 1 (<1%) | 2 (<1%) | 3 (<1%) |
| Total | 377 (100%) | 380 (100%) | 757 (100%) |

[1] On or before last day of study medication

[2] After last day of study medication

The table above summarizes the number of patients who were unblinded for any reason either during or after study medication dosing. Study medication was unblinded in five patients during the study medication dosing period and they are discussed briefly as follows:

- Patient 0019-18004-6107 (telavancin) experienced an SAE of meningitis (verbatim term: suspected meningitis), which led to termination of study medication and subsequent unblinding of treatment assignment on Study Day 3. According to the SAE report only, unblinding was performed to rule out vancomycin nephrotoxicity.
- Patient 0019-02023-6108 (vancomycin): Study medication was unblinded on Study Day 4 after the patient withdrew consent. The patient died on (b) (6) due to an SAE of multi-organ failure.
- Patient 0019-02026-6312 (vancomycin) was unblinded on Study Day 10 after a transthoracic echocardiogram revealed a 1 cm aortic vegetation, and the Infectious Disease Department required unblinding of study medication before a new course of therapy could be prescribed (diagnosis was later refuted). Patient died of HAP on (b) (6).
- Patient 0019-02028-6613 (vancomycin) was unblinded on Study Day 3 because laboratory results were erroneously sent to the ward. Patient died on (b) (6) of spontaneous bacterial peritonitis.
- Patient 0019-14014-6790 (vancomycin) was unblinded on Study Day 1 when treatment was verbally communicated to the Investigator in error.

Of the three patients who were unblinded to treatment assignment after discontinuation of study medication, treatment was verbally communicated to the Investigator in error for one patient in the telavancin group. Reasons for unblinding of the two vancomycin-treated patients included accidental insertion of vancomycin blood level reports in the study file and determination that a vancomycin level was drawn after treatment ended.

FDA Medical Officer Comments: During the review cycle for this NDA, a site inspection was conducted at Theravance. During the inspection, it was noted that subsequent to treatment

unblinding, medical review determinations were made impacting patient population evaluability, assessments of potentially effective non-study antibiotics, and assessments of the adequacy of Gram-negative coverage. Medical Monitor evaluation of such issues following treatment unblinding raises concern about the potential for biased assessments.

Clinical Evaluability Criteria

Please refer to Section 5.3.1.2.6 of this report for details of the Applicant’s criteria for patient inclusion in the CE population and the FDA Medical Officer’s Comments.

The following table summarizes the reasons for exclusion from the CE and ME populations. The most common reasons for exclusion from the CE Population were “Received Potentially Effective Systemic Antibiotics”, “Clinical Response at TOC was Neither ‘Cure’ nor ‘Failure’” (i.e., clinical response at TOC was indeterminate or missing), and “Isolation of Only Gram-negative Pathogens”.

It should be noted that eight patients who were algorithmically excluded from the CE Population because of violation of inclusion or exclusion criteria were subsequently included based on the Medical Monitor’s override of the algorithmic determination of clinical evaluability. Refer to the following section for additional details.

Table 45: Reasons for Exclusion from the CE and ME Analysis Populations, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 8-2)

| | Number of patients | | |
|---|---------------------|---------------------|------------------|
| | Telavancin N=377 | Vancomycin N=380 | Overall N=757 |
| Not Clinically Evaluable [1] | 206 (55%) | 210 (55%) | 416 (55%) |
| TOC Clinical Response is neither cure nor failure | 97 (26%) | 100 (26%) | 197 (26%) |
| Did not meet Exclusion criteria | 4 (1%) | 5 (1%) | 9 (1%) |
| Did not meet Inclusion criteria | 4 (1%) | 3 (<1%) | 7 (<1%) |
| Did not receive minimum days of treatment | 11 (3%) | 8 (2%) | 19 (3%) |
| Isolation of only Gram-negative pathogens | 79 (21%) | 76 (20%) | 155 (20%) |
| TOC visit outside window | 6 (2%) | 7 (2%) | 13 (2%) |
| Received potentially effective systemic antibiotics | 61 (16%) | 87 (23%) | 148 (20%) |
| Persistently positive <i>S. aureus</i> bacteremia | 2 (<1%) | 9 (2%) | 11 (1%) |
| Pneumonia due to <i>S. maltophilia</i> or <i>B. cepacia</i> | 19 (5%) | 8 (2%) | 27 (4%) |
| Did not receive at least 80% of intended dose | 0 | 1 (<1%) | 1 (<1%) |
| Excessive prior vancomycin or teichoplanin use | 2 (<1%) | 1 (<1%) | 3 (<1%) |
| Not actually treated as randomized | 0 | 2 (<1%) | 2 (<1%) |
| Not Microbiologically Evaluable [1] | 242 (64%) | 256 (67%) | 498 (66%) |
| Not clinically evaluable | 206 (55%) | 210 (55%) | 416 (55%) |
| No Gram-positive pathogen isolated at baseline | 152 (40%) | 173 (46%) | 325 (43%) |

[1] Patients could have more than one reason for exclusion.

Applicant’s Determination of Patient Evaluability

Please refer to Section 5.3.1.2.6 of this report for details on evaluability determinations . The Medical Monitor identified eight patients who violated inclusion or exclusion criteria but were considered suitable for inclusion in the CE population as depicted in the table below:

Table 46: Patients who were included in the CE Population that violated study entry criteria and did not receive approval to enter the study, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Table 20)

| Patient ID | Treatment | CRF Documentation | Inclusion/Exclusion criteria not met | Reason for CE exclusion |
|-----------------|------------|--|--|---|
| 0019-01019-6145 | Vancomycin | | Exclusion 1: >24 h prior antibiotics | Despite prior antibiotics, baseline respiratory culture was positive |
| 0019-05003-6065 | Telavancin | ECG was not performed prior to subject randomization | Exclusion 9: QT issues | Inclusion/exclusion criteria not met is not one of the CE requirements |
| 0019-08010-6218 | Telavancin | No source supporting ‘checked’ clinical signs and symptoms | Exclusion 2b: Signs and symptoms | Clinically appears to have pneumonia |
| 0019-08012-6745 | Telavancin | Ex #2: The sputum culture reported as MRSA twice within 3 days before randomization. The investigator considered the sputum culture result showed more clinical significance than the Gram stain result. | Exclusion 2: Only Gram-negative bacteria | Isolation of Gram-positive pathogen resistant to prior antibiotics |
| 0019-20009-6259 | Telavancin | The subjects satisfied only one of the inclusion criteria #2-b, but we did not try to call and rec receive enrollment approval. | Inclusion 2b: Signs and symptoms | Temperature of 38.3 Celsius after adjusting for axillary collection method so meeting inclusion criteria. |
| 0019-20019-6657 | Vancomycin | Carbenin was used the first day that is administered study drug | Exclusion 6: Infection due to resistant organism | Isolation of Gram-positive pathogen resistant to prior antibiotics |
| 0019-38108-6074 | Telavancin | Chest x-ray not done within 48 hours | Exclusion 3: chest radiograph | Clinically appears to have pneumonia, but chest x-ray not taken. However, CXR on Study Day 3 consistent with pneumonia. |
| 0019-38108-6539 | Vancomycin | Patient sputum production-yes; specimen not obtained by respiratory | Inclusion 4: Appropriate respiratory specimens | Clinically appears to have pneumonia but respiratory culture not available after failed attempt. |

FDA Medical Officer Comment: The use of axillary temperatures in critically ill adults is not acceptable, and the Applicant’s adjustment of such recorded temperatures is not appropriate. Please refer to Section 5.3.1.1.2 for additional comments on this issue.

FDA Medical Officer Review of Case Report Forms and Electronic Datasets:

This FDA Medical Officer conducted a review of a random sample of approximately 80 case report forms (CRFs) to verify the accuracy of the information compared to the electronic datasets and to provide an independent assessment of the patient’s eligibility, evaluability, and outcome. Multiple deficiencies were uncovered that adversely impact the ability to evaluate the efficacy and safety of telavancin compared to vancomycin in this clinical trial. The deficiencies are summarized in Section 5.3.1.2.6 of this report for Study 0015. Similar deficiencies were identified with respect to Study 0019.

Section 5.3.2.2.7 Clinical and Microbiological Outcomes

Clinical and Microbiological Outcomes

This study was designed as an active-controlled, noninferiority trial with a noninferiority margin (telavancin – vancomycin) of 20% for the primary endpoint of clinical response at Test-of-cure (TOC). The Follow-up/TOC visit was conducted 7 to 14 days after the last dose of study medication. The following table provides the Applicant’s summary of clinical outcomes at the TOC visit:

Table 47: Clinical Response at TOC Visit, AT and CE Populations, Study 0019 (from Applicant's 0019 Clinical Study Report, Table 8-32)

| | Number of Patients | | Difference (95% CI) [1] |
|----------------------|--------------------|--------------|-------------------------|
| | Telavancin | Vancomycin | |
| All-treated | | | |
| Cure | 227 (60.2%) | 228 (60.0%) | 0.2% (-6.8%, 7.2%) |
| Failure | 53 (14.1%) | 52 (13.75) | |
| Indeterminate | 39 (10.3%) | 38 (10.0%) | |
| Missing | 58 (15.4%) | 62 (16.2%) | |
| -Total- | 377 (100.0%) | 380 (100.0%) | |
| Clinically Evaluable | | | |
| Cure | 139 (81.3%) | 138 (81.2%) | 0.1% (-8.2%, 8.4%) |
| Failure | 32 (18.7%) | 32 (18.8%) | |
| -Total- | 171 (100.0%) | 170 (100.0%) | |

[1] Point estimate and 95% confidence interval on the treatment difference (telavancin – vancomycin) in cure rate. ^= Confidence interval uses Agresti-Caffo adjustment

According to the Applicant’s Clinical Study Report, for both of these co-primary analysis populations, telavancin was demonstrated to be clinically noninferior to vancomycin. The lower bound of the 95% CI around the difference (telavancin - vancomycin) in cure rates was greater than the prospectively defined -20% noninferiority margin. Telavancin was also demonstrated to be clinically noninferior to vancomycin based on the post hoc noninferiority margin for clinical response, as evidenced by the lower bound of the 95% CI around the difference (telavancin - vancomycin) in cure rates being greater than -14% in the AT and CE Populations. In both populations, the lower bound of the 95% CI around the difference between treatments in cure rates exceeded -10%. The 95% CI also included zero.

FDA Medical Officer Comments: The clinical response data provided in the table above is not informative in distinguishing ineffective from effective treatments, because there is no historical evidence to support a NI margin based on a clinical response endpoint. Thus, it is not possible to make any conclusions as to whether telavancin is noninferior to vancomycin based on this data. Please refer to Sections 5.3.1.1.3 and 5.3.1.2.7 of this report for additional FDA Medical Officer Comments regarding the Applicant's choice of NI margin.

Reasons for failure at TOC are summarized in the following table. The percentage of patients with clinical outcome of failure was approximately the same in both treatment groups. Most of the failures occurred by EOT and were primarily due to persistence or progression of pneumonia. Other reasons for failure included lack of efficacy/initiation of antistaphylococcal antibiotic, relapsed pneumonia, and death due to HAP on or after Study Day 3.

Table 48: Reasons for Failure at TOC Visit, AT and CE Populations, Study 0019 (from Applicant's 0019 Clinical Study Report, Table 8-33)

| | Number of Patients | | Overall |
|---|--------------------|------------|-------------|
| | Telavancin | Vancomycin | |
| Population | | | |
| All-treated | 377 | 380 | 757 |
| Clinically evaluable | 171 | 170 | 341 |
| Reason for Failure: All-treated population | | | |
| Failure at End-of-therapy | 46 (12.2%) | 45 (11.8%) | 91 (12.0%) |
| Persistence or progression of pneumonia | 31 (8.2%) | 34 (8.9%) | 65 (8.6%) |
| Lack of efficacy/Initiation of antistaphylococcal antibiotics | 5 (1.3%) | 12 (3.2%) | 17 (2.2%) |
| Death on or after Study Day 3 attributable to HAP | 14 (3.7%) | 5 (1.3%) | 19 (2.5%) |
| Relapsed pneumonia (TOC) | 6 (1.6%) | 6 (1.6%) | 12 (1.6%) |
| Death on or after Study Day 3 attributable to HAP [1] | 1 (0.3%) | 0 | 1 (0.1%) |
| Death after End-of-therapy attributable to HAP [1] | 0 | 1 (0.3%) | 1 (0.1%) |
| -Total- | 53 (14.1%) | 52 (13.7%) | 105 (13.9%) |
| Reason for Failure: Clinically evaluable population | | | |
| Failure at End-of-therapy | 28 (16.4%) | 29 (17.1%) | 57 (16.7%) |
| Persistence or progression of pneumonia | 18 (10.5%) | 20 (11.8%) | 38 (11.1%) |
| Lack of efficacy/Initiation of antistaphylococcal antibiotics | 2 (1.2%) | 8 (4.7%) | 10 (2.9%) |
| Death on or after Study Day 3 attributable to HAP | 10 (5.8%) | 4 (2.4%) | 14 (4.1%) |
| Relapsed pneumonia (TOC) | 3 (1.8%) | 3 (1.8%) | 6 (1.8%) |
| Death after End-of-therapy attributable to HAP [1] | 1 (0.6%) | 0 | 1 (0.3%) |
| -Total- | 32 (18.7%) | 32 (18.8%) | 64 (18.8%) |

[1] Includes patients whose clinical response at TOC was set to failure due to death on or after study day 3 and the cause of death was due to HAP.

Table 49: Table of Key Clinical Response Efficacy Parameters, Study 0019 (from Applicant's Summary of Clinical Efficacy, Module 2.7.3, Table 12)

| Efficacy Parameter | Analysis Population | Number (%) of Patients | | Diff (95% CI) [1] |
|--|---------------------|------------------------|-----------------|-----------------------------------|
| | | Telavancin | Vancomycin | |
| Clinical cure rate | AT | 227/377 (60.2%) | 228/380 (60.0%) | 0.2% (-6.8%, 7.2%) |
| | CE | 139/171 (81.3%) | 138/170 (81.2%) | 0.1% (-8.2%, 8.4%) |
| Clinical Cure Rates for Patients with Single Gram-positive Pathogen Only | ME | 71/82 (86.6%) | 59/77 (76.6%) | 10.0% (-2.0%, 22.0%) |
| MRSA | ME | 30/38 (78.9%) | 32/46 (69.6%) | 9.4% (-9.7%, 27.2%) [^] |
| MSSA | ME | 31/34 (91.2%) | 16/19 (84.2%) | 7.0% (-11.7%, 27.6%) [^] |
| Clinical Cure Rate by Pathogen | | | | |
| <i>S. aureus</i> (combined) | ME | 91/121 (75.2%) | 80/105 (76.2%) | -1.0% (-12.2%, 10.2%) |
| MRSA | ME | 47/69 (68.1%) | 52/70 (74.3%) | -6.2% (-21.2%, 8.9%) |
| MSSA | ME | 44/52 (84.6%) | 29/37 (78.4%) | 6.2% (-10.1%, 23.0%) [^] |
| By-Patient Microbiological Eradication Rate | MAT | 186/303 (61.4%) | 167/282 (59.2%) | 2.2% (-5.8%, 10.1%) |
| | ME | 103/135 (76.3%) | 96/124 (77.4%) | -1.1% (-11.4%, 9.2%) |

[1] Difference (telavancin – vancomycin); 2-sided 95% CI.

[^]= Confidence interval uses Agresti-Caffo adjustment

According to the Applicant's Summary of Clinical Efficacy, for patients in the ME Population in Study 0019 who had a single Gram-positive pathogen and no Gram-negative pathogens isolated at Baseline, cure rates were numerically higher in the telavancin group compared with the vancomycin group (86.6% vs. 76.6%). The 95% CI around the treatment difference included zero. In patients who had only MRSA or only MSSA, clinical cure rates were numerically higher in the telavancin group compared with the vancomycin group (78.9% vs. 69.6% and 91.2% vs. 84.2%, respectively). For these patients, the 95% CI around the treatment difference included zero. In patients with mixed Gram-positive and Gram-negative pathogens at Baseline, cure rates were numerically lower in the telavancin group compared with the vancomycin group (62.5% vs. 77.5%) and the 95% CI around the treatment difference included zero. The lower cure rates in patients with mixed infections in the telavancin group was mostly due to higher rates of inappropriate Gram-negative coverage (11 vs. 3), prior treatment failures (9 vs. 0), and multi-resistant infections including *P. aeruginosa* and *A. calcoaceticus* (14 vs. 2) in the telavancin group compared with the vancomycin group.

For patients in the ME Population, the most common pathogen isolated at Baseline (without regard to whether patients had one or multiple baseline pathogens) was *S. aureus*, and clinical cure rates against this pathogen were similar in both treatment groups. Cure rates were also evaluated by methicillin susceptibility of the *S. aureus* isolated at Baseline. In patients with MSSA, the clinical cure rate was numerically higher in the telavancin group than in the vancomycin group; whereas in patients with MRSA, the clinical cure rate was numerically higher in the vancomycin group than in the telavancin group. It should be noted, however, that cure rates in patients with MRSA as the only pathogen at Baseline were numerically higher in the telavancin group compared with the vancomycin group, and therefore the result for all MRSA (with or without other pathogens) may be confounded by the presence of other

pathogens. Microbiological eradication rates in the MAT and ME Populations were similar to the clinical cure rates in these populations.

Microbiological Data

In the MAT population, 7% of telavancin–treated and 9% of vancomycin-treated patients were bacteremic at baseline. Bacterial pathogens were isolated from blood cultures only in 2% of telavancin-treated and 1% of vancomycin-treated patients. There were comparable numbers of patients in each treatment arm who had Gram-positive bacteria at baseline as primary pathogens. The following table summarizes data related to baseline Gram-positive pathogens.

Table 50: FDA Medical Officer Summary Table of Baseline Gram-positive Pathogens, Study 0019, MAT Population

| | TLV | VAN |
|-------------------------------------|-----------|-----------|
| Baseline Gram-positive Pathogens | 220 (73%) | 205 (73%) |
| MRSA | 117 (39%) | 117 (41%) |
| MSSA | 83 (27%) | 63 (22%) |
| PVL (-) <i>S. aureus</i> (combined) | 79% | 83% |
| <i>Streptococcus pneumoniae</i> | 14 (5%) | 23 (8%) |
| <i>Enterococcus faecalis</i> | 10 (3%) | 13 (5%) |
| <i>Enterococcus faecium</i> | 3 (<1%) | 1 (<1%) |
| VAP | | |
| MRSA VAP | 35 (42%) | 28 (38%) |
| MSSA VAP | 23 (28%) | 23 (32%) |

TLV=telavancin, VAN=vancomycin, PVL (-)=absence of Panton-Valentine Leukocidin gene, VAP=ventilator-associated pneumonia, MRSA=methicillin-resistant *S. aureus*, MSSA=methicillin-susceptible *S. aureus*

Quality of Respiratory Tract Specimens

In assessing the various sources of respiratory tract specimens obtained from patients enrolled in Study 0019, sputum and endotracheal aspirates were obtained from approximately 85-90% of the total patients. Sputum samples were the most common respiratory tract specimens collected from approximately 40-43% of all patents enrolled in this trial across both treatment arms. Approximately 45% of the patients in both treatment groups had ETA as the primary respiratory tract specimen and approximately 3-4% had the primary respiratory tract specimen listed as missing.

Table 51: Summary Table of Respiratory Specimen Source by Subject Count*, Study 0019

| RESPIRATORY SPECIMEN SOURCE | Study 0019 | |
|---|------------------------------|------------------------------|
| | Telavancin N=377 n (%) | Vancomycin N=380 n (%) |
| SPUTUM | 151 (40.1) | 164 (43.2) |
| ENDOTRACHEAL ASPIRATION | 171 (45.4) | 180 (47.4) |
| MINI-BRONCHOALVEOLAR LAVAGE | 19 (5.0) | 10 (2.6) |
| BRONCHOALVEOLAR LAVAGE | 34 (9.0) | 27 (7.1) |
| MISSING | 15 (4.0) | 10 (2.6) |
| BLIND BRONCHIAL SUCTIONING | 6 (1.6) | 2 (0.5) |
| OTHER: QUANTITATIVE TRACHEAL LAVAGE | 0 (0.0) | 0 (0.0) |
| PROTECTED SPECIMEN BRUSH | 0 (0.0) | 1 (0.3) |
| OTHER: NARES | 0 (0.0) | 0 (0.0) |
| OTHER: QUANTITATIVE TRACHEAL LAVAGE > 10 | 0 (0.0) | 0 (0.0) |
| OTHER: QUANTITATIVE TRACHEAL LAVAGE >10 POLYS | 0 (0.0) | 0 (0.0) |
| OTHER: PROTECTED ENDOTRACHEAL SPECIMEN | 0 (0.0) | 0 (0.0) |
| OTHER: QTL WBC >10 QUANTITATIVE TRACHEAL LAVAGE | 0 (0.0) | 0 (0.0) |
| OTHER: QUANTITATIVE TRACHEAL LAVAGE >10 | 0 (0.0) | 0 (0.0) |
| OTHER: BRONCHIAL SUCTION VIA FIBROBRONCHOSCOPY | 1 (0.3) | 0 (0.0) |
| OTHER: PLEURAL EFFUSION | 1 (0.3) | 0 (0.0) |
| OTHER: PLEURAL FLUID | 0 (0.0) | 1 (0.3) |
| OTHER: TRACHEOSTOMY ASPIRATE | 0 (0.0) | 1 (0.3) |
| OTHER: QUANTITATIVE TRACHEAL LAVAGE <5 | 0 (0.0) | 0 (0.0) |

* Some subjects had specimens from multiple respiratory sources

The Applicant provided overall quality assessments of sputum specimens as summarized in the table below:

Table 52: Quality and Culture Positivity of Baseline Sputum Specimens, Study 0019, AT Population (from Applicant's 0019 Clinical Study Report, Supporting Table 64)

| | Telavancin | Vancomycin | Overall |
|---|------------|------------|---------|
| Any Sputum Specimen Quality | 232 (100) | 248 (100) | 480 |
| Culture positive | 152 (65.5) | 154 (62.1) | 306 |
| Culture negative | 80 (34.5) | 94 (37.9) | 174 |
| Appropriate Sputum Specimen Quality | 173 (74.6) | 194 (78.2) | 367 |
| Culture positive | 115 (49.6) | 123 (49.6) | 238 |
| Culture negative | 58 (25) | 71 (28.6) | 129 |
| Potentially Appropriate Sputum Specimen Quality | 28 (12.1) | 30 (12.1) | 58 |
| Culture positive | 21 (9.1) | 18 (7.3) | 39 |
| Culture negative | 7 (3.0) | 12 (4.8) | 19 |
| Inappropriate Sputum Specimen Quality | 21 (9.1) | 19 (7.7) | 40 |
| Culture positive | 11 (4.7) | 10 (4.0) | 21 |
| Culture negative | 10 (4.3) | 9 (3.6) | 19 |
| Quality Unknown | 10 (4.3) | 5 (2.0) | 15 |
| Culture positive | 5 (2.2) | 3 (1.2) | 8 |
| Culture negative | 5 (2.2) | 2 (0.8) | 7 |

n (%)=number of sputum specimens (% of any sputum specimen quality)

FDA Medical Officer Comments: The FDA Medical Officer conducted a sensitivity analysis of the microbiological evaluability of all patients who had sputum specimens of inappropriate or unknown quality, as their specimens were considered inadequate for the identification of true pathogens. Of the 151 telavancin-treated patients with sputum specimens at baseline, 9 (6.0%) patients had specimens assessed as inappropriate or unknown sputum quality. Four (44.4%) of the 9 patients were assessed as clinically and microbiologically evaluable by the Applicant. However, only one of the four patients (patient 0019-22006-6640) had a confirmatory positive BAL culture for the Gram-negative pathogens (but not for the MRSA isolated concomitantly) from the sputum culture, and the remaining three patients did not have other confirmatory respiratory tract or blood cultures for the bacterial isolate (all MRSA) originally identified from the sputum specimens. Thus, it is this FDA Medical Officer's opinion that those three patients (0019-02016-6003, 0019-40006-6348, and 0019-47003-6820) should be considered non-evaluative for the ME population, and patient 0019-22006-6640 should be considered non-evaluative with respect to MRSA.

Similarly, of the 164 vancomycin-treated patients with sputum specimens at baseline, 12 (7.3%) patients had specimens assessed as inappropriate or unknown sputum quality. Five (41.7%) of the 12 patients were assessed as clinically and microbiologically evaluable by the Applicant. However, three of the five patients did not have other confirmatory respiratory tract or blood cultures for the bacterial isolates (2 MRSA, 1 Streptococcus pneumoniae) originally identified from the sputum specimens, and one patient had positive cultures of endotracheal aspirates (but their quality is suspect in view of the report of ≥ 10 squamous epithelial cells/HPF in each specimen). Thus, it is this FDA Medical Officer's opinion that those four patients (0019-06005-

6540, 0019-20009-6446, 0019-38069-6034, and 0019-40006-6493) should be considered non-evaluative for the ME population.

The FDA Medical Officer conducted an exploratory analysis of all ETA specimens using published rejection criteria (4). The authors of that publication recommended that ETA specimens that show no organisms by Gram stain and those with > 10 squamous epithelial cells per LPF should be rejected. As depicted in the tables below, a total of 26 subjects had ETA with ≥ 10 Epithelial Cells/HPF and a total of 31 patients had ETA with negative Gram stains; those ETA specimens should have been rejected, the specimens classified as inadequate, and any identified bacterial isolates should not have been considered as pathogens.

Table 53: FDA Medical Officer Table of Subject Count with Inadequate Endotracheal Aspirate specimens based on published rejection criteria

| Rejection Criteria | Telavancin | Vancomycin | Total |
|--------------------------------|------------|------------|-------|
| Negative Gram stain | 12 | 19 | 31 |
| ≥ 10 Epithelial Cells/HPF | 17 | 9 | 26 |

This FDA Medical Officer contends that all patients for which the bacterial pathogens identified from ETA specimens meeting the above rejection criteria that cannot be confirmed based on another acceptable respiratory tract culture or blood culture should be considered non-evaluative for the ME population.

All-cause Mortality

A total of 177 patients who participated in this study died: 148 patients within the predefined data collection window and 29 patients outside the death analysis window. The data collection window as defined in the Statistical Analysis Plan was through the Follow-up Visit or 28 days after EOT for patients who did not have a Follow-up Visit.

Of the 148 patients who died within the data collection window as per the following table, 70 patients (18.5%) were in the telavancin group and 78 patients (20.6%) were in the vancomycin group. Of the 148 total patients, 79 patients died while receiving study medication: 44 (12%) telavancin-treated patients and 35 (9%) vancomycin-treated patients. The remainder of the deaths occurred after EOT: 26 (7%) patients in the telavancin group and 43 (11%) patients in the vancomycin group.

Table 54: Timing of Deaths, Study 0019, AT Safety Population (from Applicant's 0019 Clinical Study Report, Table 9-4)

| | Number of patients | |
|--|---------------------|---------------------|
| | Telavancin N=379 | Vancomycin N=378 |
| Deaths due to any cause | | |
| While receiving study medication [1] | 44 (11.6%) | 35 (9.3%) |
| After end-of-therapy [2] | 26 (6.9%) | 43 (11.4%) |
| -Total- | 70 (18.5%) | 78 (20.6%) |
| Death on or after Day 3 prior to EOT attributable to primary infection | | |
| n (%) | 14 (3.7%) | 5 (1.3%) |
| Death after EOT attributable to primary infection | | |
| n (%) | 0 (0.0%) | 1 (0.3%) |

[1] Deaths occurred within 1 day after last date of study medication

[2] Deaths occurred at least 2 days after last date of study medication

FDA Medical Officer Comments: The time interval used for collection of mortality data was variable, as patients who died after their Follow-up/TOC visit were not captured. Thus, due to the non-uniform period for reporting time of death, an information request was issued by the Division to the Applicant to request more detailed mortality data, which is discussed in Section 6.1.5 of this report.

As the data above primarily included deaths that occurred before the Follow-up visit, there were concerns that some deaths that occurred between the Follow-up visit and Day 28 post-treatment as a uniform reporting time period may have been missed. Thus, the Agency requested additional data delineating the deaths that occurred up to 28 days post-treatment in an information request dated February 25, 2009. The Applicant provided the following table to summarize the requested mortality information. Please refer to Section 6.1.5 of this report for further discussion of the new mortality data.

Table 55: Applicant's Summary of Analysis of Deaths for Studies 0015 and 0019, AT Safety Population

| | Number of patients | |
|--|---------------------|---------------------|
| | Telavancin N=749 | Vancomycin N=754 |
| Deaths between Start of Study Drug and EOT Visit + 28 days | 160 (21.4%) | 147 (19.5%) |
| Deaths between EOT Visit and EOT Visit + 28 days | 113 | 104 |
| Deaths between TOC Visit and EOT Visit + 28 days | 11 | 6 |

Subsequent to providing the mortality data above, the Applicant notified the Division of additional mortality data identified from the clinical database, safety database, and data collected in a 10-week pharmacoeconomic (PE) study and provided the additional data in response to an information request from the Division dated June 9, 2009.

The Applicant noted in the response to that information request that the CRFs for the PE study did not explicitly prompt for date of death. The Applicant inferred date of death by algorithmic consideration of multiple data fields collected on the substudy CRF. The algorithm was unable to infer dates of death for 43 patients and, following a manual review in a blinded fashion, dates of death were inferred for 10 patients. Thus, there were 33 patients with no date of death. According to the Applicant's analysis, 391 deaths occurred on Study Day 49 (which encompasses the maximum protocol-specified treatment period of 21 days plus 28 days post end-of therapy), 33 deaths occurred on Study Day 50 or later, and 33 deaths have an unknown death date.

In response to an information request from the Division dated July 31, 2009, the Applicant provided summary tables for the study deaths, a list of patients for which mortality status is unknown up to Study Day 28, a list of patients for whom mortality status is unknown up to last study day + 28 days, and an electronic dataset. The Applicant also provided narratives for the deaths. The two summary tables are provided below:

Table 56: Applicant's Summary of Deaths occurring between Start of Study Drug and Start of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 92 (25%) | 73 (20%) | 80 (21%) | 88 (23%) | 172 (23%) | 161 (21%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 70 (19%) | 51 (14%) | 54 (14%) | 68 (18%) | 124 (17%) | 119 (16%) |
| Alive or censored | 280 (75%) | 301 (80%) | 299 (79%) | 290 (77%) | 579 (77%) | 591 (79%) |
| Censored* | 126 (34%) | 134 (36%) | 113 (30%) | 103 (27%) | 239 (32%) | 237 (32%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

Table 57: Applicant's Summary of Deaths Occurring between Start of Study Drug and End of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 102 (27%) | 82 (22%) | 88 (23%) | 99 (26%) | 190 (25%) | 181 (24%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 80 (22%) | 60 (16%) | 62 (16%) | 79 (21%) | 142 (19%) | 139 (18%) |
| After follow-up visit | 22 (6%) | 19 (5%) | 18 (5%) | 21 (6%) | 40 (5%) | 40 (5%) |
| Alive or censored | 270 (73%) | 292 (78%) | 291 (77%) | 279 (74%) | 561 (75%) | 571 (76%) |
| Censored* | 145 (39%) | 159 (43%) | 139 (37%) | 126 (33%) | 284 (38%) | 285 (38%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

FDA Medical Officer Comments: The risk difference for deaths occurring between start of study drug and start of study drug + 28 Days for the telavancin and the vancomycin arms in Study

0019 was -2.2% with 95% confidence interval of (-8.1%, 3.7%). Similarly, the risk difference for deaths occurring between start of study drug and end of study drug + 28 Days was -3.0% (-9.1%, 3.2%). In contrast to a risk difference of as large as 11.7% for patients treated with telavancin in Study 0015, a similar marked imbalance was not observed in Study 0019. However, as was observed in the mortality data for Study 0015, there was a large percentage of censored events among the submitted mortality data for Study 0019. In the analysis of mortality for deaths occurring between start of study drug and start of study drug + 28 Day in Study 0019, censored data was provided for 113 patients (30%) treated with telavancin and 103 (27.2%) treated with vancomycin. Similarly, in the deaths occurring between start of study drug and end of study drug + 28 Days, censored data was provided for 139 patients (36.7%) treated with telavancin and 126 (33.3%) treated with vancomycin. The high percentage of censored data is unacceptable, raising concern that the actual number of deaths is underestimated in both treatment arms. Thus, unless additional mortality data is provided for the patients currently reported with censored events, the all-cause mortality data provided by the Applicant in response to this information request is considered to be uninterpretable.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The Applicant's clinical development program for NP involved two Phase 3 studies (0015 and 0019) given the acronym ATTAIN (Assessment of Telavancin for Hospital-acquired Pneumonia) that were conducted under an identical protocol to assess the safety and efficacy of telavancin in adult patients with HAP due to Gram-positive bacteria with an emphasis on patients with infections due to MRSA. Study eligible patients were identified based on the Inclusion and Exclusion criteria described in Section 5.3.1.1 of this report.

The 1998 FDA *Guidance for Industry: Nosocomial Pneumonia-Developing Antimicrobial Drugs for Treatment* (1) defines acute nosocomial pneumonia by a new cough, auscultatory findings consistent with pneumonia, and a new infiltrate or progressive infiltrate(s) on chest radiograph, and accompanied by at least some of the following clinical findings:

- Fever or hypothermia
- Leukocytosis
- Sputum production or a change in the character of the sputum, acquired by a patient in a hospital or long-term-care facility such as a skilled nursing home facility or rehabilitation unit after being admitted for >48 hours
- Present <7 days after a patient is discharged from the hospital with initial hospitalization of ≥ 3 days duration

In addition, an organism consistent with a respiratory pathogen should be isolated from an appropriately obtained specimen.

The ATS/IDSA guidelines for the management of adults with HAP, VAP, and HCAP characterize the spectrum of nosocomial pneumonia to include hospital-acquired pneumonia (HAP), healthcare-associated pneumonia (HCAP), and ventilator-associated pneumonia (VAP). Each disease entity is defined in the guidelines as follows: "HAP is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. HAP may be managed in a hospital ward or in the intensive care unit (ICU) when the illness is more severe. VAP refers to pneumonia that arises more than 48–72 hours after endotracheal intubation. Although not included in this definition, some patients may require intubation after developing severe HAP and should be managed similar to patients with VAP. HCAP includes any patient who was hospitalized in an acute care hospital for two or more days within 90 days of the infection; resided in a nursing home or long-term care facility; received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; or attended a hospital or hemodialysis clinic." (2)

Multiple methodological deficiencies were identified by this FDA Medical Officer that adversely impact on data interpretation and conclusions of noninferiority. The most critical

deficiencies are summarized as follows and will be discussed further in other sections of this report:

- The inclusion and exclusion criteria did not assure with a high probability that all patients had NP at enrollment. Patients who lacked fever, leukocytosis, and purulent respiratory tract secretions, three critical components of the definitions of NP in the FDA Guidance and the ATS/IDSA Guidelines document on HAP, could be enrolled.
- Chest x-ray interpretation was problematic. Some patients did not have convincing radiographic evidence of pneumonia. There was no requirement for confirmation of the investigators' interpretations of chest x-rays by a radiologist. There were instances of discrepancies between the investigators' and the radiologists' interpretations of chest radiographs.
- The global impression of disease severity as assessed by APACHE II scores and the likelihood for VAP assessed by use of CPIS scores was confounded by the Applicant's choice to adjust all axillary temperature readings by adding 1° C. This approach was utilized by the Applicant even though there have been published recommendations against the use of axillary temperatures in the evaluation of new fever in critically ill adults (6, 7).
- There was failure to adhere to protocol-specified rapid de-escalation in initial antibiotic coverage for patients treated empirically with piperacillin-tazobactam or imipenem who were infected with MSSA as the sole baseline pathogen.
- There were patients included in the microbiologically evaluable (ME) population whose baseline sputum and endotracheal aspirates did not meet quality standards and for whom there was no corroborative evidence from cultures of other respiratory specimens or blood to establish that the bacterial isolates identified from the baseline specimens were true pathogens.
- The Applicant's choice of noninferiority margin using a clinical response endpoint was not supported by published scientific evidence. The 2007 *FDA Guidance – Antimicrobial Drug Products: Use of Non-inferiority Studies to Support Approval* (13) provided current regulatory perspectives, including the need for adequate scientific evidence to justify the choice of the NI margin to be used in contemporary clinical efficacy trials. A recent review of published data from the English language scientific literature (14) that was conducted after Studies 0015 and 0019 were completed revealed that historical evidence only permits interpretation of noninferiority clinical trials for NP and VAP that use all-cause mortality as the primary endpoint. Consequently, the two ATTAIN clinical trials were not sufficiently designed, sized, or powered for a noninferiority trial using an all-cause mortality endpoint.
- Assessments of patient evaluability, determination as to whether a patient had received PEAT in addition to the study drug treatment, and determination whether Gram-negative therapy was adequate or inadequate were made by the Medical Monitor after unblinding had occurred, which raised concerns about possible biased assessments.

6.1.1 Methods

The Applicant submitted the results of two identical phase 3 clinical trials involving adults aged ≥ 18 years with hospital-acquired pneumonia with a focus on patients with infections due to methicillin-resistant *Staphylococcus aureus*. Both clinical trials were double-blind, randomized,

and active controlled with a treatment duration of up to 21 days. The clinical trials are summarized below (also described in Section 5.2 of this report).

Table 58: List of all Clinical Trials(from Applicant's Summary of Clinical Efficacy, Section 2.7.3.2.1, Table 1)

| Study Number | Title | Design / Type of Control | Treatments / Dose / Route of Administration | Efficacy Population | Duration of Treatment | # Centers / Location |
|--------------|--|---|--|---------------------|-----------------------|----------------------|
| 0015 | A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to methicillin-resistant <i>Staphylococcus aureus</i> | Randomized Double-Blind Active-Controlled | Telavancin 10 mg/kg IV q24h; Vancomycin 1 gm IV q12h; no oral switch | 746 | Up to 21 days | Multinational |
| 0019 | A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to methicillin-resistant <i>Staphylococcus aureus</i> | Randomized Double-Blind Active-Controlled | Telavancin 10 mg/kg IV q24h; Vancomycin 1 gm IV q12h; no oral switch | 757 | Up to 21 days | Multinational |

Inclusion and Exclusion Criteria

Both studies enrolled patients 18 years of age or older who exhibited clinical signs and symptoms consistent with pneumonia 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. In both studies, patients were required to have a baseline chest x-ray with findings consistent with pneumonia within 48 hours before randomization. In addition, availability of appropriate respiratory or sputum specimens for Gram stain and culture and venous access for intravenous dosing were required.

Key exclusion criteria included receipt of more than 24 hours of potentially effective systemic antibiotic therapy for Gram-positive pneumonia immediately prior to randomization, respiratory tract specimens or sputum with only Gram-negative bacteria seen on Gram stain or culture, known infection with MSSA or *S. pneumoniae* that required 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 precluded evaluation of therapeutic response (e.g., granulomatous diseases, lung cancer, or another malignancy metastatic to the lungs), cystic fibrosis, or active tuberculosis, documented or suspected meningitis, endocarditis, or osteomyelitis, refractory shock, baseline QTc >500 msec, congenital long QT syndrome, uncompensated heart failure, or abnormal K⁺ or Mg⁺⁺ blood levels that could not be corrected, and severely neutropenic (absolute neutrophil count <500/mm³) or anticipated to develop severe neutropenia during the study treatment period due to

prior or planned chemotherapy, or had HIV with CD4+ cell count <100/mm³ during the last 6 months. Refer to Section 5.3.1.1.1 of this report for further details on the inclusion and exclusion criteria.

FDA Medical Officer Comments: The inclusion criteria were too broad and did not provide a high probability that all enrolled patients had NP. Confirmation of chest radiographic findings by a radiologist was not required, such that other non-infectious illnesses that may produce similar findings were not adequately excluded. There was no pre-specified CPIS score requirement for enrollment of patients on mechanical ventilation, such that patients with CPIS scores ≤ 5 were enrolled who were less likely to have VAP.

Study Treatment Regimens

In both studies, enrolled patients were randomized in a 1:1 ratio using permuted blocks to telavancin 10 mg/kg and one 60-minute infusion of D5W (G5W) or normal saline daily at 12-hour intervals OR vancomycin 1 gm q12h. The total duration of study therapy was to be determined by the Investigator, as clinically indicated. The minimum duration of study therapy was to be 7 days and the maximum allowable duration of study therapy was to be 21 days. Patients were to be treated with IV therapy throughout and were not to have been switched to oral therapy. For patients with documented MSSA pneumonia, the Investigator had the choice of changing vancomycin to IV nafcillin or oxacillin as the comparator agent.

Since the study was designed to compare the safety and efficacy of two drugs with activity against Gram-positive pathogens, the use of concomitant Gram-negative therapy was left to the discretion of the Investigator. Therefore, in addition to study medication for Gram-positive organisms, aztreonam and/or metronidazole therapy, used in accordance with the manufacturer's prescribing information, could have been added to study therapy for patients with suspected or proven polymicrobial infections involving Gram-negative and/or anaerobic bacteria. Piperacillin-tazobactam may have been administered for Gram-negative coverage only if aztreonam was not appropriate due to an unacceptable level of resistance among Gram-negative bacteria at the particular research site. However, as piperacillin-tazobactam has activity against MSSA and *S. pneumoniae*, patients with those organisms, who required more than 24 hours of treatment with this medication, should not have been enrolled. For those patients already enrolled, wherever possible, piperacillin-tazobactam was to be discontinued or changed to aztreonam as soon as possible. Finally, therapy with metronidazole was considered to be unnecessary if piperacillin-tazobactam, which has activity against anaerobic bacteria, was administered. The Original Protocol had 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. Refer to Section 5.3.1.1.1 of this report for further details on the inclusion and exclusion criteria.

FDA Medical Officer Comments: There were multiple instances in which de-escalation in antibiotic coverage with piperacillin-tazobactam and imipenem for patients with MSSA as the sole baseline pathogen did not occur in a timely manner. The efficacy of study drug in those patients could not be assessed appropriately due to the concomitant Gram-positive coverage.

Study Evaluations

Enrolled patients in both studies were evaluated at pre-treatment (baseline), during the course of study drug administration, at the end of therapy (EOT), and at the follow-up/test of cure (TOC) visit 7-14 days after the last dose of study drug. Pharmacokinetic (PK) samples were to be collected from approximately 300 study patients at selected sites. A total of four samples were to be obtained per patient on Study Day 4 of treatment (\pm 1 day) and sent to the central laboratory for analysis.

Baseline evaluation included medical history, vital signs, clinical signs and symptoms, Glasgow coma score, chest x-ray (or CT scan), oxygenation, respiratory specimen for Gram stain and culture, two blood cultures, serum chemistry, serum hematology, urinalysis, coagulation tests, serum pregnancy test, and 12-lead ECG. The components of the Acute Physiology and Chronic Health Evaluation (APACHE II) were also collected.

The respiratory or sputum specimens were to be processed as soon as possible after collection, or they were to be refrigerated. All organisms isolated by the local laboratory were to be sub-cultured and sent to a central microbiology laboratory for identification of genus and species and MIC testing in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines. 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 $100\times$ magnification (low-power, $10\times$ 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.

All patients in the study were to undergo an End-of-therapy (EOT) Visit conducted no later than 3 days after the last dose of study medication. If a patient withdrew prior to completing the study, the reason for withdrawal was to be documented on the CRF. A Follow-up Visit and a TOC evaluation, if applicable, were to be conducted 7 to 14 days after the EOT evaluation. For patients who discontinued Gram-positive coverage because it was no longer clinically indicated, an EOT Visit was to be completed and a Follow-up Visit (including TOC) must have been performed 7 to 14 days after stopping all antibiotics for the pneumonia under investigation (instead of after only stopping study medication, per Protocol Amendment 1). A blinded Test-of-cure (TOC) assessment was conducted at the Follow-up Visit only for those patients who were evaluated as a clinical “cure” or “indeterminate” at the EOT Visit. For purposes of analysis, a Clinical Response of “failure” at EOT was extrapolated to the TOC evaluation.

Determinations of patient evaluability were made after all the data had been entered into the database, after the data had been cleaned, and before the release of the treatment

randomization code (i.e., prior to breaking of the treatment blind for the study). On a patient-by-patient basis, Theravance's Medical Monitor reviewed the patient's qualification for, or disqualification from, the various analysis populations resulting from a computer-aided algorithmic classification. (Note that the algorithmic classification required some intermediate input from the Medical Monitor, such as classification of organisms and assessment of potentially effective antimicrobials.) The Medical Monitor may have overridden the algorithmic classification according to clinical judgment. Any such overrides were documented, including the rationale for the override. An assessment by the Medical Monitor determined that some patients who violated inclusion or exclusion criteria were suitable for inclusion in the CE Population.

For each patient a determination was made whether the patient had received PEAT in addition to the study treatment. For the determinations, information about systemic and inhaled antimicrobials administered to the patient, along with other clinical information, was reviewed by Theravance's Medical Monitor on a case-by-case basis. Using these data, the Medical Monitor assessed each systemic or inhaled antimicrobial administered to the patient and determined whether it was potentially active against the Gram-positive respiratory pathogens identified in baseline cultures available for that patient.

For patients with Gram-negative pathogens only or mixed Gram-positive and Gram-negative baseline pathogens, the study medical monitors determined whether Gram-negative therapy was adequate or inadequate. This determination was made while the monitors were to have been blinded to study treatment assignment and outcome. Gram-negative therapy was considered adequate if concomitant antibiotic(s) with *in vitro* activity covering all Gram-negative pathogens isolated at Baseline was administered from Study Day 1 through EOT. Patients were considered to have received inadequate therapy if they (a) never received antibiotic(s) with *in vitro* activity covering all Gram-negative pathogens isolated at Baseline (i.e., never received adequate therapy) or (b) did not receive concomitant antibiotic(s) with *in vitro* activity covering all Gram-negative pathogens isolated at Baseline until Study Day 3 or later (i.e., inadequate initial therapy). For purposes of these determinations, in the absence of *in vitro* susceptibility data, a concomitant antibiotic with known Gram-negative activity was deemed active against the baseline Gram-negative pathogen unless the antibiotic was known to routinely not have activity against the baseline pathogen. Patients with no baseline pathogens were considered to have received inadequate Gram-negative therapy if they (a) never received at least one antibiotic with known Gram-negative activity (i.e., never received adequate therapy) or (b) did not receive at least one antibiotic with known Gram-negative activity until Study Day 3 or later (i.e., inadequate initial therapy).

The primary efficacy endpoint for both studies was the clinical response at the TOC evaluation. Possible values were cure, failure, and indeterminate; indeterminate was added as a possibility by Protocol Amendment 1. If one of these possible values was not recorded, an analysis value of missing was assigned.

The secondary and tertiary endpoints for both studies were:

- Clinical response at EOT
- By-pathogen microbiological response at TOC
- By-patient microbiological response at TOC
- Clinical Pulmonary Infection Score (CPIS)
- Duration of treatment with study medication
- Length of stay in the ICU
- Length of stay in hospital
- All-cause mortality; and mortality attributable to primary infection
- Number of days on mechanical ventilation, for patients on ventilation at randomization
- Potential superinfection
- Time to resolution of fever (defervescence), defined as the first day of the earliest 2-day period during which all temperatures were $\leq 38^{\circ}\text{C}$

Fever was defined as temperature $>38^{\circ}\text{C}$, regardless of method of measurement. The day of defervescence, assuming a patient was febrile at Baseline, was defined as the Study Day corresponding to the first day of the earliest 2-day period during which all temperatures were $\leq 38^{\circ}\text{C}$.

Temperatures recorded through Study Day 10 were evaluated. If a patient had not defervesced on or before Study Day 10, the time to defervescence was considered censored as of the study day after the last reported temperature through Study Day 10. For temperatures taken by axillary method, for purposes of analysis one degree Celsius was added to the recorded value on the CRF. No adjustments were to be made for temperatures taken by any other method .

FDA Medical Officer Comments: Determinations of evaluability, whether a patient had received PEAT in addition to the study treatment, and whether Gram-negative therapy was adequate or inadequate were made by the Medical Monitor, who was supposed to have been blinded to treatment group while making the assessments. However, following a site inspection of Theravance, it was evident that such assessments were made after unblinding to treatment group had occurred raising concerns about possible biased assessments.

The Applicant's primary endpoint was based on clinical response at TOC. However, historical evidence will only permit interpretation of non-inferiority studies for NP and VAP using all-cause mortality as the primary endpoint as will be discussed in the next section of this report. The Applicant's proposed NI margin for a clinical response endpoint cannot be justified based on published scientific evidence.

The Applicant's choice of modifying all recorded axillary temperatures for analysis purposes cannot be justified based on scientific evidence and is inconsistent with published Guidelines regarding the evaluation of new fever in critically ill adults (6, 7). Additionally, the determination of APACHE II Scores specifically involves use of rectal temperatures (9), but the Applicant did not provide scientific evidence that the modified axillary temperatures were an acceptable surrogate for rectal temperatures in the scoring system. The use of nasal and bladder

temperature measurements were not specifically permitted in the protocol, and no scientific evidence was provided by the Applicant to substantiate their use as representative of core body temperatures.

The Applicant did not provide scientific evidence to establish that bacterial isolates obtained from nares cultures were acceptable alternatives compared to the use of lower respiratory tract cultures in determining pathogens in patients with NP and VAP.

Statistical Considerations and Noninferiority Margin Determination

According to the Noninferiority Margin Justification provided in the ISE (pages 334-354) for this NDA, the Applicant prospectively selected a noninferiority margin of 20% for the primary endpoint of clinical response for Studies 0015 and 0019. This noninferiority margin was defined in the protocols and was re-stated in the Statistical Analysis Plan (SAP) submitted to FDA before the blinded treatment assignments were known. Further, the margin was selected in accordance with the principles of the ICH E9 and ICH E10 guidance documents and was consistent with other contemporary registrational trials. Subsequent to the conduct of the ATTAIn studies and analysis of the data as planned, however, there have been new insights regarding noninferiority study designs, particularly with respect to studies of hospital acquired pneumonia (HAP). In particular, at the July 16, 2008 meeting of the Anti-infective Drugs Advisory Committee, FDA presented data justifying a noninferiority margin for the endpoint of mortality (as an alternative to clinical response) in clinical trials of HAP. This prompted the Applicant to calculate noninferiority margins for the endpoints of mortality and clinical response with respect to vancomycin as the comparator and apply these margins post hoc to the data from the ATTAIn studies. The assessment of noninferiority based on mortality was conducted on the pooled studies populations to increase the number of patients in each treatment group and achieve adequate power for an analysis of an event (i.e., death) that occurs with low frequency. The Applicant estimated a noninferiority margin for the endpoint of clinical response that preserves a clinically and statistically acceptable portion of the treatment effect for the active comparator (vancomycin) relative to placebo for mortality, and applied this noninferiority margin posthoc to each of the ATTAIn studies.

For full details on the Applicant's methodology used to derive the noninferiority margins for mortality and clinical response, refer to the discussion of the Noninferiority Margin Justification provided in the Applicant's ISE. In brief, due to the lack of published placebo-controlled studies of antibacterial therapy in patients with NP, the Applicant estimated the "placebo" mortality rate for HAP based on the results of a meta-analysis of nine studies involving inappropriate, inadequate, and delayed initial antibiotic therapy as a surrogate for estimating placebo mortality rates in HAP and VAP. This approach yielded a summary overall mortality rate of 64.2% for the patients with a 95% confidence interval (CI) of (53.6%, 73.5%). The active control (vancomycin) mortality rate for HAP was then estimated from a meta-analysis of the mortality rates for vancomycin based on three comparative clinical efficacy studies evaluating vancomycin in the treatment of patients with HAP. This approach yielded an overall mortality rate for vancomycin therapy for HAP of 22.2% with 95% CI of (19.1%, 25.5%). The treatment effect of vancomycin over "placebo" was estimated as 28.1% based on the difference between the lower bound of the

95% CI for the mortality rate derived from the studies involving inappropriate, inadequate, and delayed initial antibiotic therapy and the upper bound of the 95% CI for the mortality rate for vancomycin derived from the clinical efficacy studies.

The noninferiority margin for mortality was estimated as 7% by preserving 75% of the 28.1% treatment effect calculated above. The noninferiority margin for clinical response was derived based on the 28.1% treatment effect for vancomycin over “placebo” derived from the mortality analysis by “assuming that (the) inverse relationship between mortality rates and clinical cure rates is valid, a margin that preserves a portion of the treatment effect for mortality should also preserve a portion of the treatment effect for clinical response. Applying this margin to clinical response would mean mortality benefit is still being achieved over no antibiotic treatment. Given this relationship... a noninferiority margin for clinical response is clinically and statistically appropriate if it preserves 50% of the treatment effect for vancomycin with respect to mortality. Consequently... the post hoc noninferiority margin for clinical response should be 14% ($0.5 \times 28.1\% = 14\%$).”

Given that the 20% noninferiority margin for clinical response was prospectively defined, the Applicant analyzed the results of each individual study both in accordance with the protocols and the SAP using the 20% margin. In addition, using the same statistical methodology, noninferiority with respect to clinical response at TOC was assessed in each study using the retrospectively calculated defined margin. The Applicant conducted a post hoc assessment of noninferiority with respect to mortality using a margin determined specifically for this endpoint as described previously. The analysis of mortality was reserved for the pooled results of Studies 0015 and 0019 for the reasons cited previously.

FDA Medical Officer Comments: Published historical evidence will only permit interpretation of non-inferiority studies for NP and VAP using all-cause mortality as the primary endpoint. This issue was discussed extensively at previous FDA presentations at the July 16, 2008 meeting of the Anti-infective Drugs Advisory Committee (AIDAC) and at the public workshop “Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)” co-sponsored by the Food and Drug Administration (FDA), the Infectious Diseases Society of America (IDSA), the American Thoracic Society (ATS), the Society of Critical Care Medicine (SCCM), and the American College of Chest Physicians (ACCP) held on March 31-April 1, 2009 in Silver Spring, MD. A noninferiority margin range of 6-10% was discussed at the AIDAC Meeting, and a 10% noninferiority margin for all-cause mortality was discussed at the workshop. Based on an analysis of published data, the determination of a fixed 7% noninferiority margin using all-cause mortality as the primary endpoint for clinical efficacy trials of antibacterial drugs for the treatment of NP has been described (14).

As presented at the FDA presentation at the “Issues in the Design of Clinical Trials for Antibacterial Drugs for Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)” public workshop conducted earlier this year, it is not appropriate to extrapolate the analysis of the published all-cause mortality data to the determination of a

noninferiority margin for clinical response as the primary endpoint due to several critical issues. The crucial concerns that preclude such an approach include (1) the lack of prospectively measured placebo response data in patients with NP, (2) as a consequence of the non-randomized study designs employed in the historical studies involving inappropriate, inadequate, and delayed initial antibiotic therapy, there was the potential for confounding of the relationship between the adequacy of initial empiric antibacterial therapy and all-cause mortality by measured and unmeasured prognostic factors, and (3) the lack of scientific evidence to establish that clinical response was a valid surrogate for survival. Thus, it is this FDA Medical Officer's viewpoint that the Applicant's prospectively selected 20% noninferiority margin for a clinical response endpoint and the Applicant's post hoc 14% noninferiority margin for a clinical response endpoint estimated from the mortality data analysis noted above cannot be justified based on published scientific evidence and cannot be extrapolated from the published all-cause mortality data. Interpretation of noninferiority trials for antibacterial drugs for the treatment of NP and VAP can only be justified using all-cause mortality as the primary endpoint.

Clinical trials 0015 and 0019 were not prospectively designed with sufficient size and power individually to independently assess noninferiority in a replicative manner based on a NI margin of 7% for an all-cause mortality endpoint. This FDA Medical Officer finds that the Applicant's assessment of the mortality endpoint using pooled study populations is problematic. The assessment of noninferiority based on the endpoint of mortality was limited by the Applicant to the pooled population of the two studies to increase the number of patients in each treatment group and achieve adequate power for an analysis of an event (i.e., death) that occurs with low frequency. However, this approach does not satisfy the requirement for two adequate and well-controlled studies to provide substantial evidence of effectiveness of a new treatment, which would necessitate the conduct of an additional clinical trial. Also, in consideration of the substantial differences in baseline characteristics and risk factors for death between the patient populations enrolled in Studies 0015 and 0019, attempts to pool the two study populations are unsound as described in other sections of this report. The finding of disparate all-cause mortality outcomes across the individual studies (0015 and 0019) also would not support a conclusion of noninferiority of telavancin compared to vancomycin, and would likely prompt the need for reassessment and, potentially, additional clinical trials as well.

6.1.2 Demographics

In Study 0015, 746 patients were randomized 1:1 to telavancin (n=372) and vancomycin (n=374). In Study 0019, 757 patients were randomized 1:1 to telavancin (n=377) and vancomycin (n=380). The following table summarizes selected baseline characteristics of the randomized populations.

Table 59: FDA Medical Officer Summary Table of Selected Baseline Patient Characteristics, Studies 0015 and 0019, AT Randomized Population

| | Study 0015 | | Study 0019 | |
|--------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=377 | Vancomycin N=380 |
| | n (%) | n (%) | n (%) | n (%) |
| Age | | | | |
| 18-44 | 70 (18.8) | 49 (13.1) | 71 (18.8) | 66 (17.4) |
| 45-64 | 100 (26.9) | 113 (30.2) | 111 (29.4) | 118 (31.1) |
| 65-74 | 71 (19.1) | 88 (23.5) | 96 (25.5) | 87 (22.9) |
| ≥75 | 131 (35.2) | 124 (33.2) | 99 (26.3) | 109 (28.7) |
| Median | 66 | 68 | 65 | 65 |
| Range | 18-99 | 19-97 | 18-100 | 18-97 |
| Gender | | | | |
| Male | 235 (63.2) | 213 (57.0) | 252 (66.8) | 256 (67.4) |
| Female | 137 (36.8) | 161 (43.0) | 125 (33.2) | 124 (32.6) |
| Race | | | | |
| White | 267 (71.8) | 272 (72.7) | 248 (65.8) | 254 (66.8) |
| Asian | 91 (24.5) | 87 (23.3) | 81 (21.5) | 91 (23.7) |
| Black | 10 (2.7) | 14 (3.7) | 15 (4.0) | 6 (1.6) |
| Other | 4 (1.1) | 1 (0.3) | 33 (8.8) | 29 (7.6) |
| Region | | | | |
| 01 | 201 (54.0) | 200 (53.5) | 111 (29.4) | 111 (29.2) |
| 02 | 76 (20.4) | 79 (21.1) | 44 (11.7) | 43 (11.3) |
| 03 | 95 (25.5) | 95 (25.4) | 222 (58.9) | 226 (59.5) |
| VAP | | | | |
| No | 269 (72.3) | 274 (73.3) | 264 (70.0) | 269 (70.8) |
| Yes | 103 (27.7) | 100 (26.7) | 113 (30.0) | 111 (29.2) |

As depicted above, the patient populations enrolled in each treatment group within Studies 0015 and 0019 were similar in terms of selected baseline characteristics. In addition, except for the incidence of hepatic failure/encephalopathy/coma between the two treatment groups in Study 0019, the treatment groups within each study had comparable frequencies of selected pre-treatment characteristics and various co-morbid conditions that could potentially be associated with an increased risk for death as illustrated in the following table:

Table 60: FDA Medical Officer Table of Selected Pre-treatment Characteristics and Co-morbid Conditions that could potentially be associated with a risk for death, Studies 0015 and 0019, AT Population

| Pre-treatment Characteristics and Co-morbid Conditions | Study 0015 | | | Study 0019 | | |
|--|--------------|--------------|--------------------------------|--------------|--------------|--------------------------------|
| | TLV N=372 | VAN N=374 | 95% CI for diff (TLV – VAN) | TLV N=377 | VAN N=380 | 95% CI for diff (TLV – VAN) |
| | n | n | | n | n | |
| Acute renal failure | 43 | 35 | 2.2 (-2.2, 6.6) | 30 | 29 | 0.3 (-3.5, 4.1) |
| Chronic renal failure | 32 | 35 | -0.8 (-4.9, 3.3) | 11 | 17 | -1.6 (-4.2, 1.1) |
| Baseline CrCL <50 mL/min | 141 | 135 | 1.8 (-5.1, 8.7) | 100 | 109 | -2.2 (-8.5, 4.2) |
| Serum creatinine ≤1.2 mg/dL [†] | 259 | 272 | -3.1 (-9.6, 3.4) | 301 | 295 | 2.2 (-3.6, 8.0) |
| Serum creatinine >1.2 mg/dL [†] | 103 | 89 | 3.9 (-2.4, 10.2) | 68 | 74 | -1.4 (-7.0, 4.1) |
| Hemodialysis | 11 | 9 | 0.6 (-1.8, 2.9) | 3 | 5 | -0.5 (-2.0, 0.9) |
| Diabetic status | 100 | 100 | 0.1 (-6.2, 6.5) | 69 | 65 | 1.2 (-4.2, 6.6) |
| History of diabetes mellitus | 118 | 114 | 1.2 (-5.4, 7.9) | 85 | 77 | 2.3 (-3.6, 8.1) |
| Any pulmonary co-morbidity | 247 | 231 | 4.3 (-2.2, 11.5) | 254 | 263 | -1.8 (-8.5, 4.8) |
| COPD | 98 | 96 | 0.7 (-5.6, 7.0) | 94 | 98 | -0.9 (-7.1, 5.3) |
| ARDS | 24 | 20 | 1.1 (-2.3, 4.5) | 9 | 10 | -0.2 (-2.5, 2.0) |
| Pulmonary edema | 41 | 27 | 3.8 (-0.3, 7.9) | 31 | 44 | -3.4 (-7.6, 0.9) |
| VAP | 103 | 100 | 1.0 (-5.4, 7.3) | 113 | 111 | 0.8 (-5.7, 7.3) |
| HAP | 248 | 252 | -0.7 (-7.5, 6.0) | 288 | 304 | -3.6 (-9.5, 2.3) |
| HCAP | 124 | 119 | 1.5 (-5.2, 8.2) | 89 | 75 | 3.9 (-2.0, 9.7) |
| Baseline signs/symptoms SIRS | 312 | 311 | 0.7 (-4.6, 6.0) | 312 | 321 | -1.7 (-7.0, 3.6) |
| Sepsis/septic shock/MOF at any time | 69 | 66 | 0.9 (-4.6, 6.4) | 62 | 48 | 3.8 (-1.2, 8.8) |
| Immunocompromised | 5 | 6 | -0.3 (-2.0, 1.5) | 15 | 19 | -1.0 (-4.0, 1.9) |
| Torsades de pointes | 208 | 217 | -2.1 (-9.2, 5.0) | 171 | 171 | 0.4 (-6.7, 7.4) |
| Organ failure at baseline | 69 | 67 | 0.6 (-4.9, 6.2) | 88 | 95 | -1.7 (-7.8, 4.4) |
| ICU at baseline | 224 | 216 | 2.5 (-4.6, 9.5) | 207 | 224 | -4.0 (-11.1, 3.0) |
| History of atrial fibrillation | 72 | 76 | -1.0 (-6.7, 4.8) | 65 | 48 | 4.6 (-0.5, 9.7) |
| History of congestive heart failure | 71 | 78 | -1.8 (-7.5, 4.0) | 59 | 63 | -0.9 (6.2, 4.3) |
| History of myocardial infarction | 47 | 62 | -3.9 (-9.0, 1.1) | 36 | 44 | -2.0 (-6.4, 2.3) |
| History of left ventricular hypertrophy | 16 | 12 | 1.1 (-1.6, 3.8) | 24 | 32 | -2.1 (-5.8, 1.7) |
| History other cardiac diseases | 136 | 159 | -6.0 (-13.0, 1.0) | 159 | 153 | 1.9 (-5.1, 8.9) |
| Bacteremia | 37 | 34 | 0.9 (-3.4, 5.1) | 31 | 38 | -1.8 (-5.9, 2.3) |
| Hepatic failure, encephalopathy, coma | 10 | 12 | -0.5 (-2.9, 1.9) | 3 | 12 | -2.4 (-4.3, -0.4)* |

n=subject count; CrCl=creatinine clearance; *statistically significant; [†]at baseline

HAP=hospital-acquired pneumonia; HCAP=healthcare-associated pneumonia; MOF = multi-organ failure; TLV=telavancin; VAN=vancomycin

As Studies 0015 and 0019 have an identical trial design, it is important to assess for any cross-study differences in baseline characteristics and co-morbid conditions among the two trial populations in order to determine comparability for pooling. As discussed below, there were several noteworthy cross-study differences in potential risk factors for mortality (such as diabetes mellitus and renal impairment/failure) that were statistically significantly different as depicted in the tables below.

Table 61: FDA Medical Officer Table of Selected Baseline Demographic and Medical History/Co-morbid Conditions potentially associated with Mortality, Studies 0015 and 0019, AT Population

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

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

In assessing various demographic characteristics and co-morbid conditions in the pooled treatment groups across the two trials, it is evident that there are more patients in Study 0015 with chronic renal failure, baseline CrCl<50 mL/min, serum creatinine >1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, ARDS, HCAP, torsades, history of atrial fibrillation, and history of myocardial infarction. In contrast, there were more patients in Study 0019 with serum creatinine ≤1.2 mg/dL, immunocompromise, HAP, organ failure at

baseline, and history of left ventricular hypertrophy compared to Study 0015, and the differences were statistically significant. Thus, compared to the Applicant's analytical approach where the two study populations were pooled for mortality analysis, it is evident that the populations were substantially different based on pre-treatment characteristics and co-morbid conditions such that pooling for mortality analysis was not advisable and that the mortality data for each study should be assessed individually.

In assessing various demographic characteristics and co-morbid conditions in the individual telavancin treatment groups across Studies 0015 and 0019 as depicted in the table below, it is evident that there are more patients in the telavancin treatment group of Study 0015 with chronic renal failure, baseline CrCl < 50 mL/min, serum creatinine > 1.2 mg/dL, hemodialysis, diabetic status (yes), history of diabetes mellitus, HCAP, and torsades. In contrast, there were more patients in the telavancin treatment group of Study 0019 with serum creatinine ≤ 1.2 mg/dL, immunocompromise, HAP, and organ failure at baseline compared to Study 0015, and the differences were statistically significant.

Table 62: FDA Medical Officer Table of Selected Baseline Demographic and Medical History/Co-morbid Conditions potentially associated with risk for mortality, Telavancin arms, Studies 0015 and 0019, AT Population

| Baseline Characteristic | Telavancin Study 0015 N= 372 n (%) | Telavancin Study 0019 N= 377 n (%) | 95% CI for Risk difference (Study 0015-Study 0019) |
|--|--|--|--|
| Acute renal failure | 43 | 30 | 3.60 (-0.64, 7.85) |
| Chronic renal failure | 32 | 11 | 5.68 (2.37, 9.00)* |
| Baseline CrCl<50 mL/min | 141 | 100 | 11.38 (4.73, 18.02)* |
| Serum creatinine ≤1.2 mg/dL [†] | 259 | 301 | -10.22 (-16.40, -4.03)* |
| Serum creatinine >1.2 mg/dL [†] | 103 | 68 | 9.65 (3.67, 15.63)* |
| Hemodialysis | 11 | 3 | 2.16 (0.22, 4.10)* |
| Diabetic status (yes) | 100 | 69 | 8.58 (2.62, 14.54)* |
| History of diabetes mellitus | 118 | 85 | 9.17 (2.84, 15.51)* |
| Any pulmonary co-morbidity | 247 | 254 | -0.98 (-7.72, 5.76) |
| COPD | 98 | 94 | 1.41 (-4.84, 7.66) |
| ARDS | 24 | 9 | 4.06 (1.13, 7.0)* |
| Pulmonary edema | 41 | 31 | 2.80 (-1.42, 7.02) |
| VAP | 103 | 113 | -2.29 (-8.77, 4.20) |
| HAP | 248 | 288 | -9.73 (-16.15, -3.30)* |
| HCAP | 124 | 89 | 9.73 (3.30, 16.15)* |
| Baseline signs/symptoms SIRS | 312 | 312 | 1.11 (-4.23, 6.45) |
| Immunocompromised | 5 | 15 | -2.63 (-4.93, -0.34)* |
| Torsades | 208 | 171 | 10.56 (3.43, 17.68)* |
| Organ failure at baseline | 69 | 88 | -4.79 (-10.61, 1.02) |
| ICU at baseline | 224 | 207 | 5.31 (-1.76, 12.38) |
| History of atrial fib | 72 | 65 | 2.11 (-3.42, 7.65) |
| History of CHF | 71 | 59 | 3.44 (-1.99, 8.86) |
| History of MI | 47 | 36 | 3.09 (-1.41, 7.58) |
| History of left ventricular hypertrophy | 16 | 24 | -2.06 (-5.28, 1.15) |
| History other cardiac diseases | 136 | 159 | -5.62 (-12.60, 1.37) |
| Bacteremia | 37 | 31 | 1.72 (-2.40, 5.84) |

n=subject count; CrCl=creatinine clearance; *statistically significant

HAP=hospital-acquired pneumonia; HCAP=healthcare-associated pneumonia; [†]at baseline

FDA Medical Officer Comments: The substantial differences in selected baseline characteristics and co-morbid conditions potentially associated with increased mortality as described above underscored that the patient populations enrolled in Studies 0015 and 0019 were not similar despite identical trial designs and could not be readily combined for mortality analysis (see Applicant's all-cause mortality data in Sections 5.3.1.2.7, 5.3.2.2.7, 6.1.1, and 6.1.5 of this report). Notwithstanding the Applicants's contention that the assessment of mortality should be limited to the pooled results of Studies 0015 and 0019 to achieve sufficient power for analysis,

the suitability of pooling of the two clinical trial populations without consideration of the individual study results and cross-study population differences in selected baseline characteristics and co-morbid conditions that could potentially be risk factors for death was questionable.

6.1.3 Subject Disposition

Refer to Section 7.3.3 for further details.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for both studies was the clinical response at the TOC evaluation conducted 7 to 14 days after completion of study medication. The primary efficacy analysis was an evaluation of telavancin’s clinical non-inferiority to vancomycin, with respect to clinical response at the TOC assessment, employing a prospectively determined noninferiority margin (the “Δ”) of 20% and a post hoc noninferiority margin of 14%, meaning that non-inferiority will be declared if the lower bound of the 95% CI for the difference in cure rates (telavancin – vancomycin) exceeds -Δ. In this analysis, the clinically evaluable (CE) and all-treated (AT) analysis populations were considered co-primary.

FDA Medical Officer Comment: Historical evidence will only allow interpretation of non-inferiority studies for NP and VAP that use all-cause mortality as the primary endpoint, as was discussed during the FDA presentation at the FDA/IDSA/co-sponsored HAP/VAP workshop held on March 31-April 1, 2009 in Silver Spring, MD and in a pending publication (14). The clinical response data presented in both Studies 15 and 19 is not informative in differentiating inferior from non-inferior treatments, because there is no historical evidence to support a NI margin based on a clinical response endpoint. The two studies were not designed to evaluate all-cause mortality as the primary endpoint for replicated evidence of treatment effect.

The following table summarizes the Applicant’s clinical cure rates in the CE and AT populations, the co-primary analysis populations, for Studies 0015 and 0019:

Table 63: Summary of Clinical Cure Rates at the TOC Visit, Studies 0015 and 0019 (from Applicant's Summary of Clinical Efficacy, Module 2.7.3, Tables 6 and 12)

| Analysis Population | Study 0015 | | | Study 0019 | | |
|---------------------|-----------------|-----------------|-------------------------|-----------------|-----------------|-------------------------|
| | Telavancin | Vancomycin | Diff (95% CI) (TLV-VAN) | Telavancin | Vancomycin | Diff (95% CI) (TLV-VAN) |
| AT | 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) |
| 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) |

TLV=telavancin; VAN=vancomycin

FDA Medical Officer Comments: It is noteworthy that the CE populations excluded patients with NP due to Gram-negative bacteria only, whereas a total of 292 patients who had pneumonia due to Gram-negative pathogens only were included in the AT populations. As Studies 0015 and

0019 were designed to compare the safety and efficacy of telavancin and vancomycin against Gram-positive bacterial pathogens, the inclusion of patients who had NP involving only Gram-negative pathogens in one of the primary analysis populations is not informative regarding the treatment effect of the study drugs. The number of subjects who had NP involving only Gram-negative pathogens at baseline are provided in the table below:

Table 64: FDA Medical Officer Summary Table of Subject Count who had NP involving only Gram-negative Pathogens at Baseline, Studies 0015 and 0019, AT Population

| | Study 0015 n/N (%) | Study 0019 n/N (%) |
|------------|-----------------------|-----------------------|
| Telavancin | 70/372 (18.8) | 79/377 (21.0) |
| Vancomycin | 67/374 (17.9) | 76/380 (20.0) |

FDA Medical Officer Comments: As depicted above, approximately 18-20% of the patients in the AT populations of each treatment group within Studies 0015 and 0019 had NP involving only Gram-negative pathogens at baseline. Thus, the FDA Medical Officer conducted an exploratory re-analysis of the clinical cure rates in the AT population after patients having NP involving only Gram-negative pathogens had been excluded and summarized the findings in the following table:

Table 65: FDA Medical Officer Summary Table of the Clinical Cure Rates in the AT Population for Studies 0015 and 0019 following exclusion of patients with NP due to Gram-negative bacteria only

| | Study 0015 | | | Study 0019 | | |
|---|-------------|-------------|-------------------|-------------|-------------|-------------------|
| | Telavancin | Vancomycin | Diff (95% CI)** | Telavancin | Vancomycin | Diff (95% CI)** |
| Original AT population | 372 | 374 | | 377 | 380 | |
| Patient count with NP due to GNB only* | 70 | 67 | | 79 | 76 | |
| AT excluding patients with NP due to GNB only* | 302 | 307 | | 298 | 304 | |
| Clinical Cure rate at TOC in AT excluding patients with NP due to GNB only* | 177 (58.6%) | 188 (61.2%) | -2.6 (-10.4, 5.2) | 181 (60.7%) | 194 (63.8%) | -3.1 (-10.8, 4.7) |

*GNB= Gram-negative bacteria at baseline; **Diff=Telavancin – vancomycin

FDA Medical Officer Comments: Based on the results of the above exploratory re-analysis of the clinical cure rates in the AT population after patients having NP involving only Gram-negative pathogens had been excluded, the clinical cure rates across treatment groups within each study were comparable.

6.1.5 Analysis of Secondary Endpoints(s)

All-cause Mortality data provided by the Applicant in the original NDA Submission

All-cause mortality was considered a secondary endpoint in clinical trials 0015 and 0019. In those Phase 3 HAP studies, deaths were systematically recorded up to the Follow-up/TOC Visit or 28 days after End-of-therapy (EOT) for those patients who did not have a Follow-up Visit (protocol-specified window).

Table 66: Applicant’s Summary Analysis of Deaths for Studies 0015 and 0019, AT Safety Population (from Applicant's Summary of Clinical Safety, Module 2.7.4)

| | Number of patients | | | | | |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | 0015 | | 0019 | | 0015 + 0019 Total | |
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Total Deaths in window [2] | 80 (21.5%) | 62 (16.6%) | 70 (18.5%) | 78 (20.6%) | 150 (20.0%) | 140 (18.6%) |
| Difference (95% CI) [1] | 4.9% (-0.7%, 10.6%) | | -2.2% (-7.8%, 3.5%) | | 1.4% (-2.6%, 5.3%) | |
| Deaths in window while receiving Study Medication [3] | 48 (12.9%) | 45 (12.0%) | 44 (11.6%) | 35 (9.3%) | 92 (12.3%) | 80 (10.6%) |
| Difference (95% CI) [1] | 0.9% (-3.9%, 5.6%) | | 2.4% (-2.0%, 6.7%) | | 1.6% (-1.6%, 4.8%) | |

[1] Point estimate and 95% confidence interval on the treatment difference (telavancin – vancomycin) in death rate. The pooled analysis is stratified by study.

[2] deaths based on patients with treatment-emergent adverse events with death as an outcome and deaths occurred within protocol-specified window.

[3] Deaths occurred prior to end-of-therapy (EOT) or 1 day after EOT

As depicted above, there was a notable imbalance in the mortality rates between the two treatment groups in Study 0015 with a higher death rate (by approximately 5%) in the telavancin group compared to the vancomycin group. In Study 0019, the mortality rates were comparable across the treatment groups.

FDA Medical Officer Comments: As a consequence of the broad range in duration of study drug administration, the variability of completing the TOC visit, and due to concerns that patient deaths may have occurred subsequent to the follow-up/TOC visit but before a uniform time interval (such as 28 days following randomization), the Division issued an information request on February 25, 2009 requesting 28-day post-treatment mortality data for all patients in both studies. The Applicant issued a Response to the FDA Information Request dated March 26, 2009 in which the following mortality data was reported. Of note, the Applicant’s stated analysis of mortality was reserved for the pooled results of Studies 0015 and 0019. The Applicant limited assessment to the pooled studies population in order to increase the number of patients in each treatment group and achieve adequate power for an analysis of an event (i.e., death) that occurs with low frequency.

All-cause Mortality data provided by the Applicant in response to the FDA Information Request dated March 26, 2009

In response to the FDA Information Request dated March 26, 2009, the Applicant provided the following table of all-cause mortality data using a 28-day post-therapy mortality window:

Table 67: Applicant's Summary of Mortality Data for Studies 0015 and 0019 (from Applicant's Response dated March 26, 2009 to the FDA Information Request dated February 25, 2009)

| | Number of patients | |
|--|---------------------|---------------------|
| | Telavancin N=749 | Vancomycin N=754 |
| Deaths between Start of Study Drug and EOT Visit + 28 days | 160 (21.4%) | 147 (19.5%) |
| Deaths between EOT Visit and EOT Visit + 28 days | 113 | 104 |
| Deaths between TOC Visit and EOT Visit + 28 days | 11 | 6 |

For the mortality endpoint, the Applicant calculated a NI margin of 7% as previously described. The Applicant conducted a post-hoc power calculation to support the requirement for sample size of approximately 1,500. A similar analysis with sample size of only 750 would lack sufficient power to assess noninferiority and, thus, the Applicant stipulated that the mortality analysis should be limited to the pooled studies only. Thus, the Applicant's mortality summary table above involved only pooled data and did not provide comparative all-cause mortality data for the individual studies based on differences in mortality rates across treatment arms within each study. Based on the pooled data from Studies 0015 and 0019, the all-cause mortality rates for telavancin-treated and vancomycin-treated patients appeared similar.

FDA Medical Officer Comments: Because of substantial differences in certain demographic characteristics between the patient populations across studies as described in Section 6.1.2, this FDA Medical Officer does not feel that it is appropriate to pool the populations of Studies 0015 and 0019 for mortality analysis purposes. Thus, an all-cause mortality analysis that includes consideration of findings in each study individually will be presented below.

The following table provides an exploratory analysis of the Applicant's all-cause mortality data above in the AT population (including patients with NP and VAP due to Gram negative pathogens only) stratified by individual study and pooled data. Odds ratios are included in the table and in some subsequent tables as alternatives to the the risk difference for assessing the treatment effect of telavancin compared to vancomycin.

Table 68: FDA Medical Officer Table of All-Cause Mortality rates through 28 days post-therapy for Studies 0015 and 0019 in which patients with NP and VAP due to Gram-negative pathogens only are included in the AT Efficacy Population

| | Study | Randomized Treatment Group | N (AT) | n (%) | 95%CI for risk difference (TLV-VAN) | Odds Ratio with 95%CI |
|---|--------|----------------------------|--------|------------|-------------------------------------|-----------------------|
| Deaths between Start of Study Drug and EOT Visit + 28 days post-Treatment | 0015 | TLV | 372 | 85 (22.8) | 6.0 (0.3, 11.7)* | 1.46 (1.02, 2.10)* |
| | | VAN | 374 | 63 (16.8) | | |
| | 0019 | TLV | 377 | 75 (19.9) | -2.2 (-8.0, 3.6) | 0.88 (0.62, 1.24) |
| | | VAN | 380 | 84 (22.1) | | |
| | Pooled | TLV | 749 | 160 (21.4) | 1.8 (-2.2, 5.9) | 1.12 (0.84, 1.50) |
| | | VAN | 754 | 147 (19.5) | | |
| Deaths between EOT Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 350 | 63 (18.0) | 6.4 (1.1, 11.6)* | 1.76 (1.09, 2.55)* |
| | | VAN | 352 | 41 (11.6) | | |
| | 0019 | TLV | 352 | 50 (14.2) | -3.3 (-8.7, 2.0) | 0.78 (0.52, 1.17) |
| | | VAN | 359 | 63 (17.5) | | |
| | Pooled | TLV | 702 | 113 (16.1) | 1.5 (-2.3, 5.2) | 1.12 (0.84, 1.50) |
| | | VAN | 711 | 104 (14.6) | | |
| Deaths between TOC Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 292 | 5 (1.7) | 1.4 (-0.2, 3.0) | 5.42 (0.63, 46.66) |
| | | VAN | 312 | 1 (0.3) | | |
| | 0019 | TLV | 308 | 6 (1.9) | 0.3 (-1.8, 2.4) | 1.18 (0.36, 3.90) |
| | | VAN | 301 | 5 (1.7) | | |
| | Pooled | TLV | 600 | 11 (1.8) | 0.9 (-0.5, 2.2) | 1.89 (0.69, 5.14) |
| | | VAN | 613 | 6 (1.0) | | |

*statistically significant difference; AT=all-treated population; TLV=telavancin; VAN=vancomycin; N(AT) = total # of patients in all-treated population; n (%) = patient count (%) per strata

FDA Medical Officer Comments: It is noteworthy that there were higher risk differences and odds ratio for death in the telavancin group compared to the vancomycin group in Study 0015 for deaths between start of study drug and EOT + 28 days post-therapy and for deaths between EOT and EOT + 28 days post-therapy, and the differences were statistically significant. Similar disparities were not observed with respect to the mortality data for Study 0019 or the pooled study data. Since historical evidence will only allow interpretation of non-inferiority studies for NP and VAP that use all-cause mortality as the primary endpoint as described previously, these findings indicate that telavancin is inferior to vancomycin in the treatment of NP and VAP.

Since the AT population includes patients with Gram-negative pathogens only, a separate exploratory all-cause mortality analysis was conducted by the FDA Medical Officer in which such patients were excluded from the AT population. By excluding patients with infections due only to Gram-negative pathogens, the mortality data would reflect the outcomes of patients with NP and VAP due to Gram-positive bacterial pathogens only or mixed Gram-positive and Gram-negative infections that were treated with telavancin and vancomycin alone or in combination with Gram-negative antibacterial drugs, and the findings would reflect the treatment effect of the study medications. The results of that exploratory analysis are provided below:

Table 69: FDA Medical Officer Summary Table of All-Cause Mortality rates through 28 days post-therapy in which patients with NP and VAP due to Gram-negative pathogens only have been excluded, AT Efficacy Population

| | Study | Randomized Treatment Group | N (AT) | n (%) | 95%CI for Risk difference (TLV-VAN) | Odds Ratios with 95%CI |
|---|--------|----------------------------|--------|------------|-------------------------------------|------------------------|
| Deaths between Start of Study Drug and EOT Visit + 28 days post-Treatment | 0015 | TLV | 302 | 72 (23.8) | 5.9 (-0.5, 12.4) | 1.43 (0.97, 2.13) |
| | | VAN | 307 | 55 (17.9) | | |
| | 0019 | TLV | 298 | 62 (20.8) | -0.2 (-6.7, 6.3) | 0.99 (0.67, 1.46) |
| | | VAN | 304 | 64 (21.1) | | |
| | Pooled | TLV | 600 | 134 (22.3) | 2.9 (-1.7, 7.4) | 1.19 (0.9, 1.57) |
| | | VAN | 611 | 119 (19.5) | | |
| Deaths between EOT Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 285 | 55 (19.3) | 7.4 (1.5, 13.3)* | 1.77 (1.12, 2.82)* |
| | | VAN | 286 | 34 (11.9) | | |
| | 0019 | TLV | 275 | 39 (14.2) | -1.9 (-7.8, 4.0) | 0.86 (0.54, 1.37) |
| | | VAN | 286 | 46 (16.1) | | |
| | Pooled | TLV | 560 | 94 (16.8) | 2.8 (-1.4, 7.0) | 1.24 (0.90, 1.72) |
| | | VAN | 572 | 80 (14.0) | | |
| Deaths between TOC Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 234 | 4 (1.7) | 1.3 (-0.5, 3.1) | 4.38 (0.49, 39.50) |
| | | VAN | 253 | 1 (0.4) | | |
| | 0019 | TLV | 242 | 6 (2.5) | 0.8 (-1.7, 3.3) | 1.53 (0.43, 5.47) |
| | | VAN | 244 | 4 (1.6) | | |
| | Pooled | TLV | 476 | 10 (2.1) | 1.1 (-0.5, 2.7) | 2.11 (0.72, 6.22) |
| | | VAN | 497 | 5 (1.0) | | |

*statistically significant difference; AT=all-treated population; TLV=telavancin; VAN=vancomycin; N(AT)=total # of patients in all-treated population; n(%)=patient count (%) per strata

FDA Medical Officer Comments: It is noteworthy that there was a higher risk difference and odds ratio for death in the telavancin arm compared to the vancomycin of Study 0015 for deaths between start of study drug and EOT + 28 days post-therapy and for deaths between EOT and EOT + 28 days post-therapy, and the differences were statistically significant for deaths between EOT and EOT + 28 days post-therapy. Similar disparities were not observed with respect to the mortality data for Study 0019 or the pooled study data. Since historical evidence will only allow interpretation of non-inferiority studies for NP and VAP that use all-cause mortality as the primary endpoint as described previously, the findings from Study 0015 indicate that telavancin is inferior to vancomycin in the treatment of NP and VAP.

Univariate Analysis of All-cause Mortality data provided by the Applicant in response to the FDA Information Request dated March 26, 2009

As discussed in Section 6.1.2, there are more patients (pooled telavancin and vancomycin-treated) in Study 0015 with hemodialysis, diabetic status (yes), history of diabetes mellitus, serum creatinine >1.2 mg/dL along with fewer patients with serum creatinine ≤1.2 mg/dL at baseline compared to Study 0019, and the differences were statistically significant. Those differences in baseline characteristics were also evident when their frequencies were compared between the telavancin groups across each study.

FDA Medical Officer Comments: Since diabetes mellitus and renal impairment may be independent risk factors for mortality, a sensitivity analysis was performed by the FDA Medical Officer to assess the frequencies of various parameters across each treatment group within each study to assess if there was an imbalance that could represent a signal associated with the mortality disparity among the deaths in the AT population (includes patients with pneumonia due to Gram-negative pathogens only) between start of treatment and 28 days post-treatment. As is evident from the table below, there were statistically significant differences between treatment groups within each study for certain parameters. For Study 0015, there was a higher frequency of initial inadequate Gram-negative therapy in the telavancin group compared to the vancomycin group and the difference was statistically significant. In Study 0019, there was a greater proportion of patient deaths in those having baseline serum creatinine >1.2 mg/dL in the telavancin group, while greater proportion of patient deaths having baseline serum creatinine ≤1.2 mg/dL in the vancomycin group. Both findings were statistically significant.

Table 70: FDA Medical Officer Summary of Baseline Co-morbidities for all patients who died between Start of Treatment and EOT Visit + 28 days post-treatment, Studies 0015 and 0019, AT Population (includes patients with NP and VAP due to Gram-negative pathogens only)

| Parameter | Study 0015 | | | Study 0019 | | |
|---|-------------|-------------|------------------------------|-------------|-------------|------------------------------|
| | TLV N=85 | VAN N=63 | 95% CI for Diff (TLV-VAN) | TLV N=75 | VAN N=84 | 95% CI for Diff (TLV-VAN) |
| Baseline diabetic status (yes) | 32 (28%) | 20 (32%) | -5.9 (-9.5, 21.3) | 19 (25%) | 16 (19%) | 6.3 (-6.6, 19.2) |
| History of diabetes mellitus | 38 (45%) | 23 (37%) | 8.2 (-7.7, 24.1) | 20 (27%) | 20 (24%) | 2.8 (-10.7, 16.4) |
| Hemodialysis | 3 (4%) | 2 (3%) | 0.35 (-5.5, 6.2) | 1 (1%) | 2 (2%) | -1.0 (-5.2, 3.1) |
| Baseline serum creatinine ≤1.2 mg/dL | 48 (56%) | 43 (68%) | -11.8 (-27.4, 3.8) | 46 (61%) | 64 (76%) | -14.9 (-29.2, -0.6)* |
| Baseline serum creatinine >1.2 mg/dL | 37 (44%) | 20 (32%) | 11.8 (-3.8, 27.4) | 29 (39%) | 20 (24%) | 14.9 (0.6, 29.2)* |
| VAP | 26 (31%) | 18 (29%) | 2.0 (-12.8, 16.8) | 31 (41%) | 23 (27%) | 14.0 (-0.7, 28.6) |
| Acute renal failure | 18 (21%) | 8 (13%) | 8.5 (-3.5, 20.4) | 17 (23%) | 10 (12%) | 10.8 (-1.0, 22.5) |
| Adequate Gram-negative therapy | 59 (64%) | 49 (78%) | -8.4 (-22.6, 5.8) | 45 (60%) | 52 (62%) | -1.9 (-17.1, 13.3) |
| Initial inadequate Gram-negative therapy | 5 (6%) | 0 (0%) | 5.9 (0.9, 10.9)* | 7 (9%) | 9 (11%) | -1.4 (-10.7, 8.0) |
| Never received adequate Gram-negative therapy | 21 (25%) | 14 (22%) | 2.5 (-11.3, 16.2) | 23 (31%) | 23 (27%) | 3.3 (-10.9, 17.4) |

*statistically significant difference; VAP = ventilator-associated pneumonia; TLV = telavancin; VAN = vancomycin

As depicted in the table above, there was a statistically significant difference between treatment groups for Study 0015 involving inadequate initial Gram-negative therapy. In reviewing the data for the five patient deaths in the telavancin arm of Study 0015 who were assessed as having received “Initial inadequate Gram-negative Therapy”, it was evident that three of the patients (0015-18010-4138, 0015-30905-4034, and 0015-52000-4703) had had a Gram-negative pathogen isolated from baseline respiratory tract cultures, one patient (0015-01005-4238) had only a Gram-negative pathogen (*Acinetobacter baumannii*) isolated at baseline, while one patient (0015-30905-4234) had no baseline pathogens isolated from respiratory or blood cultures. The patient with only a Gram-negative baseline pathogen does not contribute any useful information in assessing the efficacy of telavancin, since the drug does not exhibit Gram-negative antibacterial activity. Subsequent review of the CRF for patient 0015-30905-4234 revealed that the patient was treated with study drug for seven days for a right upper and lower lobe pneumonia. The respiratory tract (endotracheal specimens) and blood cultures were reported as no growth at the Pre-treatment and Day 4 study assessments, whereas *Serratia marcescens* was isolated from the respiratory tract culture at EOT (Day 7). Despite the growth of *S. marcescens* from the respiratory culture, the investigator assessed the patient as having been “cured” at EOT. The patient’s chest x-rays at EOT showed complete resolution of the previously noted lung infiltrates. The patient died from “septic shock” on the following day despite having been started on aztreonam and meropenem on [REDACTED] (b) (6). Although initially designated as a serious adverse event that prompted study drug discontinuation, the supplemental Data Clarification Form indicated that the pneumonia was cured at EOT and the patient died from septic shock that developed from another source (“septicemia”), and that the designation of septic shock as a serious adverse event would be changed to “none”. In addition, the cause of the death was to be changed to “other”. Thus, the patient did not have clinical, microbiological, or radiographic evidence of *Serratia* pneumonia to warrant Gram-negative antibacterial coverage at any time while on study drug.

FDA Medical Officer Comments: In this FDA Medical Officer’s opinion, the data indicates that the designation of “inadequate initial Gram-negative therapy” for this patient was inaccurate, and the patient should not have been included in the category of “inadequate initial Gram-negative therapy” in the telavancin group for Study 0015 in the table above. Recalculation of the 95% CI for the difference (telavancin-vancomycin) for this category using three patient deaths (rather than five) for telavancin compared to none for vancomycin results in a difference of 3.5 with 95% CI of (-0.4, 7.5). This result is not statistically significant and, thus, the risk difference for death among patients treated with telavancin compared to vancomycin in Study 0015 cannot be explained in terms of death due to inadequate initial Gram-negative therapy.

Additionally, the Medical Monitor’s evaluations of the adequacy of Gram-negative therapy were conducted following unblinding to treatment group as previously described, raising concern about potentially biased assessments.

The following table summarizes the frequencies of various parameters across each treatment group within Studies 0015 and 0019 to assess if there was an imbalance that could represent a safety signal associated with the mortality disparity among the deaths in the AT population

(includes patients with pneumonia due to Gram-negative pathogens only) between EOT and 28 days post-treatment.

Table 71: FDA Medical Officer Summary Table of Baseline Co-morbidities for patients who died between EOT Visit and EOT + 28 days post-therapy, Studies 0015 and 0019, AT Population (includes patients with NP and VAP due to Gram-negative pathogens only)

| Parameter | Study 0015 | | | Study 0019 | | |
|---|-------------|-------------|------------------------------|-------------|-------------|------------------------------|
| | TLV N=63 | VAN N=41 | 95% CI for Diff (TLV-VAN) | TLV N=50 | VAN N=63 | 95% CI for Diff (TLV-VAN) |
| Baseline diabetic status (yes) | 26 (41%) | 12 (29%) | 12.0 (-6.5, 30.5) | 14 (28%) | 12 (19%) | 9.0 (-6.8, 24.7) |
| History of diabetes mellitus | 29 (46%) | 14 (34%) | 11.9 (-7.1, 30.9) | 16 (32%) | 15 (24%) | 8.2 (-8.5, 24.9) |
| Hemodialysis | 2 (3%) | 2 (5%) | -1.7 (-9.6, 6.2) | 1 (2%) | 2 (3%) | -1.2 (-7.0, 4.6) |
| Baseline serum creatinine ≤1.2 mg/dL | 35 (56%) | 29 (71%) | -15.2 (-33.7, 3.4) | 27 (54%) | 49 (78%) | -23.8 (-41.0, -6.6)* |
| Baseline serum creatinine >1.2 mg/dL | 28 (44%) | 12 (29%) | 15.2 (-3.4, 33.7) | 23 (46%) | 14 (22%) | 23.8 (6.6, 41.0)* |
| VAP | 16 (25%) | 11 (27%) | -1.4 (-18.7, 15.9) | 23 (46%) | 15 (24%) | 22.2 (4.8, 39.6)* |
| Acute renal failure | 12 (19%) | 6 (15%) | 4.4 (-10.1, 18.9) | 15 (30%) | 7 (11%) | 18.9 (4.0, 33.8)* |
| Adequate Gram-negative therapy | 45 (71%) | 32 (78%) | -6.6 (-23.5, 10.3) | 34 (68%) | 38 (60%) | 7.7 (-10.0, 25.4) |
| Initial inadequate Gram-negative therapy | 4 (6%) | 0 (0%) | 6.3 (0.3, 12.4)* | 5 (10%) | 7 (11%) | -1.1 (-12.4, 10.3) |
| Never received adequate Gram-negative therapy | 14 (22%) | 9 (22%) | 0.3 (-16.0, 16.6) | 11 (22%) | 18 (29%) | -6.6 (-22.6, 9.4) |

*statistically significant difference; VAP = ventilator-associated pneumonia; TLV = telavancin; VAN = vancomycin

FDA Medical Officer Comments: In reviewing the mortality data for the time period of EOT to EOT + 28 days as depicted in the table above, there were statistically significant differences between treatment groups within each study for certain parameters. For Study 0015, there was a higher rate of death associated with initial inadequate Gram-negative therapy in the telavancin group compared to the vancomycin group, and the difference was statistically significant. In Study 0019, there was a greater proportion of patient deaths among those having baseline serum creatinine >1.2 mg/dL in the telavancin group in contrast to the greater proportion of patient deaths having baseline serum creatinine ≤1.2 mg/dL in the vancomycin group. Both findings were statistically significant. Additionally, there were more deaths in the telavancin group compared to the vancomycin group in Study 0019 among patients with VAP and acute renal failure at baseline, and the differences were statistically significant.

Regarding the deaths associated with inadequate initial Gram-negative therapy, it was evident that there was a statistically significant difference between treatment groups for Study 0015. For the four patient deaths in the telavancin group of Study 0015 who were assessed as having received “Initial inadequate Gram-negative Therapy”, it was discerned that three of the patients (0015-18010-4138, 0015-30905-4034, and 0015-52000-4703) had a Gram-negative pathogen isolated from baseline respiratory tract cultures while one patient (0015-30905-4234) had no baseline pathogens isolated from respiratory or blood cultures. The details of that patient’s hospital course have been described previously.

In this FDA Medical Officer’s opinion, patient 0015-30905-4234 should not be included in the category of “inadequate initial Gram-negative therapy” in the telavancin group for Study 15 in the table above. Recalculation of the 95% CI for the difference (telavancin-vancomycin) for this category using three patient deaths (rather than four) for telavancin compared to none for vancomycin results in a difference of 4.8 with 95% CI of (-0.5, 10.0). This result is not statistically significant and, thus, the 6.0% risk difference for death among patients treated with telavancin compared to vancomycin in Study 0015 cannot be explained in terms of death due to inadequate initial Gram-negative therapy.

Additionally, the Medical Monitor’s evaluations of the adequacy of Gram-negative therapy were conducted following unblinding to treatment group as previously described, raising concern about potentially biased assessments.

The original AT population included a total of 292 subjects with pneumonia due to Gram-negative pathogens only. Of those patients, a total of 54 died as depicted in the following table:

Table 72: FDA Medical Officer Summary Table of Deaths for Patients with Pneumonia due to Gram-negative Pathogens only, Studies 0015 and 0019, AT Population

| Treatment group | Study 0015 n/N (%) | Study 0019 n/N (%) |
|-----------------|-----------------------|-----------------------|
| Telavancin | 13/85 (15.3) | 13/75 (17.3) |
| Vancomycin | 8/63 (12.7) | 20/84 (23.8) |

FDA Medical Officer Comments: When an exploratory analysis was conducted in which patients with pneumonia due to Gram-negative pathogens only were excluded from the AT population, the point estimate of the difference in the all-cause mortality rates between telavancin and vancomycin rose from 6.4 to 7.4 based on deaths between EOT and EOT + 28 days post-treatment in the AT population (see Tables 67 and 68). The difference in the all-cause mortality rates revealed a statistically significant higher risk for death among patients treated with telavancin compared to vancomycin in that analysis for Study 0015. There were no within study differences between treatment arms with respect to patient demographics to account for the mortality rate disparity observed in Study 0015.

The following table summarizes the frequencies of various parameters across each treatment group within Studies 0015 and 0019 to assess if there was an imbalance that could represent a safety signal associated with the mortality disparity among the deaths in the AT population (excludes patients with pneumonia due to Gram-negative pathogens only) between start of treatment and 28 days post-treatment.

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Table 73: FDA Medical Officer Summary of Baseline Characteristics potentially associated with risk for mortality for all patients who died between Start of Treatment and EOT Visit + 28 days, Studies 0015 and 0019, AT Population (excluding patients with NP and VAP due to Gram-negative pathogens only)

| Parameter | Study 0015 | | | Study 0019 | | |
|--|-------------|-------------|------------------------------|-------------|-------------|------------------------------|
| | TLV N=72 | VAN N=55 | 95% CI for Diff (TLV-VAN) | TLV N=62 | VAN N=64 | 95% CI for Diff (TLV-VAN) |
| Baseline diabetic status (yes) | 29 (40%) | 18 (33%) | 7.5 (-9.2, 24.3) | 17 (27%) | 15 (23%) | 4.0 (-11.2, 19.2) |
| History of diabetes mellitus | 35 (49%) | 21 (38%) | 10.4 (-6.8, 27.7) | 18 (29%) | 16 (25%) | 4.0 (-11.5, 19.5) |
| Hemodialysis | 2 (3%) | 2 (4%) | -0.9 (-7.1, 5.4) | 1 (2%) | 2 (3%) | -1.5 (-6.8, 3.8) |
| Baseline serum creatinine ≤1.2 mg/dL | 43 (60%) | 36 (65%) | -5.7 (-22.7, 11.2) | 39 (63%) | 50 (78%) | -15.2 (-30.9, 0.5) |
| Baseline serum creatinine >1.2 mg/dL | 29 (40%) | 19 (35%) | 5.7 (-11.2, 22.7) | 23 (37%) | 14 (22%) | 15.2 (-0.5, 30.9) |
| VAP | 23 (32%) | 16 (29%) | 2.9 (-13.3, 19.0) | 25 (40%) | 18 (29%) | 12.2 (-4.2, 28.6) |
| Acute renal failure | 11 (15%) | 7 (13%) | 2.6 (-9.6, 14.7) | 12 (19%) | 8 (13%) | 6.9 (-5.9, 19.6) |
| Adequate Gram-negative therapy | 55 (76%) | 46 (84%) | -7.2 (-21.1, 6.6) | 40 (65%) | 48 (75%) | -10.4 (-26.4, 5.5) |
| Initial inadequate Gram- negative therapy | 4 (6%) | 0 (0%) | 5.6 (0.3, 10.8)* | 4 (6%) | 7 (11%) | -4.5 (-14.3, 5.3) |
| Never received adequate Gram- negative therapy | 13 (18%) | 9 (16%) | 1.7 (-11.5, 14.9) | 18 (29%) | 9 (14%) | 15 (0.8, 29.1)* |
| Men | 44 (61%) | 30 (55%) | 6.6 (-10.8, 23.9) | 43 (69%) | 39 (61%) | 8.4 (-8.2, 25.0) |
| Women | 28 (39%) | 25 (45%) | -6.6 (-23.9, 10.8) | 19 (31%) | 25 (39%) | -8.4 (-25.0, 8.2) |
| Age <65 | 21 (29%) | 16 (29%) | 0.08 (-15.9, 16.0) | 18 (29%) | 19 (30%) | -0.7 (-16.6, 15.2) |
| Age ≥65 | 51 (71%) | 39 (71%) | -0.07 (-16.0, 15.9) | 44 (71%) | 45 (70%) | 0.7 (-15.2, 16.6) |
| Bacteremia at baseline (yes) | 12 (17%) | 10 (18%) | -1.5 (-14.9, 11.8) | 8 (13%) | 11 (17%) | -4.3 (-16.7, 8.2) |
| History of atrial fibrillation | 24 (33%) | 17 (31%) | 2.4 (-13.9, 18.8) | 15 (24%) | 12 (19%) | 5.4 (-8.9, 19.8) |
| History of CHF | 24 (33%) | 15 (27%) | 6.1 (-10.0, 22.1) | 10 (16%) | 16 (25%) | -8.9 (-22.9, 5.1) |
| History of LVH | 6 (8%) | 2 (4%) | 4.7 (-3.4, 12.8) | 2 (3%) | 6 (9%) | -6.1 (-14.5, 2.2) |
| History of MI | 12 (17%) | 16 (29%) | -12.4 (-27.2, 2.3) | 10 (16%) | 6 (9%) | 6.8 (-4.9, 18.4) |
| History of other cardiac diseases | 34 (47%) | 30 (55%) | -7.3 (-24.8, 10.2) | 35 (56%) | 31 (48%) | 8.0 (-9.4, 25.4) |
| ≥1 cardiac condition present | 58 (81%) | 44 (80%) | 0.56 (-13.4, 14.5) | 45 (73%) | 44 (69%) | 3.8 (-12.1, 19.7) |
| Smoking (Current Smoker) | 14 (19%) | 10 (18%) | 1.3 (-12.4, 15.0) | 14 (23%) | 14 (22%) | 0.7 (-13.8, 15.2) |
| Ex-Smoker | 33 (46%) | 13 (24%) | 22.2 (6.1, 38.3)* | 21 (34%) | 24 (38%) | -3.6 (-20.3, 13.1) |
| Baseline Gram-positive pathogens only | 33 (46%) | 27 (49%) | -3.3 (-20.8, 14.3) | 23 (37%) | 29 (45%) | -8.2 (-25.3, 8.9) |
| MRSA at baseline | 33 (46%) | 22 (40%) | 5.8 (-11.5, 23.2) | 36 (58%) | 35 (55%) | 3.4 (-13.9, 20.7) |
| MSSA at baseline | 11 (15%) | 11 (20%) | -4.7 (-18.2, 8.7) | 10 (16%) | 7 (11%) | 5.2 (-6.7, 17.1) |
| Baseline mixed Gram-pos and Gram-neg RT pathogens | 15 (21%) | 7 (13%) | 8.1 (-4.8, 21.0) | 26 (42%) | 16 (25%) | 16.9 (0.7, 33.2)* |
| Baseline mixed blood pathogens | 0 (0%) | 1 (2%) | -1.8 (-5.3, 1.7) | 1 (2%) | 1 (2%) | 0.05 (-4.3, 4.4) |
| No baseline pathogens | 24 (33%) | 21 (38%) | -4.8 (-21.7, 12.0) | 13 (21%) | 19 (30%) | -8.7 (-23.8, 6.4) |
| HAP | 45 (63%) | 32 (58%) | 4.32 (-12.86, 21.49) | 47 (76%) | 50 (78%) | -2.32 (-17.02, 12.39) |
| HCAP | 27 (38%) | 23 (42%) | -4.32 (-21.49, 12.86) | 15 (24%) | 14 (22%) | 2.32 (-12.39, 17.02) |

HAP=hospital-acquired pneumonia, HCAP=healthcare-associated pneumonia; RT = respiratory tract;
CHF = congestive heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction

FDA Medical Officer Comments: In reviewing the mortality data for the time period of start of study drug treatment to EOT + 28 days as depicted in the table above in which patients with NP and VAP due to Gram-negative pathogens only were excluded, there were statistically significant differences between treatment groups within each study for certain parameters and some differed from those noted when the AT population included patients having only Gram-negative bacteria at baseline. For Study 0015, there was a higher rate of death associated with initial inadequate Gram-negative therapy and status as an ex-smoker in the telavancin group compared to the vancomycin group, and the difference was statistically significant. In Study 0019, there was a greater proportion of patient deaths among those who never received adequate Gram-negative therapy and among patients whose baseline respiratory tract cultures grew mixed Gram-pos and Gram-neg bacterial pathogens, and both findings were statistically significant. Thus, in contrast to the statistically significant imbalances in mortality associated with baseline creatinine that were noted when the AT population for the time period from start of study drug treatment to EOT + 28 days included patients having only Gram-negative baseline pathogens, such imbalances were not evident when those patients were excluded from the AT population. However, statistically significant mortality imbalances associated with the adequacy of Gram-negative therapy were observed regardless of whether such patients were excluded or included in the AT population. This FDA Medical Officer's perspective on the relevance of those designations has been discussed previously in this section and in Section 5.3.1.2.5 of this report.

The following table summarizes the frequencies of various parameters across each treatment group within Studies 0015 and 0019 to assess if there was an imbalance that could represent a safety signal associated with the mortality disparity among the deaths in the AT population (excludes patients with pneumonia due to Gram-negative pathogens only) between EOT and 28 days post-treatment.

Table 74: FDA Medical Officer Summary of Baseline Characteristics potentially associated with risk for mortality for all patients who died between EOT Visit and EOT + 28 days, Studies 0015 and 0019, AT Population (excluding patients with NP and VAP due to Gram-negative pathogens only)

| Parameter | Study 0015 | | | Study 0019 | | |
|--|-------------|-------------|------------------------------|-------------|-------------|--------------------------------|
| | TLV N=55 | VAN N=34 | 95% CI for Diff (TLV-VAN) | TLV N=39 | VAN N=46 | 95% CI for Diff (TLV-VAN) |
| Baseline diabetic status (yes) | 24 (44%) | 10 (29%) | 14.2 (-5.9, 34.4) | 12 (31%) | 12 (26%) | 4.7 (-14.6, 23.9) |
| History of diabetes mellitus | 27 (49%) | 12 (35%) | 13.8 (-7.0, 34.6) | 14 (36%) | 13 (28%) | 7.6 (-12.3, 27.5) ¹ |
| Hemodialysis | 1 (2%) | 2 (6%) | -4.1 (-12.7, 4.6) | 1 (3%) | 2 (4%) | -1.8 (-9.5, 5.9) |
| Baseline serum creatinine ≤1.2 mg/dL | 32 (58%) | 22 (65%) | -6.5 (-27.2, 14.2) | 22 (56%) | 36 (78%) | -21.9 (-41.5, -2.2)* |
| Baseline serum creatinine >1.2 mg/dL | 23 (42%) | 12 (35%) | 6.5 (-14.2, 27.2) | 17 (44%) | 10 (22%) | 21.9 (2.2, 41.5)* |
| VAP | 14 (25%) | 9 (26%) | -1.0 (-19.8, 17.8) | 18 (46%) | 10 (22%) | 24.4 (4.7, 44.1)* |
| Acute renal failure | 8 (15%) | 5 (15%) | -0.2 (-15.3, 15.0) | 10 (26%) | 5 (11%) | 14.8 (-1.6, 31.2) |
| Adequate Gram-negative therapy | 42 (76%) | 30 (88%) | -11.9 (-27.5, 3.7) | 29 (74%) | 35 (76%) | -1.7 (-20.2, 16.7) |
| Initial inadequate Gram-negative therapy | 4 (7%) | 0 (0%) | 7.3 (0.4, 14.1)* | 3 (8%) | 5 (11%) | -3.2 (-15.5, 9.1) |
| Never received adequate Gram-negative therapy | 9 (16%) | 4 (12%) | 4.6 (-10.0, 19.2) | 7 (18%) | 6 (13%) | 4.9 (-10.6, 20.4) |
| Men | 36 (65%) | 18 (53%) | 12.5 (-8.4, 33.5) | 26 (67%) | 25 (54%) | 12.3 (-8.3, 33.0) |
| Women | 19 (35%) | 16 (47%) | -12.5 (-33.5, 8.4) | 13 (33%) | 21 (46%) | -12.3 (-33.0, 8.3) |
| Age <65 | 16 (29%) | 9 (26%) | 2.6 (-16.5, 21.7) | 9 (23%) | 10 (22%) | 1.3 (-16.5, 19.1) |
| Age ≥65 | 39 (71%) | 25 (73%) | -2.6 (-21.7, 16.5) | 30 (77%) | 36 (78%) | -1.3 (-19.1, 16.5) |
| Bacteremia at baseline (yes) | 10 (18%) | 5 (15%) | 3.5 (-12.2, 19.1) | 8 (21%) | 8 (17%) | 3.1 (-13.6, 19.9) |
| History of atrial fibrillation | 17 (31%) | 10 (29%) | 1.5 (-18.1, 21.1) | 10 (26%) | 10 (22%) | 3.9 (-14.3, 22.1) |
| History of CHF | 21 (38%) | 9 (26%) | 11.7 (-7.9, 31.3) | 8 (21%) | 13 (28%) | -7.7 (-25.9, 10.4) |
| History of LVH | 5 (9%) | 2 (6%) | 3.2 (-7.8, 14.2) | 1 (3%) | 3 (7%) | -4.0 (-12.6, 4.7) |
| History of MI | 9 (16%) | 8 (24%) | -7.2 (-24.5, 10.1) | 9 (23%) | 4 (9%) | 14.4 (-1.1, 29.9) |
| History of other cardiac diseases | 24 (44%) | 17 (50%) | -6.4 (-27.7, 14.9) | 21 (54%) | 23 (50%) | 3.8 (-17.5, 25.1) |
| ≥1 cardiac condition present | 42 (76%) | 27 (79%) | -3.0 (-20.7, 14.6) | 28 (72%) | 32 (70%) | 2.2 (-17.2, 21.6) |
| Smoking (Current Smoker) | 9 (16%) | 6 (18%) | -1.2 (-17.4, 14.8) | 7 (18%) | 7 (15%) | 2.7 (-13.2, 18.6) |
| Ex-Smoker | 28 (51%) | 6 (18%) | 33.2 (14.9, 51.7)* | 14 (36%) | 20 (43%) | -7.6 (-28.3, 13.2) |
| Baseline Gram-positive pathogens only | 21 (38%) | 16 (47%) | -8.9 (-30.0, 12.3) | 17 (44%) | 22 (48%) | -4.2 (-25.5, 17.0) |
| MRSA at baseline | 24 (44%) | 12 (35%) | 8.3 (-12.4, 29.1) | 23 (59%) | 28 (61%) | -1.8 (-22.8, 19.0) |
| MSSA at baseline | 8 (15%) | 6 (18%) | -3.1 (-18.9, 12.7) | 7 (18%) | 4 (9%) | 9.3 (-5.3, 23.8) |
| Baseline mixed Gram-pos and Gram-Negative RT pathogens | 12 (22%) | 2 (6%) | 15.9 (2.5, 29.4)* | 15 (38%) | 12 (26%) | 12.4 (-7.5, 32.2) |
| Baseline mixed blood pathogens | 0 (0%) | 0 (0%) | 0 (0,0) | 1 (3%) | 0 (0%) | 2.6 (-2.4, 7.5) |
| No baseline pathogens | 22 (40%) | 16 (47%) | -7.1 (-28.3, 14.1) | 7 (18%) | 12 (26%) | -8.1 (-25.6, 9.4) |

RT = respiratory tract; CHF = congestive heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction

FDA Medical Officer Comments: In reviewing the mortality data for the time period of EOT to EOT + 28 days as depicted in the table above, there were statistically significant differences between treatment groups within each study for certain parameters. For Study 0015, there was a

higher rate of death associated with initial inadequate Gram-negative therapy, status as an ex-smoker, and having mixed Gram-positive and Gram-negative bacterial pathogens at baseline in the telavancin group compared to the vancomycin group, and the differences were statistically significant. In Study 0019, there was a greater proportion of patient deaths among those having baseline serum creatinine >1.2 mg/dL in the telavancin group in contrast to the greater proportion of patient deaths having baseline serum creatinine ≤1.2 mg/dL in the vancomycin group. Both findings were statistically significant. Additionally, there were more deaths in the telavancin group compared to the vancomycin group in Study 0019 among patients with VAP, and the difference was statistically significant. Of note, statistically significant mortality imbalances associated with the adequacy of Gram-negative therapy were observed regardless of whether patients having only Gram-negative bacterial pathogens at baseline were excluded or included in the AT population. This FDA Medical Officer’s perspective on the relevance of those designations has been discussed previously in this section and in Section 5.3.1.2.5 of this report.

Inadequate Gram-negative Therapy and All-cause Mortality

The FDA Medical Officer performed a review of patient deaths based on pre-treatment bacterial pathogens and the Applicant’s Medical Monitor’s assessments of the adequacy of Gram-negative therapy. The findings are summarized in the following table:

Table 75: FDA Medical Officer Table of Subject Count for Patients who died between Start of Treatment and EOT Visit + 28 days stratified by Treatment group, Baseline pathogens, and Adequacy of Gram-negative Therapy, Studies 0015 and 0019, AT Population (excluding infections due to Gram-negative pathogens only)

| | Study 0015 | | | | | | Study 0019 | | | | | | TOTAL DEATHS |
|---------------------------------------|---------------------------|----|----|---------------------------|----|----|---------------------------|----|----|---------------------------|----|----|--------------|
| | Telavancin N=72 deaths | | | Vancomycin N=55 deaths | | | Telavancin N=62 deaths | | | Vancomycin N=64 deaths | | | |
| Baseline Pathogens | AD | IN | NR | |
| Gram positive only | 33 | 0 | 0 | 27 | 0 | 0 | 23 | 0 | 0 | 29 | 0 | 0 | 112 |
| Mixed Gram-positive and Gram-negative | 5 | 3 | 7 | 5 | 0 | 2 | 11 | 3 | 12 | 6 | 3 | 7 | 64 |
| No Baseline Pathogens | 17 | 1 | 6 | 14 | 0 | 7 | 6 | 1 | 6 | 13 | 4 | 2 | 77 |
| TOTAL | 55 | 4 | 13 | 46 | 0 | 9 | 40 | 4 | 18 | 48 | 7 | 9 | 253 |

AD=adequate Gram-negative therapy; IN=initial inadequate Gram-negative therapy;
 NR=never received adequate Gram-negative therapy

A total of 77 patients who died between start of treatment and EOT + 28 days had no baseline pathogen and were designated as having received initial inadequate Gram-negative therapy or never received adequate Gram-negative therapy by the Medical Monitor. In reviewing the CRFs for these patients, there was substantial uncertainty as to whether the Monitor’s designations were appropriate. The following table cites multiple examples in which the Medical Monitor’s designations were not supported by information contained in the CRF and data clarification forms; instead, Gram-negative antibacterial therapy was not indicated for many of the patients according to the investigators’ assessments.

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Table 76: FDA Medical Officer Table of Patients who died between Start of Treatment and EOT Visit + 28 days who had no baseline pathogens and were designated as having received Inadequate Gram-negative Therapy by the Medical Monitor, Studies 0015 and 0019

| Subject ID# | Study | Randomized Treatment | Baseline | Other post-baseline | EOT | TOC | Adequacy of Gram-negative Therapy | FDA Medical Officer findings from review of the CRFs |
|-----------------|-------|----------------------|----------|---------------------|--------------------------|-----------|-----------------------------------|--|
| 0015-01005-4713 | 0015 | VAN | NG | | PA (blood); SM (resp) | NS | NEVER RECEIVED | "No Gram-negative coverage required" per Investigator |
| 0015-05001-4319 | 0015 | VAN | NG | | Non-path | NS | NEVER RECEIVED | "No Gram-negative coverage required" per Investigator |
| 0015-12006-4312 | 0015 | TLV | Non-path | | NS | NS | NEVER RECEIVED | Received Aztreonam concurrently with study drug x 5 days |
| 0015-18001-4579 | 0015 | VAN | NG | | NS | NS | NEVER RECEIVED | Received inhaled colistimethate sodium for 12 days prior to study drug for "pseudomonas in sputum" and also received tazocin on Study Day -1. |
| 0015-19013-4671 | 0015 | VAN | Non-path | | NS | NS | NEVER RECEIVED | Ceftazidime administered as a prior antimicrobial drug to treat "pneumonia under study". |
| 0015-23003-4097 | 0015 | TLV | NG | | AB (blood) | NS | NEVER RECEIVED | Had necrotizing fasciitis left foot; HAP assessed as cured at EOT; received ceftazidime for 3 days concurrent with study drug; no source was described for the AB bacteremia |
| 0015-23003-4099 | 0015 | VAN | Non-path | | Non-path | NS | NEVER RECEIVED | Received aztreonam concurrently with study drug for initial 1-2 days |
| 0015-30905-4234 | 0015 | TLV | NG | | SM (resp) | NS | INITIAL INADEQUATE | Patient received aztreonam for 3 days concurrent with study drug. |
| 0015-33402-4714 | 0015 | TLV | Non-path | AC (resp) | NS | NS | NEVER RECEIVED | Patient received cefuroxime and levofloxacin prior to and aztreonam concomitant with study drug. |
| 0015-38148-4218 | 0015 | VAN | Non-path | | NS | NS | NEVER RECEIVED | Gram-negative therapy not indicated |
| 0015-38348-4254 | 0015 | TLV | Non-path | | Non-path | NS | NEVER RECEIVED | No Gram-negative coverage given during study period. |
| 0015-38363-4583 | 0015 | TLV | Non-path | | NS | NS | NEVER RECEIVED | Received aztreonam 1 gm q12h for UTI concurrent with study drug |
| 0015-41002-4102 | 0015 | TLV | NG | | AC (resp) | NS | NEVER RECEIVED | Received amikacin and ceftazidime for 4 days prior to and received atreonam concurrent with study drug. |
| 0015-41016-4354 | 0015 | VAN | NG | | NS | NS | NEVER RECEIVED | No Gram-negative coverage provided due to only Gran-positive bacteria on Gram stain and sterile culture. |
| 0019-01022-6059 | 0019 | VAN | Non-path | | NS | NS | NEVER RECEIVED | Investigator confirmed that no Gram-negative antibiotics were administered; HAP assessed as cured at EOT and TOC |
| 0019-05000-6151 | 0019 | VAN | NG | | NS | NS | INITIAL INADEQUATE | Patient treated with piperacillin/tazobactam from Day 2 through date of death |
| 0019-05003-6069 | 0019 | VAN | Non-path | | NG | NS | INITIAL INADEQUATE | Cefepime was administered for 1-2 days concurrently during the course of study drug administration. |
| 0019-05003-6084 | 0019 | VAN | Non-path | | KN (blood and resp) | PA (resp) | INITIAL INADEQUATE | Patient treated with ceftazidime for 12 days prior to initial dose of study drug and received one day of |

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| Subject ID# | Study | Randomized Treatment | Baseline | Other post-baseline | EOT | TOC | Adequacy of Gram-negative Therapy | FDA Medical Officer findings from review of the CRFs |
|-----------------|-------|----------------------|----------|---------------------|-----|-----|-----------------------------------|--|
| | | | | | | | | imipenem at initiation of study drug. |
| 0019-05011-6057 | 0019 | TLV | Non-path | | NS | NS | NEVER RECEIVED | Patient developed wound infection and mediastinitis after surgery for aortic dissection. |
| 0019-08009-6211 | 0019 | TLV | NG | | NS | NS | NEVER RECEIVED | No Gram-negative coverage given during study period. |
| 0019-38108-6539 | 0019 | VAN | NG | | NS | NS | INITIAL INADEQUATE | No Gram-negative coverage given during study period. |
| 0019-38252-6646 | 0019 | TLV | NG | | NS | NS | NEVER RECEIVED | No Gram-negative coverage given during study period. |
| 0019-40001-6098 | 0019 | TLV | NG | | NS | NS | NEVER RECEIVED | Gram-negative therapy not indicated |
| 0019-40006-6178 | 0019 | TLV | NG | AB (blood and resp) | NS | NS | INITIAL INADEQUATE | Received ceftriaxone and ciprofloxacin for 6 days up to Day 1 of study drug. |
| 0019-44001-6585 | 0019 | TLV | NG | | NS | NS | NEVER RECEIVED | "No Gram-negative coverage required" per Investigator |
| 0019-44010-6452 | 0019 | VAN | NG | | NS | NS | NEVER RECEIVED | According to the investigator, the Gram stain and culture did not reveal Gram-negative organisms. Thus, no Gram negative therapy was administered. |
| 0019-50000-6667 | 0019 | TLV | NG | | NS | NS | NEVER RECEIVED | "No Gram-negative coverage required" per Investigator |

VAN=vancomycin; TLV=telavancin; NG=no growth; Non-path= non-pathogen; NS = no specimen; resp=respiratory tract
 PA= *P. aeruginosa*, SM= *S. marcescens*, AB= *A. baumannii*, KN= *K. pneumoniae*, AC=*A. calcoaceticus*

FDA Medical Officer Comments: As discussed previously in Sections 5.3.1.2.5 and 5.3.2.2.5, the assessments of the adequacy of Gram-negative therapy were conducted post-hoc by the Medical Monitor following unblinding to treatment assignment and without consideration of the investigators' opinions regarding the need for such treatment. As Studies 0015 and 0019 were not designed to be consistent with ATS/IDSA Guidance on the management of patients with HAP/VAP in terms of empiric Gram-negative therapy and the Medical Monitor's assessments were conducted following unblinding, this FDA Medical Officer feels that the Applicant's post-hoc exploratory analysis of the adequacy of Gram-negative therapy is not appropriate nor relevant to consider in the evaluation of the efficacy data for this NDA.

All-cause Mortality data provided by the Applicant in response to the FDA Information Request dated July 31, 2009

As described previously in this report, the Applicant notified the Division of additional mortality data identified from the clinical database, the safety database, and data collected in a 10-week pharmacoeconomic (PE) study and provided the additional data in response to an information request from the Division dated June 9, 2009.

In response to an information request from the Division dated July 31, 2009, the Applicant provided summary tables for the study deaths, a list of patients for whom mortality status is unknown up to Study Day 28, a list of patients for whom mortality status is unknown up to last study day + 28 days, and an electronic dataset. The Applicant also provided narratives for the deaths. The two summary tables are provided below:

Table 77: Applicant's Summary of Deaths occurring between Start of Study Drug and Start of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 92 (25%) | 73 (20%) | 80 (21%) | 88 (23%) | 172 (23%) | 161 (21%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 70 (19%) | 51 (14%) | 54 (14%) | 68 (18%) | 124 (17%) | 119 (16%) |
| Alive or censored | 280 (75%) | 301 (80%) | 299 (79%) | 290 (77%) | 579 (77%) | 591 (79%) |
| Censored* | 126 (34%) | 134 (36%) | 113 (30%) | 103 (27%) | 239 (32%) | 237 (32%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

Table 78: Applicant's Summary of Deaths Occurring between Start of Study Drug and End of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 102 (27%) | 82 (22%) | 88 (23%) | 99 (26%) | 190 (25%) | 181 (24%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 80 (22%) | 60 (16%) | 62 (16%) | 79 (21%) | 142 (19%) | 139 (18%) |
| After follow-up visit | 22 (6%) | 19 (5%) | 18 (5%) | 21 (6%) | 40 (5%) | 40 (5%) |
| Alive or censored | 270 (73%) | 292 (78%) | 291 (77%) | 279 (74%) | 561 (75%) | 571 (76%) |
| Censored* | 145 (39%) | 159 (43%) | 139 (37%) | 126 (33%) | 284 (38%) | 285 (38%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

FDA Medical Officer Comments: For Study 0015 as described in Section 5.3.1.2.7, the risk difference for all deaths occurring between start of study drug and start of study drug + 28 Days for the telavancin and the vancomycin groups was 5.2%, but the size of the difference could be substantial (>11% higher among the telavancin-treated patients). Similarly, although the risk

difference for deaths occurring between start of study drug and end of study drug + 28 Days was 5.5%, the size of the risk difference for death could be negligible or it could be quite large (>11%) for patients treated with telavancin. In contrast, comparable risk differences for death were not observed in Study 0019 for both time intervals of observation for all-cause mortality as described in Section 5.3.2.2.7. Assessment of pooled telavancin and vancomycin data at both time intervals revealed a risk difference with 95% confidence intervals of 1.5% (-2.7%, 5.7%) for the deaths occurring between start of study drug and start of study drug + 28 days and a risk difference of 1.2% (-3.1%, 5.6%) for deaths occurring between start of study drug and end of study drug + 28 days.

When the all-cause mortality data is analyzed in terms of an NI margin range of 7-10% using all-cause mortality as the primary endpoint for efficacy, the results for Study 0015 suggest that telavancin is inferior to vancomycin. In contrast, the results for Study 0019 and the results of the pooled telavancin and pooled vancomycin data suggest that the drug is non-inferior to vancomycin. However, due to the large percentage of censored events among the submitted mortality data for both studies as described above and in Sections 5.3.1.2.7 and 5.3.2.2.7 of this report, this FDA Medical Officer has concerns that the actual number of deaths is underestimated in both treatment arms of both studies. The uncertainty resulting from the considerable amount of censored data makes the all-cause mortality data uninterpretable and, thus, the efficacy of telavancin compared to vancomycin cannot be assessed based on either the individual study results or the pooled data. The Applicant plans to conduct a follow-up query of all study sites and then submit the updated mortality data to the Division in the future.

6.1.6 Other Endpoints

Microbiology

The following table summarizes the number of patients in the AT and CE populations of both trials who had bacterial pathogens isolated from respiratory specimens, blood, or both at baseline. The majority of patients had bacterial pathogens isolated from respiratory specimens only or from both respiratory and blood specimens. Few patients had pathogens isolated only from blood specimens in both trials. There were a higher percentage of mixed respiratory infections in Study 0019 compared to Study 0015. Note that patients with only Gram-negative pathogens isolated at baseline were excluded from the CE population, but they were included in the AT population. Please refer to the report of the Microbiology Reviewer, Kerry Snow, for further details on the microbiologic data in this NDA.

Table 79: FDA Medical Officer Table of Subject Count in AT and CE Populations stratified by Respiratory and Blood Pathogens

| Study ID | AT Population | | | | CE Population | | | |
|--|---------------|---------------|---------------|---------------|----------------|----------------|----------------|----------------|
| | Study 0015 | | Study 0019 | | Study 0015 | | Study 0019 | |
| Treatment | TLV N=372 | VAN N=374 | TLV N=377 | VAN N=380 | TLV CE= 141 | VAN CE= 172 | TLV CE= 171 | VAN CE= 170 |
| Any respiratory BL pathogen isolated | 249 (66.9) | 245 (65.5) | 297 (78.8) | 279 (73.4) | 105 (74.5) | 113 (65.7) | 134 (78.4) | 123 (72.4) |
| •MRSA at baseline | 111 (29.8) | 113 (30.2) | 117 (31.0) | 117 (31.0) | 67 (47.5) | 84 (48.8) | 69 (40.3) | 70 (41.2) |
| •MSSA at baseline | 61 (16.4) | 57 (15.2) | 83 (22.0) | 63 (16.6) | 32 (22.7) | 25 (14.5) | 51 (29.8) | 36 (21.2) |
| •Gram-negative at baseline | 118 (31.7) | 111 (29.7) | 171 (45.4) | 155 (40.8) | 20 (14.2) | 23 (13.4) | 48 (28.1) | 40 (23.5) |
| Any blood BL pathogen (bacteremia) | 37 (10) | 34 (9.1) | 31 (8.2) | 38 (10.0) | 14 (9.9) | 12 (7.0) | 6 (3.5) | 14 (8.2) |
| •MRSA at baseline | 13 (3.5) | 14 (3.7) | 8 (2.1) | 13 (3.4) | 7 (5.0) | 5 (2.9) | 3 (1.8) | 4 (2.4) |
| •MSSA at baseline | 8 (2.2) | 5 (1.3) | 6 (1.6) | 10 (2.6) | 3 (2.1) | 2 (1.2) | 3 (1.8) | 4 (2.4) |
| •Gram-negative at baseline | 13 (3.5) | 13 (3.5) | 15 (4.0) | 13 (3.4) | 3 (2.1) | 5 (2.9) | 1 (0.6) | 5 (2.9) |
| Only respiratory BL pathogen isolated | 220 (59.1) | 213 (57) | 272 (72.2) | 243 (64.2) | 94 (66.7) | 101 (58.7) | 129 (75.4) | 110 (64.7) |
| •Mixed respiratory infection at baseline | 42 (11.3) | 35 (9.4) | 84 (22.3) | 68 (17.9) | 16 (11.4) | 18 (10.5) | 47 (27.5) | 33 (19.4) |
| •Only Gram-positive at baseline | 115 (30.9) | 118 (31.6) | 119 (31.6) | 105 (27.6) | 78 (55.3) | 83 (48.3) | 82 (48.0) | 77 (45.3) |
| •Only Gram-negative at baseline | 63 (16.9) | 60 (16.0) | 69 (18.3) | 71 (18.7) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| •MRSA at baseline | 101 (27.2) | 99 (26.5) | 106 (28.1) | 97 (25.6) | 63 (44.7) | 77 (44.8) | 65 (38.0) | 61 (35.9) |
| •MSSA at baseline | 50 | 50 | 77 | 54 | 27 | 21 | 50 | 33 |

| Study ID | AT Population | | | | CE Population | | | |
|------------------------------------|---------------|--------------|---------------|---------------|---------------|--------------|--------------|--------------|
| | Study 0015 | | Study 0019 | | Study 0015 | | Study 0019 | |
| | (13.4) | (13.4) | (20.4) | (14.2) | (19.2) | (12.2) | (29.2) | (19.4) |
| •Gram-negative at baseline | 105 (28.2) | 95 (25.4) | 153 (40.6) | 139 (36.6) | 16 (11.4) | 18 (10.5) | 47 (27.5) | 33 (19.4) |
| Only blood BL pathogen isolated | 8 (2.2) | 2 (0.5) | 6 (1.6) | 3 (0.8) | 3 (2.1) | 0 (0.0) | 1 (0.6) | 1 (0.6) |
| •Mixed blood infection at baseline | 0 (0.0) | 1 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| •Only Gram-positive at baseline | 6 (1.6) | 1 (0.3) | 4 (1.1) | 1 (0.3) | 3 (2.1) | 0 (0.0) | 1 (0.6) | 1 (0.6) |
| •Only Gram-negative at baseline | 2 (0.5) | 0 (0.0) | 2 (0.5) | 2 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| •MRSA at baseline | 4 (1.1) | 1 (0.3) | 1 (0.3) | 0 (0.0) | 3 (2.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| •MSSA at baseline | 0 (0.0) | 0 (0.0) | 1 (0.3) | 1 (0.3) | 0 (0.0) | 0 (0.0) | 1 (0.6) | 1 (0.6) |
| •Gram-negative at baseline | 2 (0.5) | 1 (0.3) | 2 (0.5) | 2 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

TLV=telavancin; VAN=vancomycin; BL=baseline

Microbiological Evaluable Populations

For patients in the ME Population, the most common pathogen isolated at Baseline (without regard to whether patients had one or multiple baseline pathogens) was *S. aureus*. In the pooled results of Studies 0015 and 0019, cure rates for *S. aureus* and MRSA were similar between treatment groups. In patients with MSSA, the clinical cure rate was numerically higher in the telavancin group compared with the vancomycin group for the two studies pooled. There were relatively few patients in the ME Population with *S. pneumoniae*, but cure rates were numerically higher in the telavancin group compared with the vancomycin group for this pathogen in the individual studies and for the two studies pooled.

The clinical cure rates by pathogen for patients in the ME population were depicted in Tables 24 (Study 0015) and 49 (Study 0019). The comparative efficacy of telavancin and vancomycin in the ME population in both trials was discussed in previous sections of this report.

6.1.7 Subpopulations

Ventilator-associated Pneumonia (VAP)

Since patients with VAP constitute one of the most severely ill subpopulations among those with HAP, efficacy results were analyzed in this cohort. As depicted in the table below, there were comparable numbers of patients with VAP in the AT populations of both studies. For Study 0019, there were numerically more patients with VAP in the telavancin arm in the CE and ME populations, but the differences compared to the vancomycin arm were not statistically significant.

Table 80: FDA Medical Officer Table of Subject Count with VAP in various analysis populations, Studies 0015 and 0019

| | Study 0015 | | Study 0019 | |
|-----|------------|------------|------------|------------|
| | Telavancin | Vancomycin | Telavancin | Vancomycin |
| AT* | 103 | 100 | 113 | 111 |
| CE | 29 | 33 | 41 | 32 |
| ME | 26 | 26 | 38 | 28 |

*including NP due to Gram-negative pathogens only

Clinical Response Efficacy Data for Patients with VAP

The clinical cure rates for patients with VAP in the AT population were comparable across the two treatment arms in both studies as depicted below. In Study 0015, there were higher cure rates in the telavancin compared to vancomycin arm in the CE and ME populations, and the differences were statistically significant. Although cure rates were higher in the telavancin arm in the CE and ME populations in study 0019, the difference compared to vancomycin did not reach statistical significance.

Table 81: FDA Medical Officer Table of Clinical Cure Rates for Patients with VAP in various analysis populations, Studies 0015 and 0019

| | Study 0015 | | | Study 0019 | | |
|-----|------------------|------------------|-------------------------------|------------------|------------------|---------------------------|
| | Telavancin n (%) | Vancomycin n (%) | 95% CI for diff (TLV-VAN) | Telavancin n (%) | Vancomycin n (%) | 95% CI for diff (TLV-VAN) |
| AT* | 52/103 (50.5) | 54/100 (54.0) | -3.4 (-17.2, 10.2) | 54/113 (47.8) | 58/111 (52.3) | -4.5 (-17.5, 8.6) |
| CE | 26/29 (89.7) | 21/33 (63.6) | 26.0 (6.2, 45.8) [†] | 30/41 (73.2) | 22/32 (68.8) | 4.4 (-16.6, 25.4) |
| ME | 23/26 (88.5) | 15/26 (57.7) | 30.7 (8.2, 53.4) [†] | 27/38 (71.1) | 18/28 (64.3) | 6.7 (-16.1, 29.6) |

*including NP due to Gram-negative pathogens only; [†]statistically significant difference;
 AT=all treated; CE=clinically evaluable; ME=microbiologic evaluable

Among the patients in the ME population with VAP, *S. aureus* was a common pathogen. As depicted in the following table, cure rates were consistently higher in the telavancin group compared with the vancomycin group for patients with VAP due to MSSA, although none reached statistical significance. Among patients with VAP due to MRSA, there was a higher cure rate in the telavancin compared to vancomycin arm in the ME population in Study 0015, and the difference was statistically significant. In Study 0019, the cure rates were comparable across the two treatment arms in the patients with VAP due to MRSA.

Table 82: FDA Medical Officer Table of Clinical Cure Rates for Patients with VAP with MRSA or MSSA as a baseline analysis pathogen, ME population, Studies 0015 and 0019

| | Study 0015 | | | Study 0019 | | |
|------|------------------|------------------|--------------------------------|------------------|------------------|---------------------------|
| | Telavancin n (%) | Vancomycin n (%) | 95% CI for diff (TLV-VAN) | Telavancin n (%) | Vancomycin n (%) | 95% CI for diff (TLV-VAN) |
| MRSA | 15/17 (88.2) | 9/18 (50.0) | 38.2 (10.5, 66.0) [†] | 12/19 (63.1) | 10/15 (66.7) | -3.5 (-35.8, 28.7) |
| MSSA | 6/7 (85.7) | 5/7 (71.4) | 14.2 (-28.0, 56.6) | 13/17 (76.5) | 6/10 (60.0) | 16.5 (-20.0, 52.9) |

*including NP due to Gram-negative pathogens only; [†]statistically significant difference

FDA Medical Officer Comments: As discussed in previous sections of this report, published historical evidence will only permit interpretation of non-inferiority studies for NP and VAP using all-cause mortality as the primary endpoint. The clinical response data is provided above for completeness only.

All-cause Mortality Data for Patients with VAP

Using the Applicant’s protocol-specified window (deaths were systematically recorded up to the Follow-up/TOC Visit or 28 days after End-of-therapy (EOT) for those patients who did not have a Follow-up Visit), the mortality rates for the patients with VAP are summarized in the following table:

Table 83: FDA Medical Officer Table of Mortality Rates for Patients with VAP, AT Safety population, Studies 0015 and 0019

| | Study 0015 | | | Study 0019 | | |
|------------------|---------------------|---------------------|------------------------------|---------------------|---------------------|------------------------------|
| | Telavancin n (%) | Vancomycin n (%) | 95% CI for diff (TLV-VAN) | Telavancin n (%) | Vancomycin n (%) | 95% CI for diff (TLV-VAN) |
| AT | 80/372 (22%) | 62/374 (17%) | 4.9 (-0.7, 10.6) | 70/379 (18%) | 78/378 (21%) | -2.1 (-7.8, 3.5) |
| VAP [‡] | 24/103 (23%) | 18/100 (18%) | 5.3 (-5.8, 16.4) | 28/113 (25%) | 23/111 (21%) | 4.1 (-6.9, 15.0) |

*including NP due to Gram-negative pathogens only; †statistically significant difference; ‡subset of AT population; TLV=telavancin; VAN=vancomycin; AT=all treated; VAP=ventilator-associated pneumonia

As depicted above for the VAP subset, using the Applicant’s protocol-specified window, the mortality rates in the telavancin treatment groups in the two trials were higher than the comparator groups although the differences were not statistically significant.

In response to the FDA Information Request dated March 26, 2009, the Applicant provided additional all-cause mortality data using a 28-day post-therapy mortality window. As depicted in the table below, there was a higher risk difference and odds ratio for death in the pooled telavancin arms compared to the pooled vancomycin arms for deaths between EOT and EOT + 28 days post-therapy and for deaths between TOC and EOT + 28 days post-therapy, and the differences were statistically significant.

Table 84: FDA Medical Officer Table summarizing VAP All-cause Mortality Rates through 28 days post-therapy (in which patients with NP and VAP due to Gram-negative pathogens only have been excluded), AT Efficacy Population, Studies 0015 and 0019

| | Study | Randomized Treatment Group | N (VAP) | n (%) | 95%CI for Risk difference (TLV-VAN) | Odds Ratios with 95%CI |
|---|--------|----------------------------|---------|-------|-------------------------------------|------------------------|
| Deaths between Start of Study Drug and EOT Visit + 28 days post-Treatment | 0015 | TLV | 80 | 23 | 9.0 (-4.2, 22.2) | 1.6 (0.79, 3.4) |
| | | VAN | 81 | 16 | | |
| | 0019 | TLV | 89 | 25 | 7.6 (-4.9, 20.2) | 1.5 (0.76, 3.04) |
| | | VAN | 88 | 18 | | |
| | Pooled | TLV | 169 | 48 | 8.3 (-0.8, 17.4) | 1.6 (0.95, 2.61) |
| VAN | 169 | 34 | | | | |
| Deaths between EOT Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 71 | 14 | 7.6 (-4.3, 19.4) | 1.8 (0.71, 4.41) |
| | | VAN | 74 | 9 | | |
| | 0019 | TLV | 82 | 18 | 9.5 (-2.1, 21.0) | 2.0 (0.85, 4.58) |
| | | VAN | 80 | 10 | | |
| | Pooled | TLV | 153 | 32 | 8.6 (0.3, 16.9)* | 1.9 (1.01, 3.49)* |
| VAN | 154 | 19 | | | | |
| Deaths between TOC Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 59 | 2 | 3.4 (-1.2, 8.0) | Cannot be calculated |
| | | VAN | 65 | 0 | | |
| | 0019 | TLV | 67 | 3 | 4.5 (-0.5, 9.4) | Cannot be calculated |
| | | VAN | 70 | 0 | | |
| | Pooled | TLV | 126 | 5 | 4.0 (0.6, 7.4)* | Cannot be calculated |
| VAN | 135 | 0 | | | | |

*statistically significant difference; AT=all-treated population; TLV=telavancin; VAN=vancomycin; N(VAP)=total # of patients with VAP in AT population; n(%)=patient count (%) per strata

Additional Patient Deaths identified in Studies 0015 and 0019

In the original NDA submission, 341 deaths were identified across Studies 0015 and 0019. However, an additional 116 deaths were identified subsequently, and the updated mortality data and narratives were provided in response to two information requests from the Division dated June 9, 2009 and July 31, 2009. The Applicant provided narratives for patients who died up to Study Day 90 (the end of a pharmacoeconomic study) but who had not been identified previously.

FDA Medical Officer Comments: In assessing the revised all-cause mortality data, there was uncertainty resulting from the considerable amount of censored data such that the all-cause mortality data was uninterpretable (see Sections 5.3.1.2.7 and 5.3.2.2.7 of this report). In view of these issues, an FDA analysis of all-cause mortality in the subpopulation of patients with VAP was not performed. The Applicant plans to conduct a follow-up query of all study sites and then provide the updated mortality data in the future.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

As described in Section 6.4.4 of the Applicant's 0019 Clinical Study Report, telavancin pharmacokinetic (PK) and pharmacodynamic (PD) characteristics support a once-daily dosing regimen. The latter include concentration-dependent killing, prolonged postantibiotic effect, and

efficacy largely independent of dosing interval (as shown in studies of the murine neutropenic thigh infection model with the ratio of the telavancin area under the curve [AUC] to the minimum inhibitory concentration [MIC], i.e., AUC/MIC, as the primary pharmacodynamically-linked variable). The dose of 10 mg/kg was based on available nonclinical and clinical data. In particular, the anticipated clinical efficacy of the 10 mg/kg dose was supported by results from experimental animal models of infection, as well as the results of a clinical pharmacology study of penetration into pulmonary epithelial lining fluid (ELF) and alveolar macrophages (AM) in healthy subjects.

The Applicant's 0019 Clinical Study Report also described a PD evaluation utilizing three data sets: (a) the distribution of MICs for clinical isolates, (b) the distribution of the values of PK parameters for the test medication in the population, and (c) the PD target developed from the neutropenic mouse thigh infection model. Telavancin MICs were determined for a large number of isolates. Population PK data were collected from Phase 1 studies in healthy subjects and a Phase 2 study in patients with complicated skin and skin structure infection (Study 202b). The data were analyzed using a nonparametric expectation maximization approach. The PD target was identified using a 1-log₁₀ reduction in colony counts in the neutropenic mouse thigh infection model (a target used for anticipated clinical efficacy). The population values for the model parameters and population covariance matrix were used to generate Monte Carlo simulations. The probability of attaining the PD target was approximately 99% for a dose of 750 mg (~10 mg/kg) to be clinically efficacious in infections caused by organisms with a MIC as high as 2 µg/mL.

FDA Medical Officer Comments: Clinical trials 0015 and 0019 used an identical telavancin regimen (10 mg/kg once daily) to assess the efficacy and safety of the drug in the treatment of NP. However, the ability to conclude whether the drug is safe and efficacious at that dosage will be based on a review of the all-cause mortality and adverse events data. The various methodological deficiencies described in Section 5.3.1.2.6 of this report also confound such assessments.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

As noted by the Applicant in Module 2.7.3, Summary of Clinical Efficacy, telavancin is intended for short term administration in the treatment of NP such that persistence and/or tolerance effects were considered non-applicable.

6.1.10 Additional Efficacy Issues/Analyses

Potentially effective antibiotic therapy (PEAT)

As described previously in Section 5.3.2.2.4, a patient was defined as having received potentially effective antibiotic therapy (PEAT) if he/she was treated on 3 or more calendar days—either prior to and/or concomitantly with study medication—with one or more antibiotics that either (1) had activity against all of the patient's baseline Gram-positive respiratory pathogens or, (2) if no baseline Gram-positive respiratory pathogen had been identified, had activity against any Gram-

positive respiratory pathogen. If the baseline Gram-positive pathogen(s) was resistant to the prior antibiotics, then the prior antibiotics were not considered PEAT. The PEAT classification was used in the determining the CE and ME analysis populations.

In order to assess the specific PEAT agents administered, their frequency of administration, and use of vancomycin as PEAT, the FDA Medical Officer conducted an exploratory analysis. As depicted in the table below, the number of patients in both treatment arms in Study 0015 who received PEAT were similar. However, substantially fewer patients in the telavancin arm of Study 0019 received PEAT compared to vancomycin-treated patients, and the difference was statistically significant.

Table 85: FDA Medical Officer Table of Subject Count who received Potentially Effective Non-study Antibiotics (PEAT) from randomization through the TOC Visit, Studies 0015 and 0019, AT Efficacy Population

| Study | Treatment | N (AT) | n, PEAT Subject count | 95% CI for difference (TLV-VAN) |
|-------|------------|--------|-----------------------|---------------------------------|
| 0015 | Telavancin | 372 | 108 (29.0%) | 3.1 (-3.3, 9.5) |
| | Vancomycin | 374 | 97 (25.9%) | |
| 0019 | Telavancin | 377 | 61 (16.2%) | -6.7 (-12.3, -1.1)* |
| | Vancomycin | 380 | 87 (22.9%) | |

*statistically significant difference; N (AT) = subject count in AT population; TLV=telavancin; VAN=vancomycin

As depicted in the table below, piperacillin-tazobactam and vancomycin were the most frequently prescribed PEATs in the two treatment groups in Studies 0015 and 0019:

Table 86: FDA Medical Officer Table of the most frequently used PEAT with Subject Count, Studies 0015 and 0019

| | Study 0015 | | Study 0019 | |
|----------------------------|------------|------------|------------|------------|
| | Telavancin | Vancomycin | Telavancin | Vancomycin |
| Total subjects PEAT, N | 108 | 97 | 61 | 87 |
| n, piperacillin/tazobactam | 36 | 33 | 25 | 30 |
| n, vancomycin | 26 | 26 | 17 | 24 |
| n, levofloxacin | 13 | 16 | 6 | 4 |
| n, meropenem | 13 | 9 | 6 | 12 |
| n, amikacin | 11 | 7 | 3 | 3 |
| n, imipenem | 11 | 13 | 8 | 16 |
| n, ciprofloxacin | 9 | 14 | 5 | 3 |
| n, gentamicin | 6 | 5 | 3 | 4 |
| n, linezolid | 7 | 6 | 3 | 2 |
| n, ceftriaxone | 4 | 10 | 6 | 5 |

N=total subject count who received PEAT; n= subject count who received specified drug

Vancomycin was the comparator agent in Studies 0015 and 0019, and the drug was also used as PEAT in both treatment groups in those studies. In order to further evaluate the use of

vancomycin as PEAT, the FDA Medical Officer assessed the administration of the drug within and across the trials in the table below:

Table 87: FDA Medical Officer Summary Table of Measures of Central Tendency for the Use and Duration of Vancomycin as a PEAT for Subjects who received such antibacterial treatment from randomization through TOC Visit, Studies 0015 and 0019, AT Efficacy Population

| | Study 0015 | | Study 0019 | |
|---|-------------------|------------|-------------------|------------|
| | Telavancin | Vancomycin | Telavancin | Vancomycin |
| Total Subjects who received PEAT, N | 108 | 97 | 61 | 87 |
| n, vancomycin | 26 | 26 | 17 | 24 |
| # who received ≥2 courses of vancomycin | 11 | 8 | 7 | 6 |
| total # courses of vancomycin | 43 | 38 | 31 | 33 |
| Duration of vancomycin as PEAT (# subjects for which duration was specified) | 36 | 31 | 27 | 25 |
| Mean (days) | 2.61 | 3.65 | 3.07 | 3.32 |
| SD | 2.0 | 3.53 | 2.56 | 2.67 |
| Median (days) | 2.0 | 2.0 | 2.0 | 2.0 |
| Range (days) | 1-8 | 1-14 | 1-11 | 1-11 |
| 95% CI for difference (TEL-VAN) for subject count (n) for vancomycin | -2.7 (-14.7, 9.2) | | 0.3 (-14.4, 14.9) | |

As is evident from the table above, there were no statistically significant differences in the numbers of subjects who received vancomycin as PEAT from randomization through the TOC visit in Studies 0015 and 0019. The median duration of vancomycin use as PEAT was consistent at 2.0 days across the telavancin and vancomycin treatment arms in both studies, although the range of days administered varied from as few as one day up to 14 days.

Efficacy Conclusions

The efficacy data submitted in this NDA do not provide substantial evidence that telavancin is effective for the treatment of nosocomial pneumonia in adults caused by susceptible strains of Gram-positive pathogens. The two identical phase 3 clinical trials, Studies 0015 and 0019, were designed based on a 20% noninferiority margin (14% post hoc margin) for a clinical response efficacy endpoint. However, published historical evidence will only permit interpretation of non-inferiority efficacy trials for NP and VAP using all-cause mortality as the primary endpoint. As Studies 0015 and 0019 were not independently designed and statistically powered to assess the noninferiority of telavancin compared to vancomycin in a replicative manner based on all-cause mortality, the Applicant planned to pool the study populations for that analysis to achieve sufficient statistical power. Based on a review of the baseline patient characteristics for each trial population as conducted by this FDA Medical Officer, it was evident that despite identical trial designs the two study populations differed substantially with respect to the frequencies of various baseline characteristics and co-morbid conditions that could potentially affect the risk for mortality making it inadvisable to pool them. Review of the data provided by the Applicant revealed a mortality imbalance in Study 0015 with more deaths and higher odds ratios for death in the telavancin arm compared to the vancomycin arm that reached statistical significance in some analyses. This finding raised concerns that telavancin was inferior to vancomycin and that the drug may not be safe to administer in some subpopulations. However, on further

investigation in response to information requests from the Division, the Applicant uncovered additional mortality data that had not been provided previously. On review, it was apparent that the additional data did not provide adequate information about whether the treated patients had either withdrawn alive, died, dropped out, or were lost to follow-up by the end of the observation period. A large amount of censored information was included, which made it impossible to reach any specific conclusions regarding the efficacy of the drug despite the mortality imbalance observed in earlier analyses. The Applicant is expected to submit additional mortality data to the Division in the future. The updated data will need to be reviewed by the Division to assess whether telavancin is effective for the treatment of NP caused by susceptible strains of Gram-positive pathogens.

7 Review of Safety

Safety Summary

7.1 Methods

According to the Applicant's Summary of Clinical Safety (module 2.7.4), adverse events were to be monitored throughout the study period of the Phase 3 HAP studies. An adverse event or adverse experience (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Pre-existing events, which increased in frequency or severity or changed in nature during or as a consequence of use of a drug in human clinical trials, were also to be considered adverse events. Adverse events also were to include pre- or post-treatment complications that occurred as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies). Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration, and up to the last day on study (including the off-study medication period of the study before the Follow-up Visit), was to be recorded as an AE on the appropriate CRF page(s) and would be considered treatment-emergent (TEAE).

Serious adverse events (SAE) included any adverse drug experience that occurred at any dose and resulted in any of the following outcomes:

- Death;
- Life-threatening situation (subject/patient was at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events);
- Persistent or significant disability/incapacity;
- Congenital anomaly/birth defect in the offspring of a subject/patient who received study drug;
- Other: Important medical events that may not have resulted in death, were immediately life-threatening, or required hospitalization, may have been considered a SAE when, based upon appropriate medical judgment, they may have jeopardized the subject/patient and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such events were to be:

- o Intensive treatment in an emergency room or at home for allergic bronchospasm
- o Blood dyscrasias or convulsions that did not result in hospitalization
- o Development of drug dependency or drug abuse

Death was to be considered an outcome of an AE and not an AE in itself. In reports of death due to “Disease Progression”, where no other information was provided, the death was to be assumed to have resulted from progression of the disease being treated with the study drug(s).

In the Phase 3 HAP studies, deaths were systematically recorded up to the Follow-up/TOC Visit or 28 days after End-of-therapy (EOT) for those patients who did not have a Follow-up Visit. Serious adverse events and AEs were recorded using the same data capture window.

Follow-up of AEs was to continue through the last day on study (including the follow-up, off-study medication period of the study), until the Investigator and/or Theravance determined that the subject’s condition was stable, or up to 28 days after the last dose of study drug, whichever was longer. Theravance could request that certain AEs be followed until resolution.

Medical coding was performed according to the Dictionary Coding Guidelines documented in the DMP. Medications were coded according to the World Health Organization (WHO) Drug Dictionary (2004, 1st Quarter). All AE coding was performed by using the MedDRA dictionary, Version 6.1.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The relevant data sources for the safety assessment for this NDA consisted of the two Phase 3 clinical trials, Studies 0015 and 0019. They were identical randomized, double-blind, parallel-group, multinational studies designed to enroll non-ventilated patients with NP and ventilated patients with VAP. Safety analyses were performed on the AT safety population, which consisted of all enrolled patients who received any dose of study medication. Individual study and integrated data were provided by the Applicant in the NDA submission.

Table 88: List of Clinical Studies (from Applicant's Summary of Clinical Efficacy, Section 2.7.3.2.1, Table 1)

| Study Number | Title | Design / Type of Control | Treatments / Dose / Route of Administration | Efficacy Population | Duration of Treatment | # Centers / Location |
|--------------|--|---|--|---------------------|-----------------------|----------------------|
| 0015 | A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to methicillin-resistant <i>Staphylococcus aureus</i> | Randomized Double-Blind Active-Controlled | Telavancin 10 mg/kg IV q24h; Vancomycin 1 gm IV q12h; no oral switch | 746 | Up to 21 days | Multinational |
| 0019 | A Phase 3, Randomized, Double-Blind, Parallel-Group, Multinational Trial of Intravenous Telavancin Versus Vancomycin for Treatment of Hospital-Acquired Pneumonia with a Focus on Patients with Infections Due to methicillin-resistant <i>Staphylococcus aureus</i> | Randomized Double-Blind Active-Controlled | Telavancin 10 mg/kg IV q24h; Vancomycin 1 gm IV q12h; no oral switch | 757 | Up to 21 days | Multinational |

7.1.2 Categorization of Adverse Events

Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration, and up to the last day on study (including the off-study medication period of the study before the Follow-up Visit), was to be recorded as an AE on the appropriate CRF page(s) and would be considered treatment-emergent. Serious adverse events were defined in Section 7.1 of this report.

Table 89: FDA Medical Officer Summary Table of Treatment-emergent Adverse Events (TEAE), Serious Adverse Events (SAE), and Deaths while on Study, Studies 0015 and 0019, AT Population

| | Study 0015 | | Study 0019 | |
|-------------------------|------------|-----------------------|------------|------------|
| | Telavancin | Vancomycin | Telavancin | Vancomycin |
| | N=372 | N=374 | N=379 | N=378 |
| | n (%) | n (%) | n (%) | n (%) |
| Any TEAE | 321 (86%) | 317 (85%) | 295 (78%) | 296 (78%) |
| Drug-related TEAE | 126 (34%) | 93 (25%) [†] | 86 (23%) | 81 (21%) |
| Serious TEAE (SAE) | 127 (34%) | 88 (24%) [*] | 107 (28%) | 109 (29%) |
| Deaths (while on study) | 80 (22%) | 62 (17%) | 70 (18%) | 78 (21%) |

[†]95% CI for difference (telavancin – vancomycin) was 9.0 (2.5, 15.5);

^{*}95% CI for difference (telavancin – vancomycin) was 10.6 (4.2, 17.1)

As depicted in the table above, there were similar instances of TEAEs, drug-related TEAEs, SAEs, and deaths (within the protocol-specified window) across the telavancin and vancomycin

treatment groups of Study 0019. In contrast, there were marked imbalances related to the incidences of drug-related TEAEs, SAEs, and deaths (within the protocol-specified window) across the telavancin and vancomycin treatment groups of Study 0015. The higher rates of drug-related TEAEs and SAEs in the telavancin group compared to the vancomycin group in that study were statistically significant.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant analyzed the safety findings of each study individually and provided pooled data. However, the Applicant's analysis of mortality was reserved for the pooled results for Studies 0015 and 0019. The Applicant limited this assessment to the pooled studies' population to increase the number of patients in each treatment group and to achieve adequate power for an analysis of an event (i.e., death) that occurs with low frequency.

FDA Medical Officer Comments: Based on analyses described previously, there were significant differences in baseline characteristics for the study populations in Studies 15 and 19 demonstrating that they were not similar and could not be readily combined for mortality analysis despite implementation of the identical clinical trial protocol. Notwithstanding the Applicant's contention that the assessment of mortality should be limited to the pooled results of Studies 0015 and 0019 to achieve sufficient power for analysis, use of that approach without consideration of the individual study results was inadequate.

7.2 Adequacy of Safety Assessments

In response to an information request from the Division, the Applicant provided an electronic dataset that identified safety laboratory data that was missing from the original datasets. Based on this FDA Medical Officer's, it was apparent that there was a significant amount of missing safety laboratory data, which is summarized in the Tables below by the type of laboratory test (chemistry, hematology, and urinalysis). Overall, the lowest rates for missing all chemistry, hematology, and urinalysis safety laboratory test results were at baseline. At the end of therapy, >20% of patients in both clinical trials were missing all chemistry, hematology, and urinalysis test results. At TOC (and after accounting for missing laboratory data due to patient deaths), 6-9% were missing results from all of the chemistry tests, 7-13% were missing results from all of the hematology tests, and 12-17% were missing results from all of the urinalysis tests. Thus, the ability to assess the incidence and clinical significance of TEAEs (especially rare events) was hampered due to the substantial amount of missing laboratory data.

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Table 90: FDA Medical Officer Summary Table of Missing Chemistry Tests by Study, Treatment Group, and Study Visit, Studies 0015 and 0019

| | | | BASELINE | | EOT | | TOC | | | |
|----------|-------------|-----|----------------------|-----------------------|----------------------|-----------------------|----------------------|-----------------------|-------------------|--|
| Study | Study Group | N | Missing ≥1 Chemistry | Missing ALL Chemistry | Missing ≥1 Chemistry | Missing ALL Chemistry | Missing ≥1 Chemistry | Missing ALL Chemistry | All deaths by TOC | Patients missing ALL Chemistry not due to deaths |
| Study 15 | TLV | 372 | 180 (48.4) | 1 (0.3) | 372 (100) | 23 (6.2) | 372 (100) | 100 (26.9) | 78 (21.0) | 22 (5.9) |
| | VAN | 374 | 184 (49.2) | 1 (0.3) | 374 (100) | 15 (4.0) | 374 (100) | 86 (23.0) | 61 (16.3) | 25 (6.7) |
| Study 19 | TLV | 379 | 216 (57.0) | 1 (0.3) | 379 (100) | 23 (6.1) | 379 (100) | 103 (27.2) | 68 (17.9) | 35 (9.2) |
| | VAN | 378 | 209 (55.3) | 2 (0.5) | 378 (100) | 14 (3.7) | 378 (100) | 110 (29.1) | 74 (19.6) | 36 (9.5) |

EOT=end of treatment; TOC=test of cure; TLV=telavancin; VAN=vancomycin

Table 91: FDA Medical Officer Summary Table of Missing Hematology Tests by Study, Treatment Group, and Study Visit, Studies 0015 and 0019

| | | | BASELINE | | EOT | | TOC | | | |
|----------|-------------|-----|-----------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|-------------------|--|
| Study | Study Group | N | Missing ≥1 Hematology | Missing ALL Hematology | Missing ≥1 Hematology | Missing ALL Hematology | Missing ≥1 Hematology | Missing ALL Hematology | All deaths by TOC | Patients missing ALL Hematology not due to death |
| Study 15 | TLV | 372 | 139 (37.4) | 50 (13.4) | 89 (23.9) | 35 (9.4) | 131 (35.2) | 105 (28.2) | 78 (21.0) | 27 (7.3) |
| | VAN | 374 | 155 (41.4) | 70 (18.7) | 73 (19.5) | 27 (7.2) | 138 (36.9) | 100 (26.7) | 62 (16.6) | 38 (10.1) |
| Study 19 | TLV | 379 | 141 (37.2) | 62 (16.4) | 105 (27.7) | 42 (11.1) | 157 (41.4) | 111 (29.3) | 68 (17.9) | 43 (11.3) |
| | VAN | 378 | 131 (34.7) | 51 (13.5) | 95 (25.1) | 34 (9.0) | 170 (45.0) | 125 (33.1) | 74 (19.6) | 51 (13.5) |

EOT=end of treatment; TOC=test of cure; TLV=telavancin; VAN=vancomycin

Table 92: FDA Medical Officer Summary Table of Missing Urinalysis Tests by Study, Treatment Group, and Study Visit, Studies 0015 and 0019

| | | | BASELINE | | EOT | | TOC | | | |
|----------|-------------|-----|-----------------------|------------------------|-----------------------|------------------------|-----------------------|------------------------|-------------------|--|
| Study | Study Group | N | Missing ≥1 Urinalysis | Missing ALL Urinalysis | Missing ≥1 Urinalysis | Missing ALL Urinalysis | Missing ≥1 Urinalysis | Missing ALL Urinalysis | All deaths by TOC | Patients missing ALL Urinalysis not due to death |
| Study 15 | TLV | 372 | 55 (14.8) | 24 (6.5) | 56 (15.1) | 43 (11.6) | 132 (35.5) | 126 (33.9) | 79 (21.2) | 47 (12.6) |
| | VAN | 374 | 53 (14.2) | 24 (6.4) | 50 (13.4) | 37 (9.9) | 135 (36.1) | 125 (33.4) | 62 (16.6) | 63 (16.8) |
| Study 19 | TLV | 379 | 58 (15.3) | 25 (6.6) | 46 (12.1) | 36 (9.5) | 138 (36.4) | 129 (34.0) | 68 (17.9) | 61 (16.1) |
| | VAN | 378 | 57 (15.1) | 29 (7.7) | 49 (13.0) | 35 (9.3) | 151 (39.9) | 139 (36.8) | 76 (20.1) | 63 (16.7) |

EOT=end of treatment; TOC=test of cure; TLV=telavancin; VAN=vancomycin

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As depicted in the table below, the overall measures of central tendency (mean and median) for the duration of treatment with telavancin and vancomycin were similar in Studies 0015 and 0019. However, the range of treatment duration was broad in each treatment group from one to 23 days.

Table 93: FDA Medical Officer Summary Table of Treatment Duration using Measures of Central Tendency, Studies 0015 and 0019, AT Safety Population

| | Study 0015 | | Study 0019 | |
|------------------------|---------------|-----------------|---------------|----------------|
| | Telavancin | Vancomycin n | Telavancin | Vancomycin |
| N, subjects (ITT) | 372 | 374 | 379 | 378 |
| Mean (\pm SD), days | 9.1 \pm 4.7 | 9.4 \pm 4.2 | 9.9 \pm 4.7 | 10.0 \pm 4.7 |
| Median, days | 8.0 | 9.0 | 9.0 | 9.0 |
| Range, days | 1 - 23 | 1 - 22 | 1 - 22 | 1 - 23 |

SD=standard deviation

As illustrated in the following table summarizing study drug exposure using various treatment duration strata, the most frequently employed duration of study drug treatment was 7-11 days. However, in Study 0015, there were substantially more telavancin-treated patients who were administered study drug for the pooled strata of 1-2 days plus 3-6 days (n=100) compared to the analogous patient strata in the vancomycin group (n=77), and the difference was statistically significant (95% CI for difference telavancin – vancomycin: 6.3 (0.2, 12.4).

Table 94: FDA Medical Officer Summary Table of Subject Exposure to Study Drug, Studies 0015 and 0019, AT Safety Population

| Treatment Duration Strata | Study 0015 | | Study 0019 | |
|---------------------------|------------------------------|-----------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin n N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| 1-2 days | 23 (6.2) | 15 (4.0) | 17 (4.5) | 17 (4.5) |
| 3-6 days | 77 (20.7) | 62 (16.6) | 53 (14.0) | 52 (13.8) |
| 7-11 days | 172 (46.2) | 194 (51.9) | 195 (51.5) | 184 (48.7) |
| 12-14 days | 59 (15.9) | 63 (16.8) | 64 (16.9) | 72 (19.0) |
| 15-23 days | 41 (11.0) | 40 (10.7) | 50 (13.2) | 53 (14.0) |
| missing | 0 | 0 | 0 | 0 |

FDA Medical Officer Comment: Using the Applicant's mortality data (protocol-specified window), there were 37 deaths in the telavancin group and 28 deaths in the vancomycin group of Study 0015 among the patients treated for a duration of 1-6 days with study drug (telavancin, n=100; vancomycin, n=77). However, the risk difference (telavancin – vancomycin) was 0.6 with a 95% CI of (-13.7, 15.9), which was not statistically significant. Thus, despite having more patients treated for 1-6 days in the telavancin group compared to the vancomycin group in Study

0015, there was not a corresponding imbalance in mortality to account for the short duration of telavancin treatment in that 1-6 day treatment duration stratum.

However, when the patients treated from 1 to 14 days with study drug were assessed for mortality in Study 0015, it appeared that although a comparable number of patients were treated with telavancin (n=331) and comparator (n=334), a substantially higher number of those patients in the telancin group died (76 deaths versus 55 deaths for the vancomycin group) in that time period. The difference was statistically significant (95% CI for difference telavancin – vancomycin: 6.5 (0.5, 12.5), suggesting that more of the deaths in the telavancin group in Study 0015 occurred early in the treatment course and the difference was not due to chance alone. There was no similar imbalance in the distribution of deaths in Study 0019 across treatment groups for the same time interval.

7.2.2 Explorations for Dose Response

The phase 3 clinical trials used identical dosing regimens for telavancin of 10 mg/kg q24 h for patients without renal impairment. Dosage adjustments were made for patients with renal impairment. No alternative dosing regimens for telavancin in patients with normal renal function were studied in the two ATTAIN trials.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the reports of the Clinical Pharmacology, Pharmacology/Toxicology, and Microbiology Reviewers for details.

7.2.4 Routine Clinical Testing

In general, clinical testing of study subjects appeared adequate in the conduct of the clinical trials. However, there was considerable missing laboratory data as described in Section 7.2 of this report. It is also notable that determinations of serum calcium, glucose, sodium, and uric acid were not performed as part of the central laboratory chemistry panel. In the Applicant's response to an information request from the Division dated February 25, 2009, the Applicant stated that "the choice of analytes for the safety laboratory panel was based on data from the preclinical and Phase 1 and 2 studies, which did not detect signals in any of these parameters".

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the report of the Clinical Pharmacology Reviewer for details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Vancomycin is a similar drug to telavancin and was used as the comparator agent in both of the phase 3 clinical trials. Assessment for renal-related adverse events was a crucial part of the safety evaluation of telavancin and is discussed further in Section 7.3.5 of this report.

7.3 Major Safety Results

7.3.1 Deaths

Please refer to Section 6.1.5 for full details. The following provides a brief summary of relevant information.

All-cause Mortality data provided by the Applicant in the original NDA Submission

All-cause mortality was considered a secondary endpoint in both clinical studies. In the Phase 3 HAP studies, deaths were systematically recorded up to the Follow-up/TOC Visit or 28 days after End-of-therapy (EOT) for those patients who did not have a Follow-up Visit (protocol-specified window).

Table 95: Applicant Summary of Analysis of Deaths for studies 0015 and 0019, AT Safety Population (from Applicant's 2.7.4 Summary of Clinical Safety)

| | Number of patients | | | | | |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | 0015 | | 0019 | | 0015 + 0019 Total | |
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Total Deaths in window [2] | 80 (21.5%) | 62 (16.6%) | 70 (18.5%) | 78 (20.6%) | 150 (20.0%) | 140 (18.6%) |
| Difference (95% CI) [1] | 4.9% (-0.7%, 10.6%) | | -2.2% (-7.8%, 3.5%) | | 1.4% (-2.6%, 5.3%) | |
| Deaths in window while receiving Study Medication [3] | 48 (12.9%) | 45 (12.0%) | 44 (11.6%) | 35 (9.3%) | 92 (12.3%) | 80 (10.6%) |
| Difference (95% CI) [1] | 0.9% (-3.9%, 5.6%) | | 2.4% (-2.0%, 6.7%) | | 1.6% (-1.6%, 4.8%) | |

[1] Point estimate and 95% confidence interval on the treatment difference (telavancin – vancomycin) in death rate. The pooled analysis is stratified by study.

[2] Deaths based on patients with treatment-emergent adverse events with death as an outcome and deaths occurred within protocol-specified window.

[3] Deaths occurred prior to end-of-therapy (EOT) or 1 day after EOT

As depicted above, there was a notable imbalance in the mortality rates between the two treatment groups in Study 0015 with a higher death rate (by approximately 5%) in the telavancin group compared to the vancomycin group. In Study 0019, the mortality rates were comparable across the treatment groups.

All-cause Mortality data provided by the Applicant in response to the FDA Information Request dated March 26, 2009

In response to the FDA Information Request dated March 26, 2009, the Applicant provided the following table of all-cause mortality data using a 28-day post-therapy mortality window:

Table 96: Applicant Summary of Mortality Data for Studies 0015 and 0019 (from Applicant's Response dated March 26, 2009 to the FDA Information Request dated February 25, 2009)

| | Number of patients | |
|--|---------------------|---------------------|
| | Telavancin N=749 | Vancomycin N=754 |
| Deaths between Start of Study Drug and EOT Visit + 28 days | 160 (21.4%) | 147 (19.5%) |
| Deaths between EOT Visit and EOT Visit + 28 days | 113 | 104 |
| Deaths between TOC Visit and EOT Visit + 28 days | 11 | 6 |

The Applicant's mortality summary table above involved only pooled data and did not provide comparative all-cause mortality data for the individual trials based on differences in mortality rates across treatment groups within each study. Based on the pooled data from Studies 0015 and 0019, the all-cause mortality rates for telavancin-treated and vancomycin-treated patients were similar.

The following table provides an exploratory analysis of the Applicant's all-cause mortality data above in the AT population (including patients with NP and VAP due to Gram negative pathogens only) stratified by individual trial and pooled data.

Table 97: FDA Medical Officer Summary Table of All-cause Mortality Rates through 28 days post-therapy for Studies 0015 and 0019 with pooled data, AT Safety Population

| | Study | Actual Treatment Group | N (AT) | n (%) | 95%CI for risk difference (TLV-VAN) | Odds Ratio with 95%CI |
|---|--------|------------------------|--------|------------|-------------------------------------|-----------------------|
| Deaths between Start of Study Drug and EOT Visit + 28 days post-Treatment | 0015 | TLV | 372 | 85 (22.8) | 6.0 (0.3, 11.7)* | 1.46 (1.02, 2.10)* |
| | | VAN | 374 | 63 (16.8) | | |
| | 0019 | TLV | 379 | 76 (20.1) | -1.9 (-7.7, 3.9) | 0.89 (0.63, 1.27) |
| | | VAN | 378 | 83 (22.0) | | |
| | Pooled | TLV | 751 | 161 (21.4) | 2.0 (-2.1, 6.1) | 1.13 (0.88, 1.46) |
| VAN | 752 | 146 (19.4) | | | | |
| Deaths between EOT Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 350 | 63 (18.0) | 6.4 (1.1, 11.6)* | 1.67 (1.09, 2.55)* |
| | | VAN | 352 | 41 (11.6) | | |
| | 0019 | TLV | 353 | 50 (14.2) | -3.4 (-8.8, 1.9) | 0.77 (0.52, 1.16) |
| | | VAN | 358 | 63 (17.6) | | |
| | Pooled | TLV | 703 | 113 (16.1) | 1.4 (-2.3, 5.2) | 1.12 (0.84, 1.49) |
| VAN | 710 | 104 (14.6) | | | | |
| Deaths between TOC Visit and EOT Visit + 28 days post-Treatment | 0015 | TLV | 292 | 5 (1.7) | 1.4 (-0.2, 3.0) | 5.42 (0.63, 46.66) |
| | | VAN | 312 | 1 (0.3) | | |
| | 0019 | TLV | 309 | 6 (1.9) | 0.3 (-1.8, 2.4) | 1.17 (0.35, 3.87) |
| | | VAN | 300 | 5 (1.7) | | |
| | Pooled | TLV | 601 | 11 (1.8) | 0.8 (-0.5, 2.2) | 1.88 (0.69, 5.12) |
| VAN | 612 | 6 (1.0) | | | | |

*statistically significant difference; AT=all-treated population; TLV=telavancin; VAN=vancomycin; N(AT)=total # of patients in all-treated population; n(%)=patient count (%) per strata

Based on the data table above, there was a higher all-cause mortality rate in the telavancin group compared to the vancomycin group of Study 0015 in relation to deaths from start to EOT + 28 days and deaths between EOT and EOT + 28 days, and the differences were statistically significant. For Study 0019 and the pooled study data, no substantial differences across treatment groups in either study were evident.

All-cause Mortality data provided by the Applicant in response to the FDA Information Request dated July 31, 2009

As described previously in this report, the Applicant notified the Division of additional mortality data identified from the clinical database, the safety database, and data collected in a 10-week pharmaco-economic (PE) study and provided the additional data in response to an information request from the Division dated June 9, 2009.

In response to an information request from the Division dated July 31, 2009, the Applicant provided summary tables for the trial deaths, a list of patients for which mortality status is unknown up to Study Day 28, a list of patients for whom mortality status is unknown up to last study day + 28 days, and an electronic dataset. The Applicant also provided narratives for the deaths. The two summary tables are provided below:

Table 98: Applicant's Summary of Deaths occurring between Start of Study Drug and Start of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 92 (25%) | 73 (20%) | 80 (21%) | 88 (23%) | 172 (23%) | 161 (21%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 70 (19%) | 51 (14%) | 54 (14%) | 68 (18%) | 124 (17%) | 119 (16%) |
| Alive or censored | 280 (75%) | 301 (80%) | 299 (79%) | 290 (77%) | 579 (77%) | 591 (79%) |
| Censored* | 126 (34%) | 134 (36%) | 113 (30%) | 103 (27%) | 239 (32%) | 237 (32%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

Table 99: Applicant's Summary of Deaths Occurring between Start of Study Drug and End of Study Drug + 28 Days (from Response to Information Request of July 31, 2009)

| | Study 0015 | | Study 0019 | | Total | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 | Telavancin N=751 | Vancomycin N=752 |
| Death | 102 (27%) | 82 (22%) | 88 (23%) | 99 (26%) | 190 (25%) | 181 (24%) |
| On therapy | 22 (6%) | 22 (6%) | 26 (7%) | 20 (5%) | 48 (6%) | 42 (6%) |
| After end of study drug | 80 (22%) | 60 (16%) | 62 (16%) | 79 (21%) | 142 (19%) | 139 (18%) |
| After follow-up visit | 22 (6%) | 19 (5%) | 18 (5%) | 21 (6%) | 40 (5%) | 40 (5%) |
| Alive or censored | 270 (73%) | 292 (78%) | 291 (77%) | 279 (74%) | 561 (75%) | 571 (76%) |
| Censored* | 145 (39%) | 159 (43%) | 139 (37%) | 126 (33%) | 284 (38%) | 285 (38%) |
| -Total- | 372 (100%) | 374 (100%) | 379 (100%) | 378 (100%) | 751 (100%) | 752 (100%) |

*This data line was added by the FDA Medical Officer based on an analysis of the Applicant's submission.

FDA Medical Officer Comments:

As described previously in Section 5.3.1.2.7, the risk difference for all deaths occurring between start of study drug and start of study drug + 28 Days for the telavancin and the vancomycin groups was 5.2%, but the size of the difference could be substantial (>11% higher among the telavancin-treated patients). Similarly, although the risk difference for deaths occurring between start of study drug and end of study drug + 28 Days was 5.5%, the size of the risk difference for death could be negligible or it could be quite large (>11%) for patients treated with telavancin. This finding represents a significant safety signal in terms of higher all-cause mortality in the telavancin group of Study 0015. In contrast, comparable risk differences for death were not observed in Study 0019 for both time intervals of observation for all-cause mortality as described in Section 5.3.2.2.7. Assessment of pooled telavancin and vancomycin data at both time intervals revealed a risk difference with 95% confidence intervals of 1.5% (-2.7%, 5.7%) for the deaths occurring between start of study drug and start of study drug + 28 days and a risk difference of 1.2% (-3.1%, 5.6%) for deaths occurring between start of study drug and end of study drug + 28 days.

When the all-cause mortality data is analyzed from the safety perspective, the results for Study 0015 suggest that there is a substantially higher risk for death in the telavancin group compared

to the vancomycin group. The results for Study 0019 and the results of the pooled telavancin and pooled vancomycin data do not suggest a similar conclusion. However, due to the large percentage of censored events among the submitted mortality data for both studies as described in Sections 5.3.1.2.7 and 5.3.2.2.7 of this report, this FDA Medical Officer has concerns that the actual number of deaths is underestimated in both treatment groups of both studies. The uncertainty resulting from the considerable amount of censored data makes the all-cause mortality data uninterpretable and, thus, the safety of telavancin compared to vancomycin in terms of all-cause mortality cannot be assessed based on either the individual study results or the pooled data. The Applicant plans to conduct a follow-up query of all study sites and then submit the updated mortality data to the Division in the future.

Patient Deaths in Study 0015:

The following table summarizes the most frequent causes for death in both treatment groups in Study 0015.

Table 100: FDA Medical Officer Summary Table of the Most Frequent Causes (>3%) for Death, Study 0015, AT Population

| | | Telavancin | Vancomycin |
|---|----------------------------|------------|------------|
| All Treated | N (%) | 372 | 374 |
| Total Subject Deaths | n (%) | 80 (21.5%) | 62 (16.6%) |
| Causes for Death n (% of all deaths) | Not specified | 16 (20.0%) | 10 (16.1%) |
| | Multi-organ failure* | 11 (13.8%) | 6 (9.7%) |
| | Septic shock** | 7 (8.8%) | 6 (9.7%) |
| | Respiratory Arrest | 6 (7.5%) | 10 (16.1%) |
| | Heart Failure [#] | 3 (3.8%) | 2 (3.2%) |
| | Sepsis [†] | 3 (3.8%) | 2 (3.2%) |

*includes the following PT: multiple organ failure, multi organ failure, multorgan system failure, multiple organ failure syndrome, multiple organ failure/cardiogenic shock, multiple organ failure/end stage liver disease/primary biliary cirrhosis

** includes the following PT: septic shock, septic shock/source septicemia, septic shock with multiorgan failure, septicemia shock (A. baumannii), septicemic shock with multiorgan failure, septic shock due to P. aeruginosa bacteremia, septic shock secondary to second episode of VAP, septic shock caused by suspected right sided empyema progressed

[#]includes the following PT: congestive heart failure, heart failure

[†]includes the following PT: sepsis, severe sepsis with burst abdomen, severe sepsis syndrome, worsening sepsis

As depicted in the table above, the most frequent cause for death among patients treated with either study medication was not specified. In terms of identified causes for death, multi-organ failure was the most common cause reported among the telavancin-treated patients, whereas respiratory arrest was the most frequent cause in the vancomycin-treated patients. Septic shock, heart failure, and sepsis accounted for comparable numbers of patient deaths in both treatment groups.

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The following tables summarize information derived from the Applicant's narratives provided in association with Supporting Table 202 of the 0015 Clinical Study Report for each of the telavancin- and vancomycin-treated patients who died during participation in the study.

Table 101: FDA Medical Officer's Composite List of all Individual Study Deaths* (within protocol-specified window) among Telavancin-treated Patients, Study 0015

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|---|--|--------------------------|
| 01005-4238 | 82/F/H | 8 | Multi-organ failure | Clinical cure | (b) (6) |
| 01008-4439 | 76/F/W | 3 | Shock, respiratory failure | Indeterminate | |
| 01014-4037 | 81/F/H | 16 | Pulmonary embolism, respiratory arrest | Clinical cure | |
| 01014-4042 | 79/M/H | 8 | Multi-organ failure | Indeterminate (due to discontinuation of study drug as a result of QTc prolongation) | |
| 01014-4081 | 69/M/H | 14 | Multi-organ failure | Indeterminate | |
| 01014-4087 | 57/M/H | 8 | Hemorrhagic stroke | Clinical failure (persistent signs and symptoms of pneumonia) | |
| 01014-4233 | 73/M/H | 7 | Acute renal failure, hypovolemic shock (secondary to extensive left limb hematoma with progression into thorax) | Clinical cure (study drug discontinued due to renal failure) | |
| 01028-4228 | 78/M/H | 10 | Septic shock (new lung infiltrates and new Gram-negative bacterial pathogens on respiratory cultures) | Indeterminate | |
| 01028-4641 | 67/M/H | 11 | Congestive cardiac failure; respiratory failure secondary to pneumothorax due to barotrauma | Indeterminate | |
| 02011-4096 | 76/M/W | 3 | Respiratory failure (following extubation) | Indeterminate | |
| 02011-4605 | 66/M/W | 4 | Aspiration | Clinical Cure | |
| 02024-4142 | 83/M/W | 3 | Respiratory failure | Indeterminate | |
| 02024-4676 | 64/M/W | 3 | Cardiogenic shock | Indeterminate | |
| 05001-4047 | 76/F/H | 10 | Cerebrovascular accident | Indeterminate | |
| 05001-4482 | 78/M/H | 3 | Bronchopneumonia | Clinical failure | |
| 05004-4556 | 50/F/H | 16 | Acute respiratory failure (medical care was withdrawn) | Indeterminate | |
| 06013-4221 | 82/F/W | 8 | Atelectasis, respiratory failure (patient was "do not resuscitate" status) | Clinical cure | |
| 06013-4346 | 54/M/W | 8 | Clostridium colitis, hepatorenal syndrome (patient was "do not resuscitate" status) | Indeterminate | |
| 06013-4570 | 82/F/W | 2 | Respiratory failure (patient had been placed on "comfort measures") | Indeterminate (study drug discontinued as Gram-positive coverage was no longer needed; patient had only Gram-negative baseline pathogen) | |
| 07002-4239 | 61/M/H | 7 | Cerebrovascular accident | Indeterminate | |
| 07002-4463 | 27/M/H | 7 | Cerebral infarction | Indeterminate (due to neurologic damage) | |
| 09004-4639 | 87/F/W | 3 | Pneumonia, chronic pyelonephritis | Clinical failure | |
| 09008-4540 | 84/M/W | 2 | Respiratory failure, agitation, confusional state, sneezing, skin burning sensation | Indeterminate (withdrawn due to possible allergic reaction) | |
| 09011-4701 | 69/M/W | 1 | Pneumonia | Indeterminate | |
| 09011-4761 | 91/F/W | 10 | Hypoalbuminemia | Clinical cure | |
| 12006-4312 | 73/M/W | 9 | Hemorrhagic shock | Indeterminate | |
| 12006-4522 | 81/M/H | 9 | Septic shock | Clinical failure | |
| 12016-4158 | 37/M/H | 16 | Renal failure acute, septic shock | Clinical failure | |
| 12016-4649 | 38/F/W | 14 | Multi-organ failure | Clinical cure | |
| 18000-4191 | 64/F/W | 14 | Peritonitis, shock | Clinical cure | |
| 18001-4188 | 61/M/W | 10 | Multi-organ failure | Clinical cure | |
| 18009-4001 | 83/M/W | 3 | Pneumonia | Indeterminate (study drug discontinued as Gram-positive coverage was no longer needed) | |
| 18009-4027 | 81/M/W | 6 | Pneumonia | Clinical failure | |
| 18009-4580 | 79/F/W | 3 | Pneumonia | Clinical failure | |
| 18009-4584 | 77/M/W | 5 | Complete atrioventricular block | Clinical failure | |
| 18010-4138 | 76/M/W | 10 | Fatigue (patient was "do not resuscitate" status) | Clinical failure | |
| 18010-4586 | 67/F/W | 2 | Cardio-respiratory arrest | Indeterminate (patient died within 1.5 hours of | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|---|--|--------------------------|
| | | | | study drug administration) | (b) (6) |
| 23003-4097 | 48/M/A | 8 | Septic shock | Clinical cure | |
| 23004-4360 | 75/F/A | 9 | Sepsis, hypoxic encephalopathy | Indeterminate | |
| 23004-4497 | 49/M/A | 11 | Abdominal sepsis | Clinical failure | |
| 30905-4034 | 87/F/W | 3 | Cardiac failure | Indeterminate | |
| 30905-4234 | 80/M/W | 7 | Septic shock (source not identified) | Clinical cure | |
| 33017-4715 | 92/F/A | 13 | Septic shock (discharged from hospital against medical advice on Day 36) | Indeterminate | |
| 33018-4644 | 54/M/A | 5 | Septic shock | Clinical failure | |
| 33402-4714 | 58/M/A | 7 | Hemorrhagic shock | Indeterminate | |
| 38020-4350 | 49/F/H | 2 | Sepsis | Indeterminate | |
| 38024-4248 | 73/F/A | 11 | Respiratory arrest | Clinical cure (Patient treated concomitantly with vancomycin from Study Day 2 for MSSA bacteremia) | |
| 38024-4268 | 53/M/W | 8 | Septic shock | Clinical cure | |
| 38024-4344 | 87/M/W | 7 | Respiratory arrest (patient had been placed on "comfort measures") | Indeterminate | |
| 38024-4376 | 44/F/W | 2 | Respiratory arrest (mechanical ventilation was discontinued prior to the event) | Indeterminate | |
| 38045-4592 | 78/F/W | 5 | Respiratory failure (telavancin discontinued on Study Day 5 per family's request) | Clinical failure | |
| 38045-4707 | 62/M/W | 9 | Respiratory failure (family refused further treatment on Study Day 10) | Clinical failure | |
| 38049-4187 | 80/F/W | 4 | Acute renal failure | Indeterminate | |
| 38049-4192 | 55/F/W | 7 | Septic shock (patient was "do not resuscitate" status on Study Day 8) | Clinical failure | |
| 38083-4020 | 77/F/W | 6 | Failure to thrive (antibiotics and fluid support was withdrawn on Study Day 16) | Clinical failure | |
| 38101-4016 | 99/M/A | 3 | Respiratory distress, electrocardiogram QT corrected interval prolonged (changed to "comfort care" on Study Day 4) | Indeterminate (Study drug was discontinued due to prolonged QT interval) | |
| 38101-4277 | 77/M/B | 6 | Multi-organ failure, fluid overload (patient was changed to "do not resuscitate" status on Study Day 13) | Clinical failure | |
| 38148-4769 | 64/M/W | 4 | Oliguria, blood creatinine increased, multi-organ failure (patient was changed to "do not resuscitate" status on Study Day 7 and all medical measures were withdrawn) | Indeterminate (Study drug was discontinued due to increased creatinine and oliguria) | |
| 38148-4786 | 77/F/W | 12 | UGI hemorrhage, GI hemorrhage | Clinical cure | |
| 38270-4753 | 85/M/W | 3 | Respiratory failure (patient was changed to "do not resuscitate" status and comfort measures were provided on Study Day 3) | Indeterminate | |
| 38271-4115 | 85/M/W | 12 | Respiratory distress (patient was changed to "do not resuscitate" status and comfort measures were provided on Study Day 17) | Clinical failure | |
| 38271-4176 | 93/F/H | 5 | Respiratory failure (patient was changed to "do not resuscitate" status on Study Day 6) | Clinical cure | |
| 38271-4725 | 77/M/W | 21 | Respiratory distress, pneumonia | Clinical cure at EOT; Clinical failure at TOC | |
| 38337-4511 | 89/F/W | 1 | Respiratory failure (patient was "do not resuscitate" status) | Indeterminate | |
| 38337-4527 | 89/M/W | 1 | Acute coronary syndrome (patient was changed to "do not resuscitate" status and comfort measures were provided on Study Day 2) | Indeterminate (patient treated with telavancin, vancomycin and aztreonam beginning on Study Day 1 without explanation for vancomycin use) | |
| 38348-4254 | 80/F/W | 4 | Acute renal failure, multi-organ failure (patient was changed to "do not resuscitate" status and comfort measures were provided on Study Day 7) | Indeterminate (Study drug was discontinued to allow more frequent monitoring of PTT in view of enlarging RUE hematoma) | |
| 38351-4400 | 88/M/W | 11 | Atrial fibrillation, congestive cardiac failure | Clinical cure (narrative describes concurrent CHF throughout the course of study) | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|---|--|--------------------------|
| | | | | participation that eventually lead to death) | (b) (6) |
| 38363-4583 | 78/F/W | 5 | COPD exacerbated (patient placed on “hospice care” and consent withdrawn by family on Study Day 5) | Indeterminate (due to withdrawn consent) | |
| 41001-4552 | 40/M/A | 1 | Bradycardia (developed four hours after the Study Day 1 telavancin dose) | Indeterminate | |
| 41002-4102 | 76/F/A | 2 | Acute respiratory distress syndrome | Clinical failure | |
| 41002-4695 | 66/M/A | 3 | Multi-organ failure | Indeterminate (due to multi-organ failure; the Applicant considered it possible that study medication may have contributed to worsening renal failure) | |
| 41006-4297 | 71/M/A | 8 | Sepsis | Indeterminate | |
| 41006-4408 | 65/M/A | 8 | Encephalopathy, shock, septic shock | Clinical failure | |
| 41009-4199 | 35/M/A | 3 | Septic shock, multi-organ failure | Indeterminate | |
| 41009-4501 | 40/M/A | 7 | Bradycardia | Indeterminate | |
| 41009-4504 | 34/M/A | 9 | Death due to unknown cause (Consent withdrawn on Study Day 9 and patient discharged against medical advice) | Indeterminate (due to early withdrawal from study) | |
| 41009-4635 | 76/M/A | 9 | Mediastinitis | Indeterminate | |
| 41010-4380 | 55/M/A | 2 | Status epilepticus | Indeterminate | |
| 41013-4414 | 70/M/A | 4 | Myocardial ischemia | Indeterminate | |
| 52000-4703 | 71/M/W | 12 | Congestive cardiac failure (patient was changed to “do not resuscitate” status) | Clinical cure | |

*Data derived from Supporting Table 202 (page 3844) and the Applicant’s narrative summaries in the 0015 Clinical Study Report

Several important observations are evident from the preceding table, which summarizes the individual patient narratives for the telavancin-treated subjects who died during participation in Study 0015. Many of the patients were elderly (age ≥65 years) and had serious underlying medical disorders, suffered trauma, experienced post-operative complications, or had central nervous system bleeds, which compromised multiple organ systems and could have potentially increased their risk for death. Many of the patients experienced new complications (such as stroke, gastrointestinal bleeding, or aspiration events) that could not be attributed to study drug.

It was difficult to assess the relationship of some of the adverse events and deaths to study drug exposure due to the paucity of details provided in the narratives. The reason(s) underpinning the Investigators’ and the Applicant’s assessments of whether specific adverse events were considered to have been related (or not) to study drug exposure were not clearly articulated in many instances. None of the deaths appeared to be due to a hypersensitivity reaction to telavancin, although study drug was discontinued in one patient due to a possible allergic reaction. Telavancin was withdrawn in two patients due to QTc prolongation.

In terms of EOT outcome assessments, many patients who died had indeterminate EOT outcomes that were so assessed “due to the patient’s death” during the course of study medication treatment. The study drug treatment duration (which ranged from 2 to 16 days) was considered incomplete.

For some patients who died and had experienced septic shock, the most probable source for sepsis was not clearly identified in the narratives; if the source of septic shock was the primary lung infection under study, then the patients should have had an outcome assessment of clinical

failure (rather than indeterminate) in this FDA Medical Officer’s opinion; for some patients who were assessed as clinical failures in the setting of septic shock, the rationale for not attributing the event (death) to the failure to adequately treat HAP under study was not clarified (as in case # 41006-4408). In addition, one patient (41006-4297), who had only *P.aeruginosa* at baseline and eventually died of Gram-negative sepsis, was assessed as indeterminate (rather than clinical failure) at EOT for unclear reasons.

For the six patients in which pneumonia was listed as a SAE, four patients had EOT outcome assessments of clinical failure and two had EOT outcome assessments of indeterminate.

Life support measures were withdrawn in 17 patients, mechanical ventilation was discontinued in three subjects, and consent was withdrawn in four patients, which are interventions that further confounded assessment of study drug efficacy in those cases. Twelve patients died due to respiratory distress, which developed after comfort care measures were instituted.

Table 102: FDA Medical Officer's Composite List of all Individual Study Deaths* (out of protocol-specified window) among Telavancin-treated Patients, Study 0015

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|---|--|-------------------------------------|
| 02024-4216 | 80/F/W | 7 | Respiratory failure | Clinical cure | |
| 05004-4555 | 65/M/H | 21 | Worsening septic shock | Clinical failure | |
| 07002-4069 | 80/M/H | 10 | Congestive cardiac failure | Clinical cure | |
| 18000-4211 | 79/M/W | 5 | Sepsis | Indeterminate | |
| 18001-4246 | 91/F/W | 7 | Red man syndrome, anxiety, increased blood creatinine, cause of death unknown | Clinical cure | |
| 18010-4139 | 75/M/W | 10 | Renal insufficiency, anuria | Clinical cure | |
| 38070-4309 | 66/M/H | 14 | Respiratory distress | Indeterminate (study medication discontinued “due to unknown source of primary infection”) | |
| 38148-4114 | 81/F/W | 8 | Hypotension, general physical health deterioration | Clinical cure | |
| 38271-4124 | 91/M/W | 3 | Cardiopulmonary arrest | Indeterminate | |
| 41002-4198 | 49/M/A | 10 | Cerebral vasospasm | Indeterminate (study drug discontinued as Gram-positive coverage was no longer needed) | |
| 01012-4086 | 21/M/H | 7 | UGI hemorrhage, gastric ulcer perforation | Clinical failure | |

*Data derived from the Applicant’s narrative summaries in the 0015 Clinical Study Report

Among the out of window study deaths in the telavancin group of Study 0015 as summarized in the table above, most of these patients were elderly (age ≥65 years) and had serious co-morbid medical conditions. One patient developed “red man syndrome”. None of the patients were reported to have experienced pneumonia as a serious adverse event. Life support measures were not withdrawn in any of the patients.

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Table 103: FDA Medical Officer's Composite List of all Individual Study Deaths* (within protocol-specified window) among Vancomycin-treated Patients, Study 0015

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|---|---|--------------------------|
| 01005-4713 | 84/F/H | 12 | Septic shock | Indeterminate | (b) (6) |
| 01013-4065 | 81/F/W | 10 | Cardiac arrest | Indeterminate | |
| 01014-4082 | 76/F/H | 14 | Multi-organ failure | Indeterminate | |
| 01015-4435 | 87/M/H | 5 | Myocardial ischemia, sepsis | Clinical failure | |
| 01028-4436 | 77/F/H | 12 | Septic shock | Indeterminate (new episode of HAP) | |
| 02011-4347 | 72/F/W | 3 | Multi-organ failure | Indeterminate | |
| 04001-4567 | 73/F/W | 3 | Cardiac arrest | Clinical failure | |
| 05001-4319 | 59/M/W | 8 | Bronchospasm | Indeterminate | |
| 05002-4048 | 77/M/H | 6 | Renal insufficiency, septic shock | Clinical failure | |
| 05004-4044 | 68/F/H | 15 | Acute respiratory failure | Clinical cure | |
| 05004-4459 | 72/F/H | 22 | Acute respiratory failure | Clinical cure | |
| 05004-4460 | 61/M/H | 16 | Cardiac failure | Indeterminate | |
| 05007-4231 | 59/M/H | 10 | Acute renal failure (possibly related to study drug), acute pancreatitis, septic shock | Indeterminate | |
| 06026-4508 | 80/M/W | 9 | Acute respiratory distress syndrome | Indeterminate | |
| 07002-4553 | 26/M/H | 17 | Multi-organ failure, duodenal perforation, septic shock, UGI hemorrhage | Clinical cure | |
| 09004-4519 | 84/F/W | 18 | Myocardial infarction | Indeterminate | |
| 09004-4637 | 71/M/W | 4 | Pneumonia, chronic pyelonephritis | Clinical failure | |
| 09004-4684 | 93/F/W | 3 | Pneumonia | Clinical failure | |
| 09008-4407 | 67/M/W | 11 | Cardiac failure | Clinical failure | |
| 09008-4516 | 53/M/W | 4 | Respiratory failure | Indeterminate | |
| 09011-4632 | 79/M/W | 1 | Pneumonia | Indeterminate (death attributed to primary infection) | |
| 12012-4255 | 76/M/H | 4 | Left ventricular failure, septic shock | Indeterminate | |
| 18000-4117 | 69/M/W | 2 | Multi-organ failure, septic shock | Indeterminate (study drug discontinued due to multi-organ failure) | |
| 18001-4153 | 82/M/W | 3 | Multi-organ failure | Clinical failure | |
| 18001-4579 | 50/M/W | 5 | Respiratory failure | Clinical failure | |
| 18009-4607 | 91/F/W | 7 | Pneumonia | Clinical failure | |
| 19010-4722 | 87/M/W | 9 | Pneumonia | Clinical failure | |
| 19013-4671 | 77/F/W | 1 | Ventricular fibrillation | Indeterminate | |
| 23003-4099 | 58/M/A | 15 | Multi-organ failure | Clinical failure | |
| 30905-4237 | 84/F/W | 8 | Renal insufficiency, coronary artery disease | Indeterminate (due to renal insufficiency possibly related to study drug) | |
| 33016-4534 | 76/M/A | 7 | Septic shock | Clinical failure | |
| 33402-4070 | 76/M/A | 14 | Injury asphyxiation, congestive cardiac failure, pulmonary edema | Indeterminate | |
| 37009-4431 | 67/M/W | 3 | Respiratory failure | Clinical failure | |
| 38020-4062 | 58/F/W | 4 | Pneumonia | Clinical failure | |
| 38024-4492 | 91/M/W | 8 | Ventricular tachycardia | Clinical cure | |
| 38024-4569 | 64/F/W | 3 | Supraventricular tachycardia, multi-organ failure, ventricular tachycardia (family withdrew life support and placed patient on "comfort measures" only) | Indeterminate | |
| 38024-4775 | 53/F/W | 4 | Respiratory failure (family withdrew life support) | Indeterminate | |
| 38045-4279 | 60/M/W | 8 | Hepatic failure | Clinical cure | |
| 38045-4310 | 58/M/W | 7 | Respiratory failure (family withdrew life support) | Clinical cure | |
| 38049-4143 | 69/M/W | 17 | Sepsis (patient was changed to "do not resuscitate" status and placed on "comfort measures") | Clinical cure | |
| 38101-4011 | 92/M/H | 4 | Hypoxia (patient was changed to "comfort measures" only) | Indeterminate | |
| 38101-4106 | 85/F/W | 8 | Atrial fibrillation | Clinical failure | |
| 38101-4148 | 88/F/W | 1 | Ventricular fibrillation, ventricular tachycardia (patient was on "do not resuscitate" status) | Indeterminate | |
| 38101-4274 | 75/F/B | 2 | Pneumonia, acute renal failure | Indeterminate (patient was withdrawn from the study by the investigator) | |
| 38148-4049 | 77/F/W | 11 | Respiratory failure (patient was changed to "comfort | Indeterminate | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|---|---|-------------------------------------|
| | | | care” status) | | |
| 38148-4218 | 88/F/W | 3 | Renal insufficiency | Indeterminate (family withdrew consent) | |
| 38143-4393 | 84/F/W | 3 | Congestive cardiac failure | Indeterminate | |
| 38148-4675 | 82/F/B | 14 | Cardiac arrest (patient was on “do not resuscitate” status) | Clinical failure | |
| 38148-4756 | 52/M/W | 2 | Sepsis | Indeterminate (patient withdrew consent) | |
| 38270-4620 | 75/M/W | 5 | Respiratory failure (patient was changed to “comfort care” status) | Indeterminate | |
| 38271-4108 | 93/M/A | 11 | Respiratory arrest (patient was on “do not resuscitate” status) | Indeterminate | |
| 38271-4788 | 87/M/W | 3 | Respiratory failure (patient requested no intubation and no CPR) | Clinical failure | |
| 38355-4454 | 83/F/H | 2 | Cerebrovascular accident (family had patient extubated in view of patient’s condition and unresponsiveness) | Indeterminate | |
| 38363-4757 | 84/M/W | 5 | Respiratory failure (family withdrew consent; patient placed on “comfort measures”) | Indeterminate | |
| 41001-4441 | 60/M/A | 9 | Respiratory arrest, shock | Indeterminate (vancomycin discontinued on Day 9 because “Gram-positive coverage was no longer clinically required”) | |
| 41001-4542 | 51/F/A | 10 | Multi-organ failure, gangrene, bradycardia, cardiac arrest | Indeterminate | |
| 41002-4200 | 55/F/A | 8 | Septic shock | Clinical failure | |
| 41006-4514 | 70/F/A | 5 | Septic shock | Clinical failure | |
| 41009-4329 | 44/M/A | 10 | Hematemesis | Indeterminate | |
| 41016-4354 | 77/F/A | 10 | Sepsis | Clinical | |
| 41016-4401 | 74/M/A | 7 | Sudden cardiac death | Clinical cure | |
| 41017-4699 | 80/F/A | 7 | Aspiration | Indeterminate | |

*Data derived from the Applicant’s narrative summaries in the 0015 Clinical Study Report

Similar to the within window patient deaths in the telavancin group of Study 0015, the patients who died in the vancomycin group were elderly (age ≥65 years) and had serious underlying medical disorders, suffered trauma, experienced post-operative complications, or had central nervous system bleeds, which compromised multiple organ systems and could have potentially increased their risk for death. Many of the patients experienced new complications (such as stroke, gastrointestinal bleeding, or aspiration events) that could not be attributed to study drug.

It was difficult to assess the relationship of some of the adverse events and deaths to study drug exposure due to the paucity of details provided in the narratives. The reason(s) underpinning the Investigators’ and the Applicant’s assessments of whether specific adverse events were considered to have been related (or not) to study drug exposure were not clearly articulated in many instances. None of the deaths appeared to be due to a hypersensitivity reaction to vancomycin.

In terms of EOT outcome assessments, many patients who died had indeterminate EOT outcomes that were so assessed “due to the patient’s death” during the course of study medication treatment. The study drug treatment duration (which ranged from 2 to 18 days) was considered incomplete, because the patients died prior to completing the total course.

For some patients who died and had experienced septic shock, the most probable source for sepsis was not clearly identified in the narratives; if the source of septic shock was the primary

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lung infection under study, then the patients should have had an outcome assessment of clinical failure (rather than indeterminate) in this FDA Medical Officer’s opinion; for some patients who were assessed as clinical failures in the setting of septic shock, the rationale for not attributing the event (death) to the failure to adequately treat HAP under study was not clarified (as in case # 12012-4255).

In some patients with multi-organ failure or septic shock during study drug treatment, there appeared to be inconsistencies in outcome assessments of indeterminate versus clinical failure. In two patients (18000-4117 and 18001-4153), decisions as to the attribution of serious adverse events to the HAP under study were unclear.

For the seven patients in whom pneumonia was listed as a SAE, five patients had EOT outcome assessments of clinical failure and two had EOT outcome assessments of indeterminate.

Life support measures were withdrawn in 13 patients and mechanical ventilation was discontinued in one subject, which are interventions that further confounded assessment of study drug efficacy in those cases. Seven patients died due to respiratory distress, which developed after comfort care measures were instituted.

Table 104: FDA Medical Officer's Composite List of all Individual Study Deaths* (out of protocol-specified window) among the Vancomycin-treated patients, Study 0015

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|---|---|--------------------------|
| 07002-4326 | 81/M/H | 13 | Pneumonia | Clinical cure | (b) (6) |
| 09008-4406 | 57/M/W | 14 | Respiratory arrest, acute respiratory distress syndrome | Indeterminate | |
| 39002-4359 | 63/F/A | 12 | UTI | Clinical cure | |
| 01014-4132 | 56/M/H | 13 | Multi-organ failure | Clinical cure | |
| 06013-4116 | 68/M/W | 13 | Congestive cardiac failure | Clinical cure | |
| 12016-4272 | 59/F/W | 1 | Aspiration due to stroke | Indeterminate (due to <i>S. aureus</i> resistance to methicillin) | |
| 38148-4207 | 79/F/W | 11 | HAP | Clinical cure | |
| 41002-4661 | 72/F/A | 11 | Persistent compromised neurologic status | Clinical cure | |

*Data derived from the Applicant’s narrative summaries in the 0015 Clinical Study Report

Similar to the out of window deaths with telavancin, the out of window study deaths in the vancomycin group of Study 0015 were in patients who were elderly (age ≥65 years) and had serious co-morbid medical conditions. One patient was reported to have experienced pneumonia as a serious adverse event. Life support measures were not withdrawn in any of the patients.

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Table 105: FDA Medical Officer Summary Table of the Clinical Outcome Assessments at TOC among Patients Deaths, Study 0015, AT Population

| | Telavancin n (%) | Vancomycin n (%) |
|-------------------------|---------------------|---------------------|
| Total Subject Deaths, N | 80 | 62 |
| Clinical Cure | 1 (1.3) | 0 (0) |
| Indeterminate | 4 (5) | 3 (4.8) |
| Clinical Failure | 25 (31.3) | 21 (33.9) |
| Missing | 50 (62.5) | 38 (61.3) |

Most patient deaths occurred prior to or within the EOT visit window (and are included as missing in the table above); few reached the TOC visit time window to be eligible for an outcome assessment and the number of such subjects was comparable across the two treatment groups.

Additional Narratives for Patient Deaths in Telavancin group in Study 0015

In the original NDA submission, 341 deaths were identified across Studies 0015 and 0019, and the narratives were provided for those patients. However, an additional 116 deaths were identified subsequently, and the narratives were provided in response to two information requests from the Division dated June 9, 2009 and July 31, 2009. The Applicant provided narratives for patients who died up to Study Day 90 (the end of a pharmacoeconomic study) but who had not been identified previously. The following table summarizes those additional deaths in the telavancin group of Study 0015:

Table 106: FDA Medical Officer Summary Table of Patient Deaths in Telavancin Group of Study 0015 as provided in Applicant's Response to Information Requests of June 9, 2009 and July 31, 2009

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Events reported during study participation | EOT/TOC Clinical Outcome | Study Day of death | Discharge Diagnosis/ Diagnosis at death |
|--------------|------------------|-------------------------------------|--|-----------------------------|-----------------------|--|
| 01005-4611 | 65/F/W | 10 | Renal impairment, diarrhea, decreased platelet count | Clinical cure/clinical cure | (b) (6) | NR |
| 02011-4566 | 51/M/W | 6 | Stridor - postextubation | Clinical cure/clinical cure | | NR |
| 05001-4385 | 74/F/B | 20 | Traumatic left pneumothorax after placement of intravenous catheter, tachycardia, hypocalcemia | Clinical cure/clinical cure | | NR |
| 09004-4442 | 83/F/W | 21 | Exanthema, anxiety, diarrhea, hypoproteinemia, hypokalemia | Clinical cure/clinical cure | | Myocardial infarction |
| 09011-4446 | 81/F/W | 14 | Headache, worsening hypertension, non-cardiac chest pain | Clinical cure/clinical cure | | NR |
| 09011-4799 | 81/F/W | 15 | Congestive heart failure, gastritis, low potassium | Clinical cure/clinical cure | | Pneumonia |
| 12012-4572 | 79/M/W | 7 | None reported | Clinical cure/clinical cure | | NR |
| 12016-4606 | 83/F/W | 15 | None reported | Clinical cure/clinical cure | | NR |
| 18000-4505 | 79/M/H | 6 | Upper abdominal pain, acute phlebitis at IV infusion site, decubitus ulcer, peripheral edema, pulmonary embolism, interstitial lung disease (considered due to amiodarone) | Clinical failure/NR | | NR |
| 33004-4557 | 72/F/A | 13 | Subcutaneous emphysema (ongoing at study entry) | Clinical cure/NR | | NR |
| 33004-4732 | 85/F/A | 15 | UTI, phlebitis left arm (not study drug infusion site), worsening anemia | Clinical cure/clinical cure | | NR |
| 33016-4457 | 84/M/A | 15 | Hypoalbuminemia, hypercalcemia | Clinical cure/clinical cure | | NR |
| 33018-4071 | 79/M/A | 13 | Septic shock with respiratory failure, cerebral infarct | Clinical cure/NR | | NR |
| 33018-4530 | 80/F/A | 10 | Liver function impairment | Clinical cure/clinical cure | | NR |
| 38020-4269 | 68/F/W | 3 | Increased serum creatinine and BUN [‡] , fluid overload [‡] , | Indeterminate/NR | | NR |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Events reported during study participation | EOT/TOC Clinical Outcome | Study Day of death | Discharge Diagnosis/ Diagnosis at death |
|--------------|------------------|-------------------------------------|--|------------------------------|-----------------------|--|
| | | | acute renal failure [†] | | (b) (6) | |
| 38024-4561 | 90/M/W | 9 | Right wrist hematoma, constipation, oral candidiasis [†] , excoriated periscrotal area, intermittent loose stools [†] | Clinical cure/clinical cure | | NR |
| 38024-4787 | 80/M/W | 10 | Peripheral edema, increase in blood bilirubin | Clinical cure/clinical cure | | NR |
| 38148-4721 | 53/F/B | 9 | Seizures, respiratory failure | Clinical cure/Indeterminate* | | NR |
| 38270-4747 | 60/F/W | 9 | <i>P. aeruginosa</i> bacteremia | Clinical cure/clinical cure | | NR |
| 38271-4112 | 69/M/W | 20 | Congestive heart failure, hypokalemia, decubitus ulcer, anemia [†] | Clinical cure/clinical cure | | NR |
| 38271-4220 | 74/M/W | 1 | Constipation, restlessness, oxygen desaturation, exfoliative dermatitis, deep venous thrombosis, hallucinations | Indeterminate/indeterminate | | NR |
| 38294-4249 | 54/F/W | 6 | Hypokalemia, delirium secondary to encephalopathy, UTI, back pain | Indeterminate/indeterminate | | NR |
| 38348-4709 | 55/M/W | 11 | Elevated lactic dehydrogenase | Clinical cure/clinical cure | | NR |
| 38363-4759 | 87/M/W | 11 | COPD | Clinical cure/indeterminate | | NR |
| 41009-4405 | 68/M/A | 14 | Possible brainstem dysfunction, anemia, hypokalemia | Clinical cure/NR | | NR |

EOT=end of therapy; TOC=test of cure; M=male; F=female; W=White; B=Black; A=Asian; H=Hispanic;
 NR=not reported; UNK (#)=unknown (Study Day of last contact);
[†]considered possibly/probably related to study medication by the Investigator and the Applicant
 *Patient changed to comfort measure only and subsequently died

There were 25 patient deaths reported in the table above. Six of the deaths occurred up to Study Day 28 following randomization. Twelve of the deaths occurred in the time interval up to EOT + 28 days. The Study Day of death was unknown for seven patients.

Most of the patients who died were ≥65 years of age and had multiple comorbid medical conditions. The diagnosis at the time of death was not reported in all but two patients. For the 18 patients in whom the Study Day of death was reported, all of the deaths occurred post-EOT. It was difficult to assess the relationship of some of the adverse events and deaths to study drug exposure due to the paucity of details provided in the narratives. The reason(s) underpinning the Investigators' and the Applicant's assessments of whether specific adverse events were considered to have been related (or not) to study drug exposure were not clearly articulated. Many of the narratives did not provide sufficient details as to the extent of pneumonic involvement within the right or left lungs anatomically and did not describe whether the infiltrate was patchy, interstitial, or consolidative at study entry.

Additional Narratives for Patient Deaths in Vancomycin group in Study 0015

In response to an information request from the Division dated June 9, 2009 and an additional information request dated July 31, 2009, the Applicant provided narratives for patients who died up to Study Day 90 that had not been submitted previously to the NDA. The following table summarizes the additional deaths in the vancomycin group of Study 0015:

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Table 107: FDA Medical Officer Summary Table of Patient Deaths in Vancomycin arm of Study 0015 as provided in Applicant's Response to Information Requests of June 9, 2009 and July 31, 2009

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Events reported during study participation | EOT/TOC Clinical Outcome | Study Day of death | Discharge Diagnosis/ Diagnosis at death |
|--------------|------------------|-------------------------------------|--|--------------------------------|--------------------------|---|
| 02024-4574 | 78/M/W | 11 | Atrial fibrillation, scrotal edema, peripheral edema, scrotal excoriation, buttocks excoriation, generalized pain | Clinical cure/clinical cure | (b) (6) | NR |
| 05001-4386 | 71/M/B | 7 | Arterial hypertension, hypokalemia | Clinical cure/clinical cure | | NR |
| 09004-4596 | 89/F/W | 8 | Non-serious traumatic head injury, elbow injury | Clinical cure/clinical cure | | Metastatic breast cancer |
| 09004-4640 | 72/F/W | 7 | Peripheral edema, bronchitis, sepsis | Clinical cure/clinical cure | | Sepsis |
| 09004-4702 | 79/F/W | 14 | Peripheral edema | Clinical cure/clinical cure | | NR |
| 09004-4794 | 73/F/W | 21 | Decubitus ulcer, grand mal convulsion, asymptomatic bacteriuria | Clinical cure/clinical cure | | NR |
| 09011-4444 | 73/M/W | 14 | None reported | Clinical cure/clinical cure | | CVA |
| 09011-4631 | 81/M/W | 11 | None reported | Clinical cure/clinical cure | | NR |
| 12005-4374 | 58/M/W | 2 | Generalized pain, vomiting, gastroparesis | Indeterminate/clinical cure | | NR |
| 12006-4305 | 71/M/W | 10 | Insomnia, anemia | Clinical cure/clinical failure | | NR |
| 14003-4101 | 73/F/W | 5 | Sepsis, tachycardia, labial herpes, hypoalbuminemia, low cardiac output | Clinical failure/NR | | NR |
| 14003-4498 | 74/F/W | 9 | Leucopenia [‡] , thrombocytopenia [‡] , increased serum creatinine | Indeterminate/clinical failure | | NR |
| 18000-4185 | 56/M/W | 10 | None reported | Clinical cure/clinical cure | | NR |
| 18000-4210 | 82/F/W | 4 | None reported | Indeterminate/clinical cure | | NR |
| 18000-4778 | 81/M/W | 12 | Worsening of chronic renal failure, worsening of depression, hyperkalemia, exacerbation of hemorrhoids, <i>C. difficile</i> -related enterocolitis | Clinical cure/clinical cure | | NR |
| 18001-4253 | 52/F/W | 8 | None reported | Clinical failure/NR | | Brain hemorrhage |
| 18001-4652 | 79/F/W | 11 | Atrial fibrillation, respiratory failure | Clinical cure/improved | | <i>Acinetobacter</i> bacteremia diagnosed on Study Day 21 |
| 18001-4770 | 77/M/W | 9 | Renal insufficiency, increased liver function | Clinical cure/indeterminate | | NR |
| 18009-4578 | 87/M/W | 3 | Mild abdominal pain | Indeterminate/indeterminate | | NR |
| 18010-4263 | 84/M/W | 11 | Worsening hypertension, low albumin | Clinical failure/NR | | NR |
| 18010-4656 | 70/M/W | 4 | None reported | Clinical failure/NR | | NR |
| 33001-4483 | 79/M/A | 3 | Septic shock, neutropenia, diabetic hyperosmotic hyperglycemic non-ketacidosis | Clinical failure/NR | | NR |
| 33007-4464 | 88/M/A | 9 | Worsening congestive heart failure, watery diarrhea, decubitus ulcer, constipation | Clinical cure/clinical cure | | NR |
| 33012-4531 | 76/M/A | 6 | CVA | Indeterminate/indeterminate | | NR |
| 33016-4470 | 74/M/A | 4 | Ischemic stroke, acute renal failure, peripheral occlusive disease, bacteremia | Indeterminate/NR | | NR |
| 33018-4465 | 72/F/A | 10 | Anemia, malnutrition | Clinical cure/clinical cure | | NR |
| 38024-4245 | 70/M/W | 15 | Dysphagia, acute respiratory distress syndrome, increased blood bilirubin [‡] , urethral bleeding, hypertensive episodes, recurrent bacteremia, postoperative infection, catheter site infection, bilateral frontal hygromas, elevated alkaline phosphatase [‡] , watery stools [‡] , atrial fibrillation | Clinical cure/clinical failure | | NR |
| 38024-4363 | 80/F/W | 4 | Hypotension | Indeterminate/indeterminate | | NR |
| 38024-4426 | 48/F/W | 10 | Nausea [‡] , dyspepsia [‡] , hypercoagulopathy [‡] , constipation, hypokinesia, candiduria [‡] , throat irritation [‡] | Indeterminate/clinical failure | | NR |
| 38070-4748 | 71/F/W | 18 | Hypophosphatemia, clostridium colitis, hypomagnesemia, hypocalcemia, hypoalbuminemia, anemia, supraventricular tachycardia, anasarca, intermittent hypoglycemia, respiratory failure, | Clinical cure/clinical cure | | NR |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Events reported during study participation | EOT/TOC Clinical Outcome | Study Day of death | Discharge Diagnosis/ Diagnosis at death |
|--------------|------------------|-------------------------------------|--|-----------------------------|--------------------------|--|
| | | | excoriated buttocks | | (b) (6) | |
| 38160-4174 | 74/F/W | 5 | <i>Candida glabrata</i> UTI, anemia | Indeterminate/clinical cure | | NR |
| 38270-4224 | 74/F/W | 7 | Nausea | Clinical cure/clinical cure | | NR |
| 38270-4397 | 82/M/B | 10 | Acute respiratory failure | Clinical cure/indeterminate | | NR |
| 38270-4421 | 63/F/W | 10 | Vaginitis | Clinical cure/clinical cure | | NR |
| 38363-4711 | 64/M/W | 10 | None reported | Clinical cure/clinical cure | | NR |

EOT=end of therapy; TOC=test of cure; M=male; F=female; W=White; B=Black; A=Asian;
 NR=not reported; UNK (#)=unknown (Study Day of last contact); ‡considered possibly/probably related to study medication by the Investigator and the Applicant

There were 35 patient deaths reported in the table above. Eight of the deaths occurred up to Study Day 28 following randomization. Fourteen of the deaths occurred in the time interval up to EOT + 28 days. The Study Day of death was unknown for ten patients.

Most of the patients were ≥65 years of age and had multiple comorbid medical conditions. The diagnosis at the time of death was not reported in all but five patients. For the patients in whom the Study Day of death was reported, all of the deaths occurred post-EOT. It was difficult to assess the relationship of some of the adverse events and deaths to study drug exposure due to the paucity of details provided in the narratives. The reason(s) underpinning the Investigators' and the Applicant's assessments of whether specific adverse events were considered to have been related (or not) to study drug exposure were not clearly articulated. Many of the narratives did not provide sufficient details as to the extent of pneumonic involvement within the right or left lungs anatomically and did not describe whether the infiltrate was patchy, interstitial, or consolidative at study entry.

Patient Deaths in Study 0019

The following table summarizes the most frequent causes for death among patients enrolled in Study 0019:

Table 108: FDA Medical Officer Summary Table of the Most Frequent Causes (>3%) for Death, Study 0019, AT Population

| | | Telavancin | Vancomycin |
|---|----------------------|------------|------------|
| All Treated | N (%) | 379 | 378 |
| Total Subject Deaths | n (%) | 70 (18.6%) | 78 (20.5%) |
| Causes for Death n (% of all deaths) | Septic shock | 11 (15.7%) | 6 (7.7%) |
| | Not specified | 8 (11.4%) | 18 (23%) |
| | Multi-organ failure* | 7 (10%) | 1 (1.3%) |
| | Pulmonary Embolism** | 4 (5.7%) | 1 (1.3%) |
| | Respiratory Failure† | 4 (5.7%) | 9 (11.5%) |
| | Heart failure‡ | 1 (1.4%) | 5 (6.4%) |

*includes the following PT: multi organ failure, multi-organ failure, multiorgan failure, multiple organ failure, multiple organ failure due to advanced carcinoma of right lung

**includes the following PT: pulmonary embolism, pulmonary thromboemboly, pulmonary artery thromboemboly, pulmonary embolus suspicion

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†includes the following PT: acute respiratory failure, respiratory failure, respiratory failure due to gastric contents aspiration, respiratory failure following removal of life support, acute respiratory failure due to tracheostomy obstruction, respiratory failure Type II, respiratory failure due to respiratory tract block by sputum, respiratory failure due to withdrawal of active therapy, respiratory failures

#includes the following PT: acute heart failure, cardiac failure, CHF, congestive heart failure with MI, heart failure

As depicted in the table above, the most frequent cause for death among patients treated with telavancin was septic shock, and the most frequent cause for death among patients treated with vancomycin was not specified. Other identified causes for death with a frequency of ≥10% included multi-organ failure among the telavancin-treated patients and respiratory failure in the vancomycin-treated patients. Pulmonary embolism accounted for four deaths in the telavancin group compared to one death in the vancomycin group.

The following tables summarize information derived from the Applicant’s narratives provided in association with Supporting Table 202 of the 0019 Clinical Study Report for each of the telavancin- and vancomycin-treated patients who died during participation in the study.

Table 109: FDA Medical Officer's Composite List of all Individual Study Deaths* (within protocol-specified window) among the Telavancin-treated Patients, Study 0019

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|---|---|-------------------------------------|
| 01006-6071 | 84/M/H | 7 | Cardiac arrest, Hemodynamic instability | Indeterminate (due to difficulty in determining the progression of pneumonia) | |
| 01016-6070 | 79/F/H | 1 | Shock | Indeterminate | |
| 01019-6029 | 74/M/H | 5 | Small cell lung cancer, pseudomonal lung infection | Indeterminate (due to requirement for polymixin therapy for pseudomonal pneumonia) | |
| 01019-6420 | 67/M/H | 8 | Septic shock, acute renal failure | Indeterminate (due to an “insufficient number of treatment days”; according to the narrative, telavancin was discontinued on Study Day 8 due to an ECG with QTc > 500 msec) | |
| 01019-6623 | 84/F/H | 3 | Septic shock | Indeterminate (due to incomplete treatment; according to the narrative, telavancin was discontinued on Study Day 3 due to an “unsatisfactory therapeutic response”) | |
| 01021-6627 | 69/F/H | 12 | Multi-organ failure | Clinical cure | |
| 02019-6204 | 50/F/W | 9 | Multi-organ failure | Clinical failure | |
| 02023-6037 | 61/F/H | 5 | Cardiac arrest, multi-organ failure | Clinical failure | |
| 02026-6535 | 79/M/W | 10 | Pneumonia (changed to “do not resuscitate status on Day 9) | Clinical failure | |
| 05000-6414 | 64/M/A | 11 | Septic shock, acute renal failure | Clinical cure | |
| 05003-6282 | 78/F/H | 11 | Septic shock (family declined pressors) | Indeterminate (study drug was discontinued on Day 11 because “Gram-positive coverage was no longer clinically required”) | |
| 05003-6285 | 85/M/B | 10 | Abdominal abscess, GI hemorrhage, septic shock | Indeterminate (study drug was discontinued on Day 10 because “Gram-positive coverage was no longer clinically required”) | |
| 05003-6344 | 76/M/H | 2 | Septic shock | Indeterminate | |
| 05003-6552 | 61/M/H | 14 | Pulmonary necrosis, respiratory failure | Indeterminate (study drug was discontinued on Day 14 because “Gram-positive coverage was no longer clinically required”) | |
| 05011-6057 | 61/F/B-H | 9 | Septic shock, atrial fibrillation, cardiac arrest, pneumothorax | Indeterminate | |
| 05011-6288 | 82/M/W | 4 | Septic shock | Clinical failure | |
| 08002-6233 | 88/F/A | 20 | Asphyxia (family refused reintubation) | Indeterminate | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|---|---|-------------------------------------|
| 08009-6211 | 85/M/A | 3 | Multi-organ failure | Indeterminate | |
| 08011-6546 | 68/M/A | 11 | Septic shock (family eventually refused treatment) | Clinical failure | |
| 08012-6794 | 71/F/A | 5 | Respiratory failure | Clinical failure | |
| 08016-6592 | 78/M/A | 8 | Acute respiratory failure (Family requested not treatment and patient discharged) | Clinical failure | |
| 08016-6817 | 79/M/A | 6 | Multi-organ failure | Clinical failure | |
| 08020-6221 | 80/M/A | 8 | Sepsis | Clinical failure | |
| 09005-6791 | 81/F/W | 15 | Multi-organ failure | Clinical failure | |
| 14014-6704 | 53/M/W | 13 | Septic shock | Indeterminate | |
| 18004-6056 | 70/F/W | 3 | Meningitis | Indeterminate | |
| 18004-6107 | 73/M/W | 3 | Renal insufficiency (renal insufficiency considered possibly related to study drug), septic shock, meningitis | Clinical cure (although narrative states that "study medication was discontinued due to event of meningitis") | |
| 18004-6185 | 70/F/W | 10 | Multi-organ failure | Clinical cure | |
| 18004-6187 | 79/M/W | 1 | Multi-organ failure | Indeterminate | |
| 18005-6035 | 77/F/W | 5 | Chronic renal failure | Indeterminate | |
| 18008-6156 | 78/M/W | 10 | Apnea, <i>Escherichia</i> sepsis | Indeterminate ("Gram-positive coverage was no longer clinically required") | |
| 18013-6385 | 66/M/W | 7 | Septic shock | Indeterminate (study drug discontinued due to superinfection) | |
| 20013-6241 | 83/F/A | 4 | Septic shock (Family requested discontinuation of all treatment except inotropic agents) | Clinical failure | |
| 22006-6640 | 69/M/W | 8 | Respiratory failure | Clinical failure | |
| 25023-6422 | 55/M/W | 3 | Pulmonary embolism | Indeterminate | |
| 25024-6479 | 77/M/W | 3 | Pulmonary embolism | Indeterminate | |
| 27016-6726 | 68/M/W | 11 | COPD exacerbation | Indeterminate (due to persistent sputum, dyspnea, and rales) | |
| 27022-6674 | 55/M/W | 4 | Acute cardiac failure | Indeterminate | |
| 34002-6239 | 58/F/A | 14 | Fungal sinusitis | Indeterminate | |
| 34002-6653 | 84/M/A | 9 | Staphylococcal pneumonia | Clinical failure | |
| 34002-6779 | 62/M/A | 6 | Pneumonia | Clinical failure | |
| 34003-6334 | 54/M/A | 8 | Pseudomonal lung infection | Clinical failure | |
| 34003-6591 | 63/F/A | 3 | Acute renal failure (patient refused consent and withdrew treatment) | Indeterminate | |
| 34003-6608 | 73/M/A | 17 | Sepsis | Indeterminate | |
| 36001-6692 | 71/M/W | 10 | Ischemic stroke | Indeterminate | |
| 36004-6561 | 71/F/W | 1 | Cardiac arrest | Indeterminate | |
| 38069-6010 | 79/F/W | 11 | Respiratory failure (family withdrew supportive care and study medication was discontinued) | Indeterminate | |
| 38069-6033 | 73/F/W | 12 | Respiratory failure (patient placed on comfort measures) | Clinical cure | |
| 38069-6038 | 71/F/W | 7 | Hypoxia | Clinical cure | |
| 38108-6074 | 88/M/W | 8 | Aspiration pneumonia | Clinical failure | |
| 38252-6353 | 76/F/W | 20 | Cerebrovascular accident | Indeterminate | |
| 38252-6646 | 74/F/W | 7 | Ischemic cardiomyopathy (patient withdrew consent and placed on hospice) | Indeterminate | |
| 38357-6377 | 78/M/W | 10 | Sepsis (family withdrew consent) | Indeterminate | |
| 38357-6534 | 79/M/W | 19 | DIC, sepsis (consent withdrawn) | Indeterminate | |
| 38357-6538 | 46/M/W | 4 | Pneumonia | Indeterminate | |
| 38357-6650 | 51/F/W | 3 | Sepsis | Clinical failure | |
| 40001-6098 | 76/F/AI-H | 4 | Pulmonary embolism | Indeterminate | |
| 40001-6127 | 61/M/AI-H | 5 | Brain herniation | Indeterminate | |
| 40001-6366 | 78/M/AI-H | 6 | Multi-organ failure | Indeterminate | |
| 40001-6391 | 50/M/AI-H | 3 | Multi-organ failure (life support withdrawn by family) | Clinical failure | |
| 40002-6678 | 78/M/AI-H | 14 | Acute respiratory failure | Clinical cure | |
| 40006-6178 | 65/M/AI-H | 13 | Septic shock | Clinical cure | |
| 42002-6249 | 83/M/A | 7 | Cerebrovascular accident, ventricular fibrillation, myocardial infarction | Indeterminate ("Gram-positive coverage was no longer required") | |
| 44001-6585 | 63/M/W | 2 | Multi-organ failure | Indeterminate | |
| 44006-6451 | 81/M/W | 9 | Cerebrovascular accident | Indeterminate | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|--|--|-------------------------------------|
| 44010-6452 | 82/M/W | 3 | Cerebrovascular accident | Indeterminate | |
| 47000-6461 | 49/M/W | 7 | Brain edema | Indeterminate | |
| 47001-6601 | 85/M/W | 11 | Deep vein thrombosis, pulmonary embolism | Clinical failure | |
| 50000-6667 | 53/M/W | 3 | Respiratory failure, chronic obstructive airways disease | Clinical failure | |
| 50001-6410 | 80/M/W | 2 | Pulmonary embolism | Indeterminate (“Cultures only revealed Gram-negative pathogens”) | |

*Data derived from the Applicant’s narrative summaries in the 0019 Clinical Study Report

Several important observations are evident from the preceding table, which summarizes the individual patient narratives for the telavancin-treated subjects who died during participation in study 0019. Many of the patients were elderly (age ≥ 65 years) and had serious underlying medical disorders, suffered trauma, experienced post-operative complications, or had cerebrovascular accidents, which compromised multiple organ systems and could have potentially increased their risk for death. Many of the patients experienced new complications (such as stroke, gastrointestinal bleeding, or aspiration events) that could not be attributed to study drug. None of the deaths appeared to be due to a hypersensitivity reaction to telavancin, although study drug was discontinued in one patient due to QTc prolongation >500 msec.

In terms of EOT outcome assessments, many patients who died had indeterminate EOT outcomes that were so assessed “due to the patient’s death” during the course of study medication treatment. The study drug treatment duration (which ranged from 1 to 20 days) was considered incomplete, because the patients died prior to completing the total course.

For some patients who died and had experienced septic shock, the most probable source for sepsis was not clearly identified in the narratives; if the source of septic shock was the primary lung infection under study, then the patients should have had an outcome assessment of clinical failure (rather than indeterminate) in the opinion of this FDA Medical Officer. Patient 01019-6623 experienced septic shock and had an EOT assessment of indeterminate, but the narrative reported that telavancin was discontinued due to an “unsatisfactory therapeutic response”. In the view of this FDA Medical Officer, the patient’s EOT outcome should be revised to clinical failure.

For the five patients in which pneumonia was listed as a SAE, four patients had EOT outcome assessments of clinical failure and one had EOT outcome assessment of indeterminate.

Life support measures were withdrawn in 8 patients, mechanical ventilation was discontinued in one patient, and consent was withdrawn in four patients, which are interventions that further confounded assessment of study drug efficacy in those cases. Three patients died due to respiratory failure, which developed after comfort care measures were instituted.

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Table 110: FDA Medical Officer's Composite List of all Individual Study Deaths* (out of protocol-specified window) among the Telavancin-treated Patients, Study 0019

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|--|---|--------------------------|
| 01016-6081 | 79/M/H | 15 | Pulmonary edema, shock | Indeterminate (study drug discontinued due to "unsatisfactory therapeutic response") | (b) (6) |
| 01021-6340 | 69/M/H | 14 | Arterial rupture, septic shock, Candida sepsis | Clinical cure | |
| 05000-6086 | 57/M/H | 11 | Septic shock | Clinical cure | |
| 08003-6260 | 74/M/A | 20 | Cerebrovascular accident | Indeterminate | |
| 08004-6361 | 75/F/A | 18 | Atrial fibrillation | Indeterminate | |
| 08012-6345 | 77/M/A | 13 | Hyperkalemia, diarrhea | Indeterminate | |
| 12009-6203 | 87/F/W | 7 | Sudden death | Clinical cure | |
| 34002-6707 | 78/F/A | 8 | Acute myocardial infarction | Clinical failure | |
| 38055-6175 | 64/F/W | 3 | Acute renal failure, intestinal ischemia | Indeterminate (study medication discontinued "due to renal failure") | |
| 38097-6013 | 22/M/B | 14 | Multi-organ failure (family placed patient on do not resuscitate status) | Clinical cure | |
| 38097-6113 | 78/F/B | 21 | Pneumonia | Clinical failure | |
| 38341-6384 | 59/M/B | 8 | Multi-organ failure (family placed patient on do not resuscitate status) | Indeterminate | |
| 42003-6350 | 68/M/A | 4 | Respiratory failure due to sepsis | Indeterminate (due to endotracheal aspirate growing only a Gram-negative microorganism) | |
| 43005-6738 | 87/M/W | 11 | Cardiac arrest | Clinical cure | |
| 44009-6485 | 58/M/W | 16 | Acute renal failure, gastric ulcer hemorrhage, shock | Indeterminate | |
| 18004-6111 | 69/F/W | 8 | Acute renal failure | Clinical cure | |
| 18012-6382 | 92/M/W | 15 | Pleural effusion | Clinical cure | |

*Data derived from the Applicant's narrative summaries in the 0019 Clinical Study Report

Among the out of window study deaths in the telavancin group of Study 0019 as summarized in the table above, most of the patients were elderly (≥ 65 years) and had serious co-morbid medical illnesses. One patient experienced pneumonia as a serious adverse event. Life support measures were withdrawn in two patients.

Table 111: FDA Medical Officer's Composite List of all Individual Study Deaths* (within protocol-specified window) among the Vancomycin-treated Patients, Study 0019

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|--|---|--------------------------|
| 01019-6621 | 90/F/H | 5 | Acute renal failure, septic shock | Clinical failure | (b) (6) |
| 01021-6417 | 69/F/H | 16 | Multiple myeloma | Indeterminate ("Gram-positive coverage was no longer clinically indicated") | |
| 02019-6007 | 77/F/W | 14 | Pneumonia, chronic obstructive airways disease exacerbated (patient withdrew consent and was placed on comfort measures); pulmonary embolism reported on study day 5 | Indeterminate | |
| 02023-6108 | 78/F/W | 4 | Multi-organ failure (patient withdrew consent and life support was withdrawn) | Indeterminate | |
| 02026-6162 | 71/M/W | 7 | Respiratory failure (patient requested palliative care only and study drug was discontinued) | Indeterminate | |
| 02026-6202 | 71/M/W | 5 | Respiratory failure | Indeterminate | |
| 02026-6312 | 80/M/W | 10 | Respiratory failure | Clinical failure | |
| 02028-6613 | 32/F/W | 16 | Pneumothorax, bacterial peritonitis | Clinical cure | |
| 05000-6067 | 60/F/H | 22 | Thrombocytopenia, sepsis, acute respiratory failure, septic shock | Indeterminate ("Gram-positive coverage was no longer clinically indicated") | |
| 05000-6149 | 50/M/H | 16 | Acute renal failure, pneumothorax x 2, thrombocytopenia, increased blood potassium, increased blood sodium, septic shock, pneumothorax spontaneous tension | Indeterminate | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|--|---|-------------------------------------|
| 05000-6151 | 52/M/H | 6 | Renal impairment, sepsis, septic shock | Indeterminate | |
| 05003-6068 | 68/F/H | 3 | Acute renal failure | Indeterminate | |
| 05003-6069 | 58/F/H | 7 | Urospepsis, septic shock, convulsions | Clinical cure (as "no growth was detected in respiratory cultures from Study Days 4 and 7") | |
| 05003-6284 | 22/F/H | 7 | Acute respiratory distress syndrome | Indeterminate | |
| 05003-6338 | 74/F/H | 9 | Respiratory failure | Indeterminate | |
| 05003-6416 | 71/F/H | 8 | Tracheostomy malfunction | Clinical failure | |
| 05010-6415 | 61/F/B | 7 | Cerebral hemorrhage | Indeterminate | |
| 07003-6072 | 64/F/H | 23 | Septic shock | Indeterminate (The protocol limits the maximum duration of study drug to 21 days!) | |
| 07010-6315 | 85/M/H | 14 | Hyperkalemia, congestive cardiac failure | Clinical cure | |
| 08001-6363 | 81/F/A | 5 | Respiratory failure (family withdrew consent) | Indeterminate | |
| 08006-6302 | 82/M/A | 20 | Heart failure, respiratory failure | Clinical failure | |
| 08009-6297 | 68/M/A | 8 | Pneumonia | Clinical failure | |
| 08012-6346 | 75/M/A | 15 | Respiratory failure | Clinical cure | |
| 08012-6686 | 56/M/A | 21 | Respiratory failure | Indeterminate ("Gram-positive coverage was no longer clinically indicated") | |
| 08019-6480 | 62/M/A | 7 | Respiratory failure (consent withdrawn and patient discharged) | Indeterminate | |
| 08020-6215 | 73/M/A | 7 | Acute respiratory distress syndrome | Clinical failure | |
| 09005-6656 | 79/F/W | 9 | Abdominal sepsis, septic shock | Indeterminate | |
| 09005-6740 | 75/M/W | 8 | Multi-organ failure | Clinical failure | |
| 18004-6036 | 72/M/W | 4 | Apnea, bradycardia | Indeterminate | |
| 18004-6120 | 55/M/W | 11 | Neurological symptom, increased intracranial pressure | Indeterminate | |
| 18004-6196 | 45/M/W | 8 | Cerebellar hemorrhage | Indeterminate | |
| 18004-6369 | 76/F/W | 11 | Systemic candidiasis, GI necrosis | Indeterminate | |
| 18004-6431 | 70/F/W | 1 | Hemorrhagic stroke | Indeterminate | |
| 18013-6230 | 49/M/W | 3 | Traumatic brain injury | Clinical failure | |
| 20002-6548 | 75/F/A | 4 | Acute respiratory distress syndrome | Indeterminate ("Gram-positive coverage was no longer indicated") | |
| 20010-6238 | 72/M/A | 12 | Septic shock | Clinical failure | |
| 20015-6735 | 89/M/A | 12 | Hypotension, bradycardia | Clinical failure | |
| 20017-6579 | 74/M/A | 1 | Acute respiratory failure | Indeterminate | |
| 20019-6242 | 73/F/A | 2 | Septic shock (family requested no resuscitation measures) | Indeterminate | |
| 20019-6437 | 84/F/A | 13 | Acute coronary syndrome (patient withdrew consent) | Indeterminate | |
| 20019-6605 | 70/M/A | 18 | Congestive heart failure, myocardial infarction (patient withdrew consent) | Indeterminate | |
| 20019-6609 | 74/F/A | 7 | Disease progression (patient withdrew consent) | Indeterminate | |
| 22004-6729 | 50/F/W | 5 | Septic shock | Clinical failure | |
| 22006-6519 | 65/F/W | 13 | Mesenteric occlusion | Clinical cure | |
| 22006-6630 | 80/M/W | 21 | Cerebral ischemia, congestive cardiac failure | Clinical cure | |
| 25024-6639 | 96/F/W | 11 | Congestive cardiac failure | Clinical cure | |
| 25024-6804 | 73/M/W | 5 | Shock | Indeterminate | |
| 27027-6595 | 71/M/W | 8 | Cerebrovascular accident | Indeterminate | |
| 29002-6563 | 76/M/W | 2 | Pneumonia | Indeterminate | |
| 34002-6467 | 64/M/A | 1 | Pneumonia | Indeterminate | |
| 34002-6778 | 78/M/A | 2 | Acute myocardial infarction | Clinical failure | |
| 34003-6224 | 67/M/A | 5 | Septic shock | Clinical failure | |
| 38051-6006 | 76/M/W | 2 | Cardiopulmonary failure (patient changed to "do not resuscitate" status) | Indeterminate | |
| 38092-6052 | 62/F/W | 7 | Respiratory failure (family declined dialysis and requested discontinuation of ventilator support) | Indeterminate | |
| 38097-6076 | 82/F/W | 5 | Congestive cardiac failure (consent withdrawn; placed on hospice care) | Indeterminate | |
| 38108-6539 | 79/F/W | 12 | Aspiration pneumonia (family discontinued study medication on Study Day 12) | Clinical failure | |
| 38252-6206 | 92/M/H | 21 | Esophageal carcinoma | Clinical failure | |
| 38357-6506 | 76/M/W | 17 | Congestive cardiac failure (not resuscitated by family's request) | Indeterminate | |

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| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death |
|--------------|------------------|-------------------------------------|---|---|--------------------------|
| 38357-6651 | 49/M/W | 13 | Sepsis | Clinical failure | (b) (6) |
| 40000-6093 | 88/M/AI-H | 10 | Systemic Candida | Clinical cure | |
| 40000-6125 | 80/M/AI-H | 10 | Cerebrovascular accident | Indeterminate | |
| 40000-6212 | 72/M/AI-H | 15 | Acute pulmonary edema | Clinical cure | |
| 40000-6746 | 32/M/AI-H | 1 | Acute respiratory failure | Indeterminate | |
| 40001-6094 | 83/F/AI-H | 10 | Cardiogenic shock | Clinical cure | |
| 42002-6250 | 83/M/A | 10 | Multi-organ failure | Clinical failure | |
| 42003-6328 | 37/M/A | 7 | Pneumonia | Indeterminate (“Gram-positive coverage was no longer clinically indicated”) | |
| 42007-6748 | 20/M/A | 10 | Subdural hematoma | Clinical cure | |
| 43004-6784 | 71/M/W | 5 | Multi-organ failure | Clinical failure | |
| 44001-6577 | 50/M/W | 14 | Cardiac failure | Clinical cure | |
| 44003-6795 | 74/M/W | 8 | Cardiovascular disorder | Indeterminate (“Gram-positive coverage was no longer clinically indicated”) | |
| 44004-6408 | 58/M/W | 6 | Dementia | Indeterminate (“Gram-positive coverage was no longer indicated”) | |
| 44004-6660 | 77/M/W | 9 | Cachexia | Clinical cure | |
| 44006-6390 | 74/M/W | 6 | Cerebrovascular accident | Indeterminate | |
| 44008-6839 | 76/M/W | 13 | Cardiac failure | Indeterminate (“Gram-positive coverage was no longer clinically indicated”) | |
| 47002-6459 | 22/M/W | 7 | Brain edema | Indeterminate (study medication was discontinued “due to unsatisfactory therapeutic response”) | |
| 47002-6462 | 75/M/W | 7 | Acute myocardial infarction | Clinical cure | |
| 47002-6845 | 31/M/W | 15 | Pulmonary embolism | Clinical failure (study medication was discontinued “due to unsatisfactory therapeutic response”) | |

*Data derived from the Applicant’s narrative summaries in the 0019 Clinical Study Report

Similar to the within window patient deaths in the telavancin group of Study 0019, the patients who died in the vancomycin group were elderly (age ≥65 years) and had serious underlying medical disorders, suffered trauma, experienced post-operative complications, or had cerebral hemorrhage, which compromised multiple organ systems and could have potentially increased their risk for death. Some patients experienced new complications (such as gastrointestinal bleeding or aspiration events) that could not be attributed to study drug. None of the deaths appeared to be due to a hypersensitivity reaction to vancomycin. One patient developed a pulmonary embolism during the treatment course with vancomycin.

In terms of EOT outcome assessments, many patients who died had indeterminate EOT outcomes that were so assessed “due to the patient’s death” during the course of study medication treatment. The study drug treatment duration (which ranged from 2 to 22 days) was considered incomplete, because the patients died prior to completing the total course.

For some patients who died and had experienced septic shock, the most probable source for sepsis was not clearly identified in some of the narratives; if the source of septic shock was the primary lung infection under study, then the patients should have had an outcome assessment of clinical failure (rather than indeterminate).

In some patients, there appeared to be inconsistencies in outcome assessments of indeterminate versus clinical failure for patients whose study drug was discontinued due to an unsatisfactory therapeutic response. Patient # 47002-6459 assessed as indeterminate at EOT even though the

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narrative stated that study medication was discontinued “due to unsatisfactory therapeutic response”; patient 47002-6845 was assessed as a clinical failure at EOT in which the narrative stated that study medication was discontinued “due to unsatisfactory therapeutic response”.

For the six patients in which pneumonia was listed as a SAE, two patients had EOT outcome assessments of clinical failure and four had EOT outcome assessments of indeterminate.

Life support measures were withdrawn in nine patients and consent was withdrawn in eight patients, which further confounded assessment of study drug efficacy in those cases. Four patients died due to respiratory failure, which developed after comfort care measures were instituted.

Patient # 07003-6072 was treated with 23 days of study drug, which is a violation of the maximum allowable duration of study drug for the protocol (maximum = 21 days).

Patient # 05003-6069 was assessed as clinical cure at EOT because “no growth was detected in respiratory cultures from Study Days 4 and 7”. However, this finding does not fulfill the protocol specified criteria for a clinical cure, which is based on resolution of signs/symptoms and a stable or improved chest x-ray.

Table 112: FDA Medical Officer's Composite List of all Individual Study Deaths* (out of protocol-specified window) among the Vancomycin-treated Patients, Study 0019

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Serious adverse events and Discontinuations | EOT Clinical Outcome | Study Day of death (b) (6) |
|--------------|------------------|-------------------------------------|---|--|-------------------------------------|
| 01019-6341 | 73/F/H | 12 | Thrombocytopenia, bacteremia, acute respiratory distress syndrome, septic shock | Clinical cure | |
| 01022-6059 | 72/M/W | 7 | Hypoglycemia, aspiration pneumonia | Clinical cure | |
| 05003-6084 | 87/M/H | 6 | Septic shock, multi-organ failure, acute renal failure | Indeterminate | |
| 08012-6713 | 78/M/A | 7 | Bronchial obstruction | Clinical failure | |
| 18004-6197 | 77/M/W | 8 | Sepsis | Clinical failure | |
| 18008-6116 | 84/F/W | 6 | Sepsis | Indeterminate | |
| 27026-6737 | 49/M/W | 18 | Chronic vegetative state | Clinical cure | |
| 38069-6174 | 68/F/W | 1 | Acute renal failure, hepatic failure (life support was withdrawn) | Indeterminate (need for Gram-negative coverage only) | |
| 42007-6829 | 82/F/A | 21 | End stage renal disease | Clinical cure | |
| 01022-6624 | 64/M/H | 5 | Meningitis, subarachnoid hemorrhage | Indeterminate | |
| 38055-6110 | 87/F/W | 5 | Hepatocellular damage (palliative care initiated on day 53) | Indeterminate (study drug discontinued due to hepatocellular damage) | |
| 44008-6583 | 58/M/W | 11 | Anastomotic stenosis | Indeterminate | |

*Data derived from the Applicant’s narrative summaries in the 0019 Clinical Study Report

Similar to the out of window deaths with telavancin, the out of window study deaths in the vancomycin group of Study 0019, most of the patients were elderly (age ≥65 years) and had serious co-morbid medical conditions. None of the patients were reported to have experienced pneumonia as a serious adverse event. Life support measures were withdrawn in one patient and palliative care was instituted on Day 35 in another patient.

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Table 113: FDA Medical Officer Summary Table of the Clinical Outcome Assessments at TOC among Patient Deaths, Study 0019, AT Population

| | Telavancin n (%) | Vancomycin n (%) |
|-------------------------|---------------------|---------------------|
| Total Subject Deaths, N | 70 | 78 |
| Clinical Cure | 0 (0) | 2 (2.6) |
| Indeterminate | 3 (4.3) | 5 (6.4) |
| Clinical Failure | 21 (30) | 21 (26.9) |
| Missing | 46 (65.7) | 50 (64.1) |

Most patient deaths occurred prior to or within the EOT visit window (and are included as missing in the table above); few reached the TOC visit time window to be eligible for an outcome assessment and the number of such subjects was comparable across the two treatment groups.

Additional Narratives for Patient Deaths in Telavancin group in Study 0019

In response to an information request from the Division dated June 9, 2009 and an additional information request dated July 31, 2009, the Applicant provided narratives for patients who died up to Study Day 90 that had not been submitted previously to the NDA. The following table summarizes the additional deaths in the telavancin group of Study 0019:

Table 114: FDA Medical Officer Summary Table of Patient Deaths in Telavancin Group of Study 0019 as provided in Applicant's Response to Information Requests of June 9, 2009 and July 31, 2009

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Events reported during study participation | EOT/TOC Clinical Outcome | Study Day of death | Discharge Diagnosis/ Diagnosis at death |
|-------------------------|------------------|-------------------------------------|---|---------------------------------|--------------------------|--|
| 01019-6281 | 72/F/H | 8 | Lung superinfection, increased respiratory tract secretions, atelectasis | Clinical cure/NR | (b) (6) | NR |
| 05003-6317 | 87/F/W | 12 | One maximum post-baseline QTcF value >500 msec, cardiogenic shock, cardiac arrest, acute renal failure | Clinical cure/clinical cure | | NR |
| 05003-6337 | 69/F/NR | 4 | Aspiration | Indeterminate/NR | | Respiratory infection, hemorrhagic stroke |
| 08008-6635 | 72/M/A | 10 | QTc prolongation* | Indeterminate/NR | | NR |
| 10012-6612 | 79/M/W | 8 | None reported | Clinical cure/clinical cure | | NR |
| 18004-6306 | 58/M/W | 6 | Infusion site phlebitis, hypoalbuminemia, hypophosphatemia; elevated AST, ALT, and bilirubin; increased PT, APTT, and INR; sepsis | Indeterminate/ indeterminate | | NR |
| 18004-6722 | 80/M/W | 8 | Cervical spinal fluid leak (status-post craniotomy), edema of hands and scalp | Clinical cure/clinical cure | | NR |
| 20012-6576 | 74/M/A | 4 | Acute renal failure | Indeterminate/clinical cure | | NR |
| 20015-6444 | 84/M/A | 18 | Gastrointestinal hemorrhage | Indeterminate/ indeterminate | | NR |
| 20015-6655 | 69/M/A | 21 | Hypoxemic shock | Clinical failure/NR | | NR |
| 22006-6582 | 75/F/W | 11 | None reported | Clinical cure/clinical cure | | NR |
| 29002-6603 | 70/M/W | 21 | Pleural effusion | Clinical cure/clinical cure | | NR |
| 34002-6104 | 65/M/A | 17 | None reported | Clinical cure/clinical cure | | NR |
| 34003-6123 | 100/M/A | 14 | None reported | Clinical cure/clinical cure | | NR |
| 34005-6349 | 77/F/A | 8 | None reported | Clinical failure/NR | | NR |
| 38069-6379 | 67/M/W | 10 | None reported | Clinical cure/clinical cure | | NR |
| 38108-6106 [‡] | 72/M/W | 14 | <i>Acinetobacter</i> bacteremia, recurrent pneumonia, respiratory distress | Clinical cure/clinical failure | NR | |
| 40000-6135 | 43/M/AI | 14 | None reported | Clinical cure/clinical cure | NR | |

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| | | | | | | |
|------------|---------|----|---|------------------------------|---------|----|
| 40001-6121 | 57/M/AI | 10 | Increased intracranial pressure (status-post craniotomy) | Indeterminate/indeterminate | (b) (6) | NR |
| 42002-6322 | 73/F/A | 11 | None reported | Clinical cure/clinical cure | | NR |
| 42002-6325 | 95/M/A | 8 | None reported | Indeterminate/Indeterminate | | NR |
| 44003-6751 | 68/F/W | 9 | None reported | Indeterminate/ clinical cure | | NR |
| 44008-6490 | 73/M/W | 9 | Gastric hemorrhage | Clinical cure/clinical cure | | NR |
| 47002-6716 | 59/M/NR | 8 | Constipation, hypertension, headache | Clinical cure/clinical cure | | NR |
| 47004-6739 | 56/F/NR | 7 | Supraventricular tachycardia, anxiety, metabolic encephalopathy | Clinical failure/NR | | NR |
| 50002-6785 | 43/F/W | 21 | Cerebellar infarction | Clinical cure/clinical cure | | NR |

EOT=end of therapy; TOC=test of cure; M=male; F=female; W=White; B=Black; A=Asian; AI=American Indian
 NR=not reported; UNK (#)=unknown (Study Day of last contact);

‡considered possibly/probably related to study medication by the Investigator and the Applicant

* assessed as possibly/probably related to study drug by the Investigator and the Applicant

‡Patient was treated with telavancin and aztreonam for “HAP due to *C. albicans*”. As *C. albicans* is a fungal pathogen that is not susceptible to treatment with antibacterial therapy, the patient should have been withdrawn from the study rather than having been treated for 14 days with study drug.

There were 26 patient deaths reported in the table above. Four of the deaths occurred up to Study Day 28 following randomization. Six of the deaths occurred in the time interval up to EOT + 28 days. The Study Day of death was unknown for nine patients.

Most of the patients were ≥65 years of age and had multiple comorbid medical conditions. The discharge diagnosis/diagnosis at the time of death was reported in only one patient. For the patients in whom the Study Day of death was reported, all of the deaths occurred post-EOT. It was difficult to assess the relationship of some of the adverse events and deaths to study drug exposure due to the paucity of details provided in the narratives. The reason(s) underpinning the Investigators’ and the Applicant’s assessments of whether specific adverse events were considered to have been related (or not) to study drug exposure were not clearly articulated. Many of the narratives did not provide sufficient details as to the extent of pneumonic involvement within the right or left lungs anatomically and did not describe whether the infiltrate was patchy, interstitial, or consolidative at study entry.

Additional Narratives for Patient Deaths in Vancomycin group in Study 0019

In response to an information request from the Division dated June 9, 2009 and an additional information request dated July 31, 2009, the Applicant provided narratives for patients who died up to Study Day 90 that had not been submitted previously to the NDA. The following table summarizes the additional deaths in the vancomycin group of Study 0019:

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Table 115: FDA Medical Officer Summary Table of Patient Deaths in Vancomycin Group of Study 0019 as provided in Applicant's Response to Information Requests of June 9, 2009 and July 31, 2009

| Subject ID # | Age/Sex/ Race | Duration of study drug (days) | Events reported during study participation | EOT/TOC Clinical Outcome | Study Day of death | Discharge Diagnosis/ Diagnosis at death |
|--------------|------------------|-------------------------------------|--|--------------------------------|--------------------------|--|
| 01019-6339 | 73/M/W | 10 | Septic shock | Clinical cure/clinical cure | (b) (6) | Cardiac arrest, ventricular fibrillation |
| 05003-6626 | 76/M/W | 10 | Septic shock | Clinical cure/clinical cure | | NR |
| 06005-6693 | 92/M/W | 15 | Tachycardia, non-cardiac chest pain, fatigue, left arm and feet edema, abdominal pain | Indeterminate/clinical cure | | NR |
| 07003-6320 | 75/F/H | 16 | Acute renal failure, elevated serum creatinine | Clinical cure/clinical cure | | NR |
| 08020-6491 | 43/M/A | 14 | Acute renal failure, diarrhea, drug-induced hepatitis | Clinical cure/clinical cure | | NR |
| 18004-6310 | 66/M/W | 9 | None reported | Clinical cure/clinical cure | | NR |
| 18004-6354 | 47/M/W | 9 | None reported | Clinical failure/NR | | NR |
| 18004-6717 | 54/F/W | 7 | None reported | Clinical cure/clinical cure | | NR |
| 18013-6142 | 80/F/W | 9 | Atrial fibrillation | Clinical cure/clinical cure | | NR |
| 20010-6324 | 83/F/A | 14 | Acute myocardial infarction, cardiogenic shock, upper GI bleed, hyponatremia, worsened hypokalemia, constipation, trunk skin rash due to transfusion | Indeterminate/indeterminate | | HAP |
| 20014-6423 | 53/M/A | 6 | Acute renal failure [‡] | Indeterminate/NR | | Cerebral hemorrhage |
| 20019-6464 | 67/F/A | 15 | None reported | NR/NR | | NR |
| 20019-6492 | 69/M/A | 15 | Hypotension | Clinical failure/NR | | NR |
| 20019-6657 | 44/M/A | 21 | General edema, constipation, hypertension, post-procedural hemorrhage, jaundice, urticaria, abdominal pain, abdominal distension, dry mouth, leucopenia, seizure | Clinical failure/NR | | NR |
| 27016-6688 | 70/M/W | 8 | Respiratory tract infection | Clinical cure/clinical cure | | NR |
| 31020-6109 | 64/M/W | 13 | Diarrhea, anemia, thrombocytosis, sinus bradycardia | Clinical cure/clinical cure | | NR |
| 34002-6703 | 78/F/A | 7 | Congestive heart failure, hypokalemia | Clinical cure/clinical cure | | NR |
| 34002-6705 | 66/M/A | 7 | None reported | Indeterminate/clinical cure | | NR |
| 34003-6237 | 73/F/A | 15 | None reported | Clinical cure/clinical cure | | NR |
| 38409-6570 | 58/M/W | 3 | Wound dehiscence (CABG) | Indeterminate/NR | | NR |
| 40000-6092 | 85/M/AI | 11 | None reported | Clinical cure/clinical cure | | NR |
| 40001-6396 | 74/M/AI | 12 | None reported | Clinical failure/NR | | NR |
| 40001-6589 | 52/M/AI | 12 | Soft tissue infection (site unspecified) | Clinical cure/clinical cure | | NR |
| 40006-6811 | 56/F/AI | 10 | Pleural effusion, hypertension | Clinical cure/clinical cure | | NR |
| 42003-6457 | 52/M/A | 10 | None reported | Clinical cure/clinical cure | | NR |
| 44003-6764 | 84/F/NR | 3 | None reported | Clinical failure/NR | | NR |
| 44004-6796 | 24/F/W | 10 | None reported | Indeterminate/clinical cure | | Subarachnoid hemorrhage, coma, seizure |
| 48002-6216 | 69/M/W | 11 | None reported | Clinical cure/clinical failure | | NR |
| 48002-6220 | 64/M/W | 11 | Hypoglycemia, mild renal impairment | Clinical failure/NR | | NR |
| 50001-6743 | 53/M/W | 14 | None reported | Clinical cure/clinical cure | | NR |

EOT=end of therapy; TOC=test of cure; M=male; F=female; W=White; B=Black; A=Asian; AI=American Indian
 NR=not reported; UNK (#)=unknown (Study Day of last contact);

[‡]considered possibly/probably related to study medication by the Investigator and the Applicant

There were 30 patient deaths reported in the table above. Seven of the deaths occurred up to Study Day 28 following randomization. Nine of the deaths occurred in the time interval up to EOT + 28 days. The Study Day of death was unknown or not reported for eight patients.

Most of the patients were ≥65 years of age and had multiple comorbid medical conditions. The diagnosis at the time of death was reported in only three patients. For the patients in whom the Study Day of death was reported, all of the deaths occurred post-EOT. It was difficult to assess

the relationship of some of the adverse events and deaths to study drug exposure due to the paucity of details provided in the narratives. The reason(s) underpinning the Investigators' and the Applicant's assessments of whether specific adverse events were considered to have been related (or not) to study drug exposure were not clearly articulated. Many of the narratives did not provide sufficient details as to the extent of pneumonic involvement within the right or left lungs anatomically and did not describe whether the infiltrate was patchy, interstitial, or consolidative at study entry.

7.3.2 Serious Adverse Events

Serious TEAEs

According to the Applicant's Integrated Summary of Safety, a serious adverse event (SAE) was to be defined as follows:

Any adverse drug experience that occurred at any dose and resulted in any of the following outcomes:

- Death
- Life-threatening situation (subject/patient was at immediate risk of death)
- Inpatient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other serious events)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject/patient who received study drug
- Other: Important medical events that may not have resulted in death, were immediately life-threatening, or required hospitalization, may have been considered a SAE when, based upon appropriate medical judgment, they may have jeopardized the subject/patient and may have required medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events were to be:
 - o Intensive treatment in an emergency room or at home for allergic bronchospasm
 - o Blood dyscrasias or convulsions that did not result in hospitalization
 - o Development of drug dependency or drug abuse

Additional Considerations for Serious Adverse Events:

Death was to be considered an outcome of an AE and not an AE in itself. In reports of death due to "Disease Progression", where no other information was provided, the death was to be assumed to have resulted from progression of the disease being treated with the study drug(s).

In the Phase 3 HAP studies, deaths were systematically recorded up to the Follow-up/TOC Visit or 28 days after End-of-therapy (EOT) for those patients who did not have a Follow-up Visit.

“Occurring at any dose” was not to imply that the patient was receiving study drug at the time of the event. Dosing may have been interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

“Life-threatening” meant that the patient was at immediate risk of death from the event as it occurred. This was not to include an event that might have led to death, if it had occurred with greater severity.

Complications that occurred during hospitalizations were to be recorded as AEs. If a complication prolonged hospitalization, it was to be recorded as an SAE.

“Inpatient hospitalization” meant the patient had been formally admitted to a hospital for medical reasons, for any length of time. This may or may not have been overnight. It was not to include presentation and care within an emergency department.

The Investigator was to attempt to establish a diagnosis of the event, and assess causality based on signs, symptoms and/or other clinical information. In such cases, the diagnosis was to be documented as the AE and/or SAE and not the individual signs/symptoms. If the primary infection worsened, regardless of whether it met the criteria for an SAE (except in case of death) it was not to be recorded as an AE nor was it to be recorded as a serious adverse event. The information on the worsening of the infection was to be captured in the clinical assessments sections of the CRF binder. However, if the worsening of the infection led to death, a death form and an SAE form was to be completed and submitted.

Among all patients in Study 0015, the most frequent serious TEAEs involved the system organ classes Respiratory, Thoracic, and Mediastinal disorders (8.87% for telavancin vs 7.22% of vancomycin) and Infections and Infestations (8.6% telavancin vs 7.75% for vancomycin) with higher frequencies observed in the telavancin group. These findings are illustrated in the table below.

Table 116: FDA Medical Officer Table of all Serious TEAE by System Organ Class, Study 0015, AT Safety Population

| System Organ Class | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
|---|------------------------------|------------------------------|
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 33 (8.87%) | 27 (7.22%) |
| INFECTIONS AND INFESTATIONS | 32 (8.60%) | 29 (7.75%) |
| CARDIAC DISORDERS | 18 (4.84%) | 21 (5.61%) |
| RENAL AND URINARY DISORDERS | 15 (4.03%) | 7 (1.87%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 13 (3.49%) | 9 (2.41%) |
| NERVOUS SYSTEM DISORDERS | 12 (3.23%) | 5 (1.34%) |
| VASCULAR DISORDERS | 9 (2.42%) | 4 (1.07%) |
| METABOLISM AND NUTRITION DISORDERS | 5 (1.34%) | 0 (0.00%) |
| GASTROINTESTINAL DISORDERS | 5 (1.34%) | 6 (1.60%) |
| INVESTIGATIONS | 3 (0.81%) | 0 (0.00%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 2 (0.54%) | 0 (0.00%) |
| HEPATOBIILIARY DISORDERS | 1 (0.27%) | 1 (0.27%) |
| ENDOCRINE DISORDERS | 1 (0.27%) | 0 (0.00%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 1 (0.27%) | 2 (0.53%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 1 (0.27%) | 0 (0.00%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 1 (0.27%) | 0 (0.00%) |

In the Infections and Infestations SOC, there were comparable frequencies of patients having pneumonia in the telavancin treatment group (2.96%) compared to the vancomycin group (2.14%). The Respiratory, Thoracic, and Mediastinal Disorders SOC included patients with respiratory failure and acute respiratory failure (pooled frequencies of 4.0% [15/372] for telavancin and 4.0% [15/372] for vancomycin). In addition, in the Renal and Urinary Disorders SOC, there was a marked imbalance with 11 patients in the telavancin group compared to three patients in the vancomycin group who experienced acute renal failure as a serious TEAE. Serious renal TEAEs will be discussed in later sections of this report. Comparable numbers of patients experienced septic shock and sepsis in the two treatment groups. The incidences of specific serious TEAEs in each treatment group are depicted in the table below.

Table 117: FDA Medical Officer Table of all Serious TEAE by Preferred Term, Study 0015, AT Safety Population

| Preferred term | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
|---|------------------------------|------------------------------|
| RESPIRATORY FAILURE | 14 (3.76%) | 11 (2.94%) |
| SEPTIC SHOCK | 13 (3.49%) | 13 (3.48%) |
| RENAL FAILURE ACUTE | 11 (2.96%) | 3 (0.80%) |
| MULTI-ORGAN FAILURE | 11 (2.96%) | 8 (2.14%) |
| SEPSIS | 6 (1.61%) | 4 (1.07%) |
| PNEUMONIA | 6 (1.61%) | 8 (2.14%) |
| RESPIRATORY ARREST | 5 (1.34%) | 3 (0.80%) |
| RESPIRATORY DISTRESS | 4 (1.08%) | 0 (0.00%) |
| CARDIAC FAILURE CONGESTIVE | 4 (1.08%) | 3 (0.80%) |
| RENAL INSUFFICIENCY | 3 (0.81%) | 4 (1.07%) |
| BLOOD CREATININE INCREASED | 3 (0.81%) | 0 (0.00%) |
| SHOCK HAEMORRHAGIC | 3 (0.81%) | 0 (0.00%) |
| SHOCK | 3 (0.81%) | 2 (0.53%) |
| ACUTE RESPIRATORY DISTRESS SYNDROME | 2 (0.54%) | 2 (0.53%) |
| BRADYCARDIA | 2 (0.54%) | 1 (0.27%) |
| CARDIAC ARREST | 2 (0.54%) | 4 (1.07%) |
| MYOCARDIAL ISCHAEMIA | 2 (0.54%) | 1 (0.27%) |
| ATRIAL FIBRILLATION | 2 (0.54%) | 3 (0.80%) |
| UROSEPSIS | 2 (0.54%) | 0 (0.00%) |
| UPPER GASTROINTESTINAL HAEMORRHAGE | 2 (0.54%) | 1 (0.27%) |
| GASTROINTESTINAL HAEMORRHAGE | 2 (0.54%) | 2 (0.53%) |
| CEREBRAL INFARCTION | 2 (0.54%) | 0 (0.00%) |
| CEREBROVASCULAR ACCIDENT | 2 (0.54%) | 2 (0.53%) |
| FLUID OVERLOAD | 2 (0.54%) | 0 (0.00%) |
| CLOSTRIDIUM COLITIS | 1 (0.27%) | 0 (0.00%) |
| DEATH | 1 (0.27%) | 0 (0.00%) |
| DEPENDENCE ON RESPIRATOR | 1 (0.27%) | 0 (0.00%) |
| DIABETIC HYPEROSMOLAR NON-KETOACIDOSIS | 1 (0.27%) | 0 (0.00%) |
| ENCEPHALOPATHY | 1 (0.27%) | 0 (0.00%) |
| ENDOCARDITIS | 1 (0.27%) | 0 (0.00%) |
| FAILURE TO THRIVE | 1 (0.27%) | 0 (0.00%) |
| FATIGUE | 1 (0.27%) | 0 (0.00%) |
| CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED | 1 (0.27%) | 1 (0.27%) |
| GASTRIC ULCER PERFORATION | 1 (0.27%) | 0 (0.00%) |
| CEREBRAL HAEMORRHAGE | 1 (0.27%) | 0 (0.00%) |
| HAEMORRHAGE INTRACRANIAL | 1 (0.27%) | 0 (0.00%) |
| HAEMORRHAGIC STROKE | 1 (0.27%) | 0 (0.00%) |
| CARDIOGENIC SHOCK | 1 (0.27%) | 0 (0.00%) |
| HEPATORENAL SYNDROME | 1 (0.27%) | 0 (0.00%) |
| HYPOALBUMINAEMIA | 1 (0.27%) | 0 (0.00%) |
| HYPOTENSION | 1 (0.27%) | 0 (0.00%) |
| HYPOVOLAEMIC SHOCK | 1 (0.27%) | 0 (0.00%) |
| HYPOXIA | 1 (0.27%) | 1 (0.27%) |

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| Preferred term | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
|---------------------------------|------------------------------|------------------------------|
| HYPOXIC ENCEPHALOPATHY | 1 (0.27%) | 0 (0.00%) |
| MEDIASTINITIS | 1 (0.27%) | 0 (0.00%) |
| CARDIO-RESPIRATORY ARREST | 1 (0.27%) | 0 (0.00%) |
| MYOCARDIAL INFARCTION | 1 (0.27%) | 1 (0.27%) |
| CARDIAC FAILURE | 1 (0.27%) | 2 (0.53%) |
| NERVOUS SYSTEM DISORDER | 1 (0.27%) | 0 (0.00%) |
| OBSTRUCTIVE UROPATHY | 1 (0.27%) | 0 (0.00%) |
| OESOPHAGITIS ULCERATIVE | 1 (0.27%) | 0 (0.00%) |
| PERITONITIS | 1 (0.27%) | 0 (0.00%) |
| PITUITARY HAEMORRHAGE | 1 (0.27%) | 0 (0.00%) |
| PLEURAL EFFUSION | 1 (0.27%) | 0 (0.00%) |
| BRONCHOSPASM | 1 (0.27%) | 1 (0.27%) |
| PNEUMONIA ASPIRATION | 1 (0.27%) | 0 (0.00%) |
| POLYNEUROPATHY | 1 (0.27%) | 0 (0.00%) |
| POOR PERIPHERAL CIRCULATION | 1 (0.27%) | 0 (0.00%) |
| PULMONARY EMBOLISM | 1 (0.27%) | 0 (0.00%) |
| PULMONARY HAEMORRHAGE | 1 (0.27%) | 0 (0.00%) |
| PYELONEPHRITIS CHRONIC | 1 (0.27%) | 1 (0.27%) |
| RASH MACULO-PAPULAR | 1 (0.27%) | 0 (0.00%) |
| BRONCHOPNEUMONIA | 1 (0.27%) | 0 (0.00%) |
| ATRIOVENTRICULAR BLOCK COMPLETE | 1 (0.27%) | 0 (0.00%) |
| ATELECTASIS | 1 (0.27%) | 0 (0.00%) |
| ASPIRATION | 1 (0.27%) | 1 (0.27%) |
| ANURIA | 1 (0.27%) | 0 (0.00%) |
| ANGINA UNSTABLE | 1 (0.27%) | 0 (0.00%) |
| ANAEMIA | 1 (0.27%) | 0 (0.00%) |
| ACUTE RESPIRATORY FAILURE | 1 (0.27%) | 4 (1.07%) |
| ACUTE CORONARY SYNDROME | 1 (0.27%) | 0 (0.00%) |
| STATUS EPILEPTICUS | 1 (0.27%) | 0 (0.00%) |
| SUBCUTANEOUS EMPHYSEMA | 1 (0.27%) | 0 (0.00%) |
| TRACHEAL HAEMORRHAGE | 1 (0.27%) | 0 (0.00%) |
| HEPATIC NEOPLASM MALIGNANT | 1 (0.27%) | 0 (0.00%) |
| ABDOMINAL SEPSIS | 1 (0.27%) | 0 (0.00%) |
| VENTRICULAR TACHYCARDIA | 1 (0.27%) | 3 (0.80%) |
| BACTERAEMIA | 0 (0.00%) | 1 (0.27%) |
| CATHETER SEPSIS | 0 (0.00%) | 1 (0.27%) |
| CONVULSION | 0 (0.00%) | 2 (0.53%) |
| CORONARY ARTERY DISEASE | 0 (0.00%) | 1 (0.27%) |
| DEEP VEIN THROMBOSIS | 0 (0.00%) | 1 (0.27%) |
| DUODENAL PERFORATION | 0 (0.00%) | 1 (0.27%) |
| GANGRENE | 0 (0.00%) | 1 (0.27%) |
| HAEMATEMESIS | 0 (0.00%) | 1 (0.27%) |
| HAEMOPTYSIS | 0 (0.00%) | 1 (0.27%) |
| HEPATIC FAILURE | 0 (0.00%) | 1 (0.27%) |
| INJURY ASPHYXIATION | 0 (0.00%) | 1 (0.27%) |
| ISCHAEMIC STROKE | 0 (0.00%) | 1 (0.27%) |
| LEFT VENTRICULAR FAILURE | 0 (0.00%) | 1 (0.27%) |

| Preferred term | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
|-----------------------------------|------------------------------|------------------------------|
| PANCREATITIS ACUTE | 0 (0.00%) | 1 (0.27%) |
| PNEUMOPERITONEUM | 0 (0.00%) | 1 (0.27%) |
| PULMONARY OEDEMA | 0 (0.00%) | 2 (0.53%) |
| SUDDEN CARDIAC DEATH | 0 (0.00%) | 1 (0.27%) |
| SUPRAVENTRICULAR TACHYCARDIA | 0 (0.00%) | 1 (0.27%) |
| URINARY TRACT INFECTION | 0 (0.00%) | 1 (0.27%) |
| URINARY TRACT INFECTION BACTERIAL | 0 (0.00%) | 1 (0.27%) |
| VENTRICULAR FIBRILLATION | 0 (0.00%) | 2 (0.53%) |
| WOUND DEHISCENCE | 0 (0.00%) | 1 (0.27%) |

Among all patients in Study 0019, the most frequent serious TEAEs involved the system organ classes Respiratory, Thoracic, and Mediastinal disorders (7.39% for telavancin vs 7.94% for vancomycin) and Infections and Infestations (9.76% for telavancin vs 8.47% for vancomycin). These findings are illustrated in the table below.

Table 118: FDA Medical Officer Table of all Serious TEAE by System Organ Class, Study 0019, AT Safety Population

| System Organ Class | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
|---|------------------------------|------------------------------|
| INFECTIONS AND INFESTATIONS | 37 (9.76%) | 32 (8.47%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 28 (7.39%) | 30 (7.94%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 13 (3.43%) | 6 (1.59%) |
| CARDIAC DISORDERS | 12 (3.17%) | 20 (5.29%) |
| NERVOUS SYSTEM DISORDERS | 9 (2.37%) | 14 (3.70%) |
| RENAL AND URINARY DISORDERS | 9 (2.37%) | 9 (2.38%) |
| GASTROINTESTINAL DISORDERS | 7 (1.85%) | 5 (1.32%) |
| VASCULAR DISORDERS | 6 (1.58%) | 5 (1.32%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 3 (0.79%) | 4 (1.06%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 2 (0.53%) | 2 (0.53%) |
| HEPATOBIILIARY DISORDERS | 1 (0.26%) | 2 (0.53%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 1 (0.26%) | 4 (1.06%) |
| PSYCHIATRIC DISORDERS | 1 (0.26%) | 0 (0.00%) |
| METABOLISM AND NUTRITION DISORDERS | 0 (0.00%) | 2 (0.53%) |
| INVESTIGATIONS | 0 (0.00%) | 1 (0.26%) |

In the Infections and Infestations SOC, there were comparable frequencies of patients having pneumonia in the telavancin treatment group (1.06%) compared to the vancomycin group (1.59%). The Respiratory, Thoracic, and Mediastinal Disorders SOC included patients with respiratory failure and acute respiratory failure (pooled frequencies of 2.6% [10/379] for telavancin and 3.9% [15/378] for vancomycin). In addition, in the Renal and Urinary Disorders SOC, there was no imbalance with seven patients in the telavancin group compared to eight patients in the vancomycin group who experienced acute renal failure as a serious TEAE.

Serious renal TEAEs will be discussed in later sections of this report. Comparable numbers of patients experienced septic shock and sepsis in the two treatment groups. However, there were 5 patients who experienced cardiac arrest in the telavancin group compared to no patients in the vancomycin group. The incidences of specific serious TEAEs in each treatment group are depicted in the table below.

Table 119: FDA Medical Officer Table of all Serious TEAE by Preferred Term, Study 0019, AT Safety Population

| Preferred term | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
|---|------------------------------|------------------------------|
| SEPTIC SHOCK | 17 (4.49%) | 15 (3.97%) |
| MULTI-ORGAN FAILURE | 13 (3.43%) | 6 (1.59%) |
| RESPIRATORY FAILURE | 7 (1.85%) | 11 (2.91%) |
| RENAL FAILURE ACUTE | 7 (1.85%) | 8 (2.12%) |
| PULMONARY EMBOLISM | 6 (1.58%) | 1 (0.26%) |
| SEPSIS | 6 (1.58%) | 5 (1.32%) |
| CARDIAC ARREST | 5 (1.32%) | 0 (0.00%) |
| CEREBROVASCULAR ACCIDENT | 4 (1.06%) | 3 (0.79%) |
| PNEUMONIA | 4 (1.06%) | 6 (1.59%) |
| CHRONIC OBSTRUCTIVE AIRWAYS DISEASE EXACERBATED | 3 (0.79%) | 1 (0.26%) |
| GASTROINTESTINAL HAEMORRHAGE | 3 (0.79%) | 0 (0.00%) |
| MENINGITIS | 3 (0.79%) | 2 (0.53%) |
| ACUTE RESPIRATORY FAILURE | 3 (0.79%) | 4 (1.06%) |
| SHOCK | 3 (0.79%) | 1 (0.26%) |
| PNEUMONIA ASPIRATION | 2 (0.53%) | 2 (0.53%) |
| ATRIAL FIBRILLATION | 2 (0.53%) | 2 (0.53%) |
| LUNG INFECTION PSEUDOMONAL | 2 (0.53%) | 0 (0.00%) |
| ISCHAEMIC STROKE | 2 (0.53%) | 0 (0.00%) |
| GASTRIC ULCER HAEMORRHAGE | 2 (0.53%) | 0 (0.00%) |
| DEEP VEIN THROMBOSIS | 2 (0.53%) | 1 (0.26%) |
| RESPIRATORY DISTRESS | 2 (0.53%) | 0 (0.00%) |
| DISSEMINATED INTRAVASCULAR COAGULATION | 1 (0.26%) | 0 (0.00%) |
| ESCHERICHIA SEPSIS | 1 (0.26%) | 0 (0.00%) |
| GASTRIC HAEMORRHAGE | 1 (0.26%) | 0 (0.00%) |
| CHOLECYSTITIS | 1 (0.26%) | 0 (0.00%) |
| BILE DUCT CANCER | 1 (0.26%) | 0 (0.00%) |
| HYPOXIA | 1 (0.26%) | 0 (0.00%) |
| INTRACRANIAL PRESSURE INCREASED | 1 (0.26%) | 1 (0.26%) |
| ISCHAEMIC CARDIOMYOPATHY | 1 (0.26%) | 0 (0.00%) |
| BRAIN OEDEMA | 1 (0.26%) | 1 (0.26%) |
| CARDIOGENIC SHOCK | 1 (0.26%) | 2 (0.53%) |
| BACTERIAL SEPSIS | 1 (0.26%) | 0 (0.00%) |
| MENTAL STATUS CHANGES | 1 (0.26%) | 0 (0.00%) |
| BACTERAEMIA | 1 (0.26%) | 1 (0.26%) |
| MYOCARDIAL INFARCTION | 1 (0.26%) | 0 (0.00%) |
| PERICARDIAL EFFUSION | 1 (0.26%) | 0 (0.00%) |

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| Preferred term | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
|--|------------------------------|------------------------------|
| PLEURAL EFFUSION | 1 (0.26%) | 0 (0.00%) |
| CARDIAC FAILURE ACUTE | 1 (0.26%) | 0 (0.00%) |
| CARDIAC FAILURE | 1 (0.26%) | 3 (0.79%) |
| PNEUMONIA STAPHYLOCOCCAL | 1 (0.26%) | 0 (0.00%) |
| PNEUMOTHORAX | 1 (0.26%) | 2 (0.53%) |
| POSTOPERATIVE ILEUS | 1 (0.26%) | 0 (0.00%) |
| ATELECTASIS | 1 (0.26%) | 0 (0.00%) |
| PULMONARY NECROSIS | 1 (0.26%) | 0 (0.00%) |
| ASPHYXIA | 1 (0.26%) | 0 (0.00%) |
| RENAL FAILURE CHRONIC | 1 (0.26%) | 0 (0.00%) |
| RENAL INSUFFICIENCY | 1 (0.26%) | 0 (0.00%) |
| BRAIN HERNIATION | 1 (0.26%) | 0 (0.00%) |
| ARTERIAL RUPTURE | 1 (0.26%) | 0 (0.00%) |
| APNOEA | 1 (0.26%) | 1 (0.26%) |
| CANDIDA SEPSIS | 1 (0.26%) | 0 (0.00%) |
| ABDOMINAL ABSCESS | 1 (0.26%) | 0 (0.00%) |
| SINUSITIS FUNGAL | 1 (0.26%) | 0 (0.00%) |
| SMALL CELL LUNG CANCER STAGE UNSPECIFIED | 1 (0.26%) | 0 (0.00%) |
| SUPERINFECTION LUNG | 1 (0.26%) | 0 (0.00%) |
| SYNCOPE | 1 (0.26%) | 0 (0.00%) |
| THROAT SECRETION INCREASED | 1 (0.26%) | 0 (0.00%) |
| UPPER GASTROINTESTINAL HAEMORRHAGE | 1 (0.26%) | 2 (0.53%) |
| URINE FLOW DECREASED | 1 (0.26%) | 0 (0.00%) |
| VENTRICULAR FIBRILLATION | 1 (0.26%) | 0 (0.00%) |
| WANDERING PACEMAKER | 1 (0.26%) | 0 (0.00%) |
| WOUND EVISCERATION | 1 (0.26%) | 0 (0.00%) |
| ABDOMINAL SEPSIS | 0 (0.00%) | 1 (0.26%) |
| ACUTE CORONARY SYNDROME | 0 (0.00%) | 1 (0.26%) |
| ACUTE MYOCARDIAL INFARCTION | 0 (0.00%) | 2 (0.53%) |
| ACUTE PULMONARY OEDEMA | 0 (0.00%) | 2 (0.53%) |
| ACUTE RESPIRATORY DISTRESS SYNDROME | 0 (0.00%) | 5 (1.32%) |
| ANAEMIA | 0 (0.00%) | 1 (0.26%) |
| ANASTOMOTIC STENOSIS | 0 (0.00%) | 1 (0.26%) |
| ASPIRATION | 0 (0.00%) | 1 (0.26%) |
| BLOOD POTASSIUM INCREASED | 0 (0.00%) | 1 (0.26%) |
| BLOOD SODIUM INCREASED | 0 (0.00%) | 1 (0.26%) |
| BRADYCARDIA | 0 (0.00%) | 2 (0.53%) |
| CACHEXIA | 0 (0.00%) | 1 (0.26%) |
| CARDIAC FAILURE CONGESTIVE | 0 (0.00%) | 7 (1.85%) |
| CARDIOPULMONARY FAILURE | 0 (0.00%) | 1 (0.26%) |
| CARDIOVASCULAR DISORDER | 0 (0.00%) | 1 (0.26%) |
| CEREBELLAR HAEMORRHAGE | 0 (0.00%) | 1 (0.26%) |
| CEREBRAL HAEMORRHAGE | 0 (0.00%) | 1 (0.26%) |
| CEREBRAL ISCHAEMIA | 0 (0.00%) | 1 (0.26%) |
| CHRONIC SINUSITIS | 0 (0.00%) | 1 (0.26%) |
| CONVULSION | 0 (0.00%) | 2 (0.53%) |
| DEMENCIA | 0 (0.00%) | 1 (0.26%) |

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| Preferred term | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
|----------------------------------|------------------------------|------------------------------|
| GASTROINTESTINAL NECROSIS | 0 (0.00%) | 1 (0.26%) |
| HAEMORRHAGIC STROKE | 0 (0.00%) | 1 (0.26%) |
| HEPATIC FAILURE | 0 (0.00%) | 1 (0.26%) |
| HEPATOCELLULAR DAMAGE | 0 (0.00%) | 1 (0.26%) |
| HYDROCEPHALUS | 0 (0.00%) | 1 (0.26%) |
| HYPERKALAEMIA | 0 (0.00%) | 1 (0.26%) |
| HYPOTENSION | 0 (0.00%) | 3 (0.79%) |
| MENINGITIS CANDIDA | 0 (0.00%) | 1 (0.26%) |
| MESENTERIC OCCLUSION | 0 (0.00%) | 1 (0.26%) |
| MULTIPLE MYELOMA | 0 (0.00%) | 1 (0.26%) |
| NEUROLOGICAL SYMPTOM | 0 (0.00%) | 1 (0.26%) |
| OESOPHAGEAL CARCINOMA | 0 (0.00%) | 1 (0.26%) |
| PERITONITIS | 0 (0.00%) | 1 (0.26%) |
| PERITONITIS BACTERIAL | 0 (0.00%) | 1 (0.26%) |
| PNEUMOTHORAX SPONTANEOUS TENSION | 0 (0.00%) | 1 (0.26%) |
| RENAL IMPAIRMENT | 0 (0.00%) | 1 (0.26%) |
| SUBARACHNOID HAEMORRHAGE | 0 (0.00%) | 1 (0.26%) |
| SUBDURAL HAEMATOMA | 0 (0.00%) | 1 (0.26%) |
| SYSTEMIC CANDIDA | 0 (0.00%) | 2 (0.53%) |
| THROMBOCYTOPENIA | 0 (0.00%) | 3 (0.79%) |
| TRACHEOSTOMY MALFUNCTION | 0 (0.00%) | 1 (0.26%) |
| TRAUMATIC BRAIN INJURY | 0 (0.00%) | 1 (0.26%) |
| UROSEPSIS | 0 (0.00%) | 1 (0.26%) |

Serious Drug-related TEAEs

The following table summarizes the serious TEAEs that were assessed as related to study drug by the investigators in Study 0015. There is a striking imbalance with respect to the number of renal-related events with 14 telavancin-treated compared to 5 vancomycin-treated patients having experienced acute renal failure, blood creatinine increased, and renal insufficiency as serious drug-related TEAEs. Serious renal-related TEAEs will be discussed further in later sections of this report.

Table 120: FDA Medical Officer Table of all Serious TEAE that were assessed as being related to study drug stratified by Preferred Term, study 0015, AT Safety Population

| 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 ISCHAEMIA | 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%) |

The following table summarizes the serious TEAEs that were assessed as related to study drug by the investigators in Study 0019. In contrast to Study 0015, there was a higher frequency of serious renal drug-related TEAEs in the vancomycin group compared to the telavancin group. Serious renal-related TEAEs will be discussed further in later sections of this report.

Table 121: FDA Medical Officer Table of all Serious TEAE that were assessed as being related to study drug stratified by Preferred Term, Study 0019, AT Safety Population

| Preferred term | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
|------------------------------|------------------------------|------------------------------|
| CARDIAC ARREST | 1 (0.26%) | 0 (0.00%) |
| GASTROINTESTINAL HAEMORRHAGE | 1 (0.26%) | 0 (0.00%) |
| ISCHAEMIC 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%) |

7.3.3 Dropouts and/or Discontinuations

The following table provides a summary of the number of subjects who completed the course of study medication and those who had premature discontinuation of study medication for each clinical trial.

Table 122: FDA Medical Officer Summary Table of Discontinuation of Study Medication, Studies 0015 and 0019, AT Population (from Applicant's Clinical Study Reports, adapted from Table 7-4 in each report)

| | Study 0015 | | Study 0019 | |
|---|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=377 n (%) | Vancomycin N=378 n (%) |
| Completed Course of Study Medication | 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 (0%) | 2 (<1%) | 4 (1%) |
| Infection due to Gram-negative organism only | 11 (3%) | 9 (2%) | 5 (1%) | 2 (<1%) |
| Infection due to <i>Stenotrophomonas maltophilia</i> or <i>Burkholderia cepacia</i> | 0 (0%) | 4 (1%) | 1 (<1%) | 1 (<1%) |
| Gram-positive coverage no longer clinically indicated | 27 (7%) | 18 (5%) | 42 (11%) | 45 (12%) |
| Required non-study antibiotics | 6 (2%) | 5 (1%) | 2 (<1%) | 6 (2%) |
| Other | 11 (3%) | 19 (5%) | 2 (<1%) | 7 (2%) |
| Persistent <i>S. aureus</i> bacteremia | 0 (0%) | 0 (0%) | 0 (0%) | 2 (<1%) |
| Documented Meningitis, Endocarditis, or Osteomyelitis | 0 (0%) | 0 (0%) | 1 (<1%) | 2 (<1%) |

As depicted in the table above, approximately 55-61% of subjects completed study medication in each clinical trial. Death, unsatisfactory therapeutic response, and Gram-positive coverage no longer clinically indicated were the most frequent reasons for premature discontinuation of study medication. Premature discontinuation due to adverse events occurred with a higher frequency in the telavancin group of Study 0015, whereas the frequency of such events in the two treatment groups of Study 0019 were comparable. The frequency of premature discontinuations due to having two consecutive ECGs with QTc > 500 msec was higher in the telavancin arm compared to the vancomycin arm in both studies.

Treatment-emergent Adverse Events associated with Discontinuation of Study Medication

There were a total of 50 patients each in Studies 0015 and 0019 who experienced at least one TEAE that resulted in discontinuation of study medication as depicted in the table below. In Study 0015, there were a greater number of patients who had at least one TEAE that resulted in discontinuation of study medication in the telavancin group compared to the vancomycin group, and the difference was statistically significant. However, the potential contribution of concomitant medical conditions and concurrent medications as predisposing factors to adverse events or study drug intolerance must be considered in assessing these patients.

Table 123: FDA Medical Officer Table of Subject Count with at least one TEAE that resulted in Discontinuation of Study Medication, Studies 0015 and 0019, AT Population

| Study | Treatment | N | n (%) | 95% CI (difference TLV-VAN) |
|-------|------------|-----|-----------|--------------------------------|
| 15 | Telavancin | 372 | 33 (8.9%) | (0.75, 7.90)* |
| | Vancomycin | 374 | 17 (4.5%) | |
| 19 | Telavancin | 379 | 27 (7.1%) | (-2.50, 4.58) |
| | Vancomycin | 378 | 23 (6.1%) | |

*statistically significant difference; TLV=telavancin, VAN=vancomycin;
 N=total patients (All treated population); n= number of patients

In terms of the number and types of TEAEs experienced, the 33 telavancin-treated patients in Study 0015 (see above table) experienced a total of 44 TEAEs leading to study drug discontinuation. The 17 vancomycin-treated patients in Study 0015 experienced a total of 19 TEAEs leading to study drug discontinuation. The 27 telavancin-treated patients in Study 0019 experienced a total of 29 TEAEs leading to study drug discontinuation, and the 23 vancomycin-treated patients in Study 0019 experienced a total of 24 TEAEs leading to study drug discontinuation. The following table stratifies the TEAEs by System Organ Class.

Table 124: FDA Medical Officer Table of all TEAE (stratified by System Organ Class) that resulted in Discontinuation of Study Medications, Studies 0015 and 0019, AT Population

| SYSTEM ORGAN CLASS | STUDY | | | |
|---|------------|------------|------------|------------|
| | 0015 | | 0019 | |
| | TELAVANCIN | VANCOMYCIN | TELAVANCIN | VANCOMYCIN |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 1 | 3 | 0 | 1 |
| CARDIAC DISORDERS | 3 | 2 | 1 | 0 |
| EYE DISORDERS | 0 | 0 | 1 | 0 |
| GASTROINTESTINAL DISORDERS | 0 | 0 | 2 | 1 |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 0 | 3 | 3 | 1 |
| HEPATOBIILIARY DISORDERS | 1 | 0 | 0 | 1 |
| INFECTIONS AND INFESTATIONS | 2 | 3 | 7 | 9 |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 1 | 0 | 0 | 2 |
| INVESTIGATIONS | 13 | 0 | 4 | 3 |
| METABOLISM AND NUTRITION DISORDERS | 1 | 1 | 0 | 0 |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 0 | 0 | 1 | 0 |
| NERVOUS SYSTEM DISORDERS | 3 | 1 | 4 | 0 |
| PSYCHIATRIC DISORDERS | 1 | 0 | 1 | 0 |
| RENAL AND URINARY DISORDERS | 8 | 3 | 3 | 3 |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 6 | 1 | 0 | 2 |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 4 | 2 | 1 | 0 |
| VASCULAR DISORDERS | 0 | 0 | 1 | 1 |
| Total TEAEs that resulted in discontinuation of study medication | 44 | 19 | 29 | 24 |

As depicted above, the most frequent TEAEs (stratified by System Organ Class) that resulted in discontinuation of study medication in Study 0015 included Investigations and Renal/Urinary Disorders in the telavancin group compared to Blood and Lymphatic Systems Disorders, Infections and Infestations, and Renal/Urinary Disorders in the vancomycin group. For both of the Investigations and Renal/Urinary Disorders System Organ Classes, there was an imbalance indicative of a higher frequency of events among telavancin-treated patients. The most frequent TEAEs (stratified by System Organ Class) that resulted in discontinuation of study medication in Study 0019 included Infections and Infestations in both the telavancin and vancomycin groups. In contrast to Study 0015, there were no striking imbalances in the frequency of specific TEAEs across the treatment groups in Study 0019.

Discontinuations due to two consecutive ECGs with QTc >500 msec

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. The following table summarizes the 16 patients:

Table 125: FDA Medical Officer Table of all Patients who were Discontinued from Study Medication due to having Two Consecutive ECGs with QTc > 500 msec, Studies 0015 and 0019, AT Population

| Subject # | Study | Treatment | Avg of Baseline QTcF (category) | QTc Max change from Baseline (category) |
|-----------------|-------|------------|---------------------------------|---|
| 0015-01014-4042 | 0015 | TELAVANCIN | <=450 | >30 - <=60 |
| 0015-01028-4440 | 0015 | TELAVANCIN | <=450 | >60 |
| 0015-02011-4205 | 0015 | TELAVANCIN | <=450 | >60 |
| 0015-05001-4467 | 0015 | TELAVANCIN | >450 - <=480 | <=30 |
| 0015-38024-4771 | 0015 | TELAVANCIN | <=450 | >30 - <=60 |
| 0015-38101-4016 | 0015 | TELAVANCIN | >450 - <=480 | >30 - <=60 |
| 0015-38148-4339 | 0015 | TELAVANCIN | <=450 | >30 - <=60 |
| 0015-38148-4721 | 0015 | TELAVANCIN | >480 - <=500 | <=30 |
| 0015-33008-4320 | 0015 | VANCOMYCIN | <=450 | >30 - <=60 |
| 0019-01019-6420 | 0019 | TELAVANCIN | <=450 | >60 |
| 0019-08008-6635 | 0019 | TELAVANCIN | >450 - <=480 | >30 - <=60 |
| 0019-20017-6463 | 0019 | TELAVANCIN | <=450 | >60 |
| 0019-38065-6435 | 0019 | TELAVANCIN | Missing | Missing |
| 0019-38069-6012 | 0019 | TELAVANCIN | <=450 | >60 |
| 0019-02029-6189 | 0019 | VANCOMYCIN | Missing | Missing |
| 0019-20019-6400 | 0019 | VANCOMYCIN | <=450 | <=30 |

Although five of the telavancin-treated patients across the two studies developed maximum increases of >60 msec in QTc interval, none of the patients developed Torsades de pointes. None of the vancomycin-treated patients developed a maximum increase in QTc interval of >60 msec.

Lost To Follow-up

A total of 16 patients were lost to follow-up across the two clinical trials (three vancomycin-treated and no telavancin-treated in Study 0015 and eight vancomycin-treated and five telavancin-treated in Study 0019). The following table summarizes the patients who were lost to follow-up and the reason for discontinuation of study medication. Only one patient (#0015-38045-4109 in Study 0015) was lost to follow-up following discontinuation of study medication due to an adverse event.

Table 126: FDA Medical Officer Table of Patients who were Lost to Follow-up, Studies 0015 and 0019, AT Population

| Patient # | Study | Treatment | Reason for Discontinuing Study Medication |
|-----------------|-------|------------|---|
| 0015-12005-4373 | 0015 | Vancomycin | RESOLUTION OF SIGNS AND SYMPTOMS OR IMPROVEMENT |
| 0015-33008-4136 | 0015 | Vancomycin | INFECTION DUE TO STENOTROPHOMONAS MALTOPHILIA OR BURKHOLDERIA CEPACIA |
| 0015-38045-4109 | 0015 | Vancomycin | ADVERSE EVENT (thrombocytopenia) |
| 0019-02023-6614 | 0019 | Telavancin | RESOLUTION OF SIGNS AND SYMPTOMS OR IMPROVEMENT |
| 0019-08014-6407 | 0019 | Telavancin | UNSATISFACTORY THERAPEUTIC RESPONSE |
| 0019-08020-6559 | 0019 | Telavancin | UNSATISFACTORY THERAPEUTIC RESPONSE |
| 0019-20012-6529 | 0019 | Telavancin | UNSATISFACTORY THERAPEUTIC RESPONSE |
| 0019-43002-6801 | 0019 | Telavancin | RESOLUTION OF SIGNS AND SYMPTOMS OR IMPROVEMENT |
| 0019-08016-6702 | 0019 | Vancomycin | GRAM-POSITIVE COVERAGE NO LONGER CLINICALLY INDICATED |
| 0019-18004-6186 | 0019 | Vancomycin | RESOLUTION OF SIGNS AND SYMPTOMS OR IMPROVEMENT |
| 0019-20012-6525 | 0019 | Vancomycin | GRAM-POSITIVE COVERAGE NO LONGER CLINICALLY INDICATED |
| 0019-20015-6532 | 0019 | Vancomycin | GRAM-POSITIVE COVERAGE NO LONGER CLINICALLY INDICATED |
| 0019-20017-6336 | 0019 | Vancomycin | GRAM-POSITIVE COVERAGE NO LONGER CLINICALLY INDICATED |
| 0019-29002-6133 | 0019 | Vancomycin | RESOLUTION OF SIGNS AND SYMPTOMS OR IMPROVEMENT |
| 0019-40001-6396 | 0019 | Vancomycin | PATIENT WITHDREW CONSENT |
| 0019-40006-6445 | 0019 | Vancomycin | RESOLUTION OF SIGNS AND SYMPTOMS OR IMPROVEMENT |

7.3.4 Significant Adverse Events

In response to an information request dated April 30, 2009 regarding the significant amount of missing laboratory safety data, the Applicant reported that the principal safety issue was renal dysfunction based on the safety database provided in the complicated skin and skin structure infections submission (NDA 22-110) and the available data in the current submission for NP. As renal dysfunction is measured by serum creatinine and almost 95% of patients had a serum creatinine determination at the TOC visit or within 3 days of the visit, the Applicant considered that these data would be sufficient to characterize the safety profile of telavancin.

Evaluation of telavancin for potential nephrotoxicity will be a major focus of the safety review of this report.

Table 127: FDA Medical Officer Summary Table of all Patients who experienced Renal TEAE stratified by Baseline Creatinine Category

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

Among patients with normal baseline creatinine (≤ 1.2 mg/dL), there were comparable incidences across the two studies of renal TEAEs. However, among patients with abnormal baseline creatinine (> 1.2 mg/dL), more telavancin-treated patients experienced renal TEAEs compared to vancomycin-treated patients. The differences among treatment groups within each study for patients with abnormal baseline creatinine were not statistically significant.

Table 128: FDA Medical Officer Table of all Renal-related TEAE (Serious and Non-serious), Studies 0015 and 0019

| Preferred term | 0015 | | 0019 | | Total Subjects N=1532 |
|----------------------------|--------------|--------------|--------------|--------------|--------------------------|
| | TLV N=372 | VAN N=374 | TLV N=379 | VAN N=378 | |
| 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%) |

As depicted above, the most frequently reported renal-related TEAE was acute renal failure in both of the studies. Data regarding concomitant antibacterial medication use in patients who developed renal-related TEAEs is provided in the following table:

Table 129: FDA Medical Officer Summary Table of Concomitant Antibacterial Drug Administration in patients who experienced Renal-related TEAE, Studies 0015 and 0019, AT Population

| Study | Treatment Group | Renal-related TEAEs n (%) | Concomitant antibacterial drugs n (%) | Concomitant vancomycin n (%) | Concomitant aminoglycosides n (%) | No concomitant antibacterial drugs n (%) |
|-------|-----------------|------------------------------|--|---------------------------------|--------------------------------------|---|
| 0015 | TLV (N=372) | 39 (10.5)* | 17 (4.6) | 3 (0.8) | 4 (1.1) | 22 (5.9) |
| | VAN (N=374) | 29 (7.8) | 7 (1.9) | 2 (0.5) | 1 (0.3) | 22 (5.9) |
| 0019 | TLV (N=379) | 38 (10.2)** | 0 (0.0) | 0 (0.0) | 0 (0.0) | 38 (100.0) |
| | VAN (N=378) | 31 (8.3)** | 0 (0.0) | 0 (0.0) | 0 (0.0) | 31 (100.0) |

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.

In the patients who experienced renal-related TEAEs in Study 0015, it was evident that there was more concomitant antibacterial drug administration in telavancin-treated compared to vancomycin-treated patients. Concomitant vancomycin administration was comparable across the two treatment groups. Although there was greater concomitant aminoglycoside administration in the telavancin-treated compared to vancomycin-treated patients, the difference was not statistically significant.

In the patients who experienced renal-related TEAEs in Study 0019, none of the patients in either treatment group received concomitant antibacterial drugs.

A review of the serious renal-related TEAEs is provided in Section 7.3.5 of this report.

7.3.5 Submission Specific Primary Safety Concerns

Serious renal-related TEAEs

In the pooled experience from studies 0015 and 0019, a total of 42 patients experienced serious renal-related TEAEs.

- 26 (61%) occurred in patients treated with telavancin across the trials
- 16 (38%) occurred in patients treated with vancomycin across the trials
- Renal failure acute was the most frequently reported renal-related TEAE

When the serious renal-related TEAEs were assessed by individual trial, the event “renal failure acute” was reported most frequently in both trials. Serious renal-related TEAEs occurred with equal frequency in the two treatment groups in study 0019. However, in study 0015, there was a disparity in that serious renal-related TEAEs occurred almost 2.4 times more frequently in the telavancin group, and the difference was statistically significant.

Table 130: FDA Medical Officer Table of Subject Count with Serious Renal TEAE stratified by Preferred Term, Study, and Treatment Group, Studies 0015 and 0019, AT Population

| AE Preferred Term | Study 0015 | | Study 0019 | |
|---|--------------------|----------------|---------------------|----------------|
| | TLV N=372 | VANCO N=374 | TLV N=379 | VANCO N=378 |
| | n (%) | n (%) | n (%) | 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) | |

When the incidence of serious renal-related TEAEs was stratified by baseline creatinine, the incidence of such events was similar in the treatment groups in study 0019 despite differences in renal function at baseline. However, in study 0015, there was a higher incidence of serious renal-related TEAEs in telavancin-treated patients compared to the vancomycin group regardless of whether the patient had normal or abnormal baseline creatinine, although the differences were not statistically significant. This is depicted in the following table:

Table 131: FDA Medical Officer Table of Frequency of Serious Renal TEAEs stratified by Baseline Serum Creatinine, Studies 0015 and 0019, AT Population

| Baseline Creatinine | STUDY | | | |
|---------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| | 0015 | | 0019 | |
| | TELAVANCIN N=372 n (%) | VANCOMYCIN N=374 n (%) | TELAVANCIN N=379 n (%) | VANCOMYCIN N=378 n (%) |
| ≤1.2 (normal) | 9 (2.4%) | 5 (1.3%) | 5 (1.3%) | 6 (1.6%) |
| >1.2 (abnormal) | 7 (1.9%) | 2 (0.5%) | 4 (1.1%) | 3 (0.8%) |
| Missing | 1 (0.3%) | 0 (0%) | 0 (0%) | 0 (0%) |
| Total subjects | 17 (4.6%) | 7 (1.9%) | 9 (2.4%) | 9 (2.4%) |

As depicted in the following table, the patients having serious renal-related TEAEs were assessed for exposure to various nephrotoxic medications (including antibacterial drugs, furosemide, and others). Although less than half of the patients who experienced serious renal-related TEAEs had an abnormal baseline serum creatinine (>1.2 mg/dL), renally impaired patients experienced a greater proportion of the serious renal-related TEAEs in the telavancin groups of both trials compared to the vancomycin groups. Most of the patients having serious renal-related TEAEs had received more than one prior or concomitant nephrotoxic drug. Furosemide was the most commonly administered nephrotoxic drug in all of the subgroups who experienced serious renal-related TEAEs followed in frequency by vancomycin.

Table 132: FDA Medical Officer Table of Serious Renal TEAE stratified by Exposure to Prior or Concomitant Nephrotoxic Drugs, Studies 0015 and 0019, AT Safety Population

| Study | Treatment Group | Serious Renal TEAEs n=42 | Baseline serum creatinine >1.2 mg/dL | Received any prior or concomitant nephrotoxic drugs n=39 | Received >1 prior or concomitant nephrotoxic drugs n=33 | # Patients who were administered concomitant furosemide | # Patients who were administered concomitant vancomycin | # Patients who were administered aminoglycosides and vancomycin |
|------------|--------------------|-----------------------------|--------------------------------------|---|--|---|---|---|
| Study 0015 | Telavancin (N=372) | 17 (100%) | 7 (41%) | 15 (88%) | 10 (59%) | 12 (71%) | 6 (35%) | 1 (6%) |
| | Vancomycin (N=374) | 7 (100%) | 2 (29%) | 6 (86%) | 6 (86%) | 4 (57%) | 3 (43%) | 1 (14%) |
| Study 0019 | Telavancin (N=379) | 9 (100%) | 4 (44%) | 9 (100%) | 9 (100%) | 6 (86%) | 3 (33%) | 1 (1%) |
| | Vancomycin N=378 | 9 (100%) | 3 (33%) | 9 (100%) | 8 (89%) | 9 (100%) | 1 (11%) | 1 (11%) |

There were three patients in Study 0015 who experienced serious renal-related TEAEs and had not received any prior or concomitant nephrotoxic drugs. In contrast, all of the patients in Study 0019 who experienced serious renal-related TEAEs had received prior or concomitant nephrotoxic drugs. The three patients from Study 0015 are summarized below:

Table 133: FDA Medical Officer Table of Subjects who experienced Serious Renal TEAE and did NOT receive Prior or Concomitant Nephrotoxic Drugs, Study 0015, AT Safety Population

| Subject # | Age/Race/ Gender | Baseline serum creatinine (mg/dL) | Treatment | I.V. Study Drug Duration | AE Study Day | Severity | Action taken | Related Category | Outcome | Epoch |
|-----------------|---------------------|-----------------------------------|-----------|--------------------------|--------------|----------|--------------|-------------------|-----------------------------|--------------------------------|
| 0015-12006-4126 | 67/W/M | 1.2 | TLV | 5 | 5 | Moderate | Discontinued | Possibly/Probably | Recovered | During treatment |
| 0015-38350-4774 | 47/W/M | 0.9 | TLV | 4 | 2 | Moderate | Discontinued | Possibly/Probably | Recovered | During treatment |
| 0015-30905-4237 | 84/W/F | 0.3 | VAN | 8 | 8 | Moderate | Discontinued | Possibly/Probably | Still present and unchanged | Post-Treatment (AE continuing) |

M = male; F = female; W = White; TLV = telavancin; VAN = vancomycin

The Applicant's narratives for the three patients above are provided below:

1) Patient 0015-12006-4126, a 67-year-old white male, was enrolled in Study 0015, and randomly assigned to telavancin on (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-susceptible *S. aureus* (MSSA). Telavancin therapy ended on (b) (6), for a total exposure of five days. Significant medical history included hypertension and meningioma. Additional medical history per the SAE form included asthma.

Recent medical conditions included exeresis of meningioma (neurosurgical procedure: (b) (6)) and esophageal ulcer (26 November 2005-cont). Recent medical conditions per the SAE form included anemia (18 August 2005-cont), ascending aorta repair and aortic valve replacement ((b) (6) coronary surgery (b) (6)), left ventricular hypertrophy (01 August 2005-cont), and myocardial revascularization (b) (6). Concomitant medications included heparin-fraction, esomeprazole, rilmenidine, methylprednisolone, nicardipine, nystatin, propofol, hyoscine, and urapidil.

(b) (6) prior to study entry, the patient was hospitalized and admitted to the ICU for post-operative ischemic stroke and complications related to elective removal of a meningioma. On (b) (6) (Study Day 1), the patient began treatment with telavancin. Baseline (Study Day 1) serum creatinine was 1.2 mg/dL (reference range: 0.5-1.3 mg/dL). Repeat respiratory cultures on Study Day 4 revealed *Klebsiella oxytoca*, MSSA, and *Enterococcus faecalis*. On Study Days 4 and 5, serum creatinine levels

increased to 1.7 mg/dL and 2.48 mg/dL (local laboratory value, reference range not provided), respectively. On Study Day 5, moderate renal insufficiency was diagnosed (serum creatinine of 3.11 mg/dL, local laboratory value). Telavancin was discontinued, and oxacillin was started. On Study Day 7, amoxicillin and ofloxacin were added. The patient was discharged on Study Day 27, and the event resolved on Study Day 41. Both the EOT and TOC clinical response assessments were indeterminate, as the study medication was discontinued early due to renal insufficiency. Serum creatinine values are presented in the table below.

| Study Day | Serum Creatinine (mg/dL) |
|-----------|--------------------------|
| 1 | 1.2 |
| 4 | 1.7* |
| 5 | 2.48 [†] |
| 6 | 3.11 [†] |
| 7 | 3.2* |
| 12 | 3.3* |

*Above reference range (central lab reference range 0.5-1.3 mg/dL)

[†]Local laboratory value. Local lab reference ranges unknown.

2) Patient 0015-38350-4774, a 47-year-old white male, was enrolled in Study 0015 and randomly assigned to telavancin on (b) (6) for the treatment of HAP, subsequently found due to *Escherichia coli* and *Enterobacter hormaechei*. Telavancin therapy ended on (b) (6), for a total exposure of four days. Significant medical history included asthma and brain injury. Recent medical conditions included abdominal closure (b) (6), abdominal hemorrhage with blood loss (b) (6), abdominal washout (b) (6), agitation (30 May 2007-cont), anemia (03 June 2007-cont), bronchoscopy (b) (6), decreased phosphorus level (31 May 2007-05 June 2007), devascularization of spleen (b) (6), elevated chloride level (30 May 2007-03 June 2007), elevated partial thromboplastin time (30 May-31 May 2007), elevated prothrombin time (30 May 2007-cont), exploratory laparotomy (b) (6) hemothorax (06 June 2007-cont), hypercalcemia (30 May 2007), hyperglycemia (31 May 2007-cont), hypertension (07 June 2007-cont), hypocalcemia (30 May 2007-cont), hypoglycemia (02 June 07-cont), hypotension (07 June 2007-cont), intubation (b) (6), low albumin level (02 June 2007-cont), low chloride level (08 June 2007-cont), low partial thromboplastin time (30 May 2007-cont), low platelet count (30 May 2007-04 June 2007), malnutrition (05 June 2007-cont), mid superior mesenteric artery hemorrhage (b) (6), multiple traumas due to fall from horse (b) (6) pelvic hemorrhage (b) (6), pleural effusion (b) (6), re-opening of laparotomy (b) (6), repair of superior mesenteric artery (b) (6) shocked bowel-intestinal ischemia (b) (6), small bowel resection (b) (6) terminal ileum (b) (6) tracheostomy (b) (6) and tachycardia (05 June 2007-cont).

Concomitant medications included hydralazine, lorazepam, bisacodyl, fleet enema, plasma protein fraction, haloperidol, human insulin, labetalol, heparin-fraction, metoprolol, midazolam, morphine, esomeprazole, vecuronium, RBCs, potassium, propofol, quetiapine,

carbamazepine, trazodone, and paracetamol.

(b) (6) prior to study entry, the patient experienced a fall from a horse with multiple abdominal injuries. Piperacillin/tazobactam was administered from Study Day -7 to Study Day -5 for an elevated WBC count. On (b) (6) (Study Day 1), telavancin was started for HAP, and erythromycin ethylsuccinate was also started for an elevated WBC count. Baseline (Study Day 1) serum creatinine was 0.9 mg/dL (reference range 0.5-1.2 mg/dL); baseline WBC count was not provided. On Study Day 2, aztreonam was added for Gram-negative pneumonia coverage, and serum creatinine began to rise (value not provided). By Study Day 4, serum creatinine level was 2.2 mg/dL, and telavancin was discontinued after four doses due to the increased serum creatinine. End-of-therapy clinical response assessment was indeterminate, as the patient was removed early from therapy due to serum creatinine elevations. Serum creatinine remained elevated on Study Day 6 (2.2 mg/dL), and imipenem (Study Day 6) and ciprofloxacin (Study Day 7) were started due to the persistent WBC elevations. Imipenem was discontinued on Study Day 11, and serum creatinine fell to 1.1 mg/dL by Study Day 13. Test-of-cure clinical assessment remained indeterminate on that day. The event was considered resolved on Study Day 14. Serum creatinine values are presented in the table below.

| Study Day | Serum Creatinine (mg/dL) |
|-----------|--------------------------|
| 1 | 0.9 |
| 4 | 2.2* |
| 6 | 2.2* |
| 13 | 1.1 |

*Above reference range (central lab reference range 0.5-1.3 mg/dL)

3) Patient 0015-30905-4237, an 84-year-old white female, was enrolled in Study 0015 and randomly assigned to vancomycin on (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-resistant *S. aureus* (MRSA). Vancomycin therapy ended on (b) (6), for a total exposure of eight days. No significant medical history was reported. Recent medical conditions included anemia (--June 2006-cont), bowel strangulation ((b) (6)), colon perforation ((b) (6)), hemi-colectomy ((b) (6)), hyperthyroidism (--June 2006-cont), hypoalbuminemia (--June 2006-cont), infected stoma (21 July 2006-cont), percutaneous endoscopic gastrostomy tube placement ((b) (6)), phlebitis (21 July 2006-cont), and possible agranulocytosis (--July 2006 to --July 2006).

Concomitant medications included human albumin, heparin-fraction, paracetamol, ipratropium bromide/fenoterol hydrobromide, ispaghula husk, levoglutamide, loperamide, potassium, nystatin, and fat/carbohydrates/protein enteral feeding. Additional concomitant medications per the SAE form included amlodipine, dalteparin, and morphine.

One day prior to study entry, the patient was hospitalized with signs and symptoms of pneumonia, and treated with cefepime (stopped Study Day 1). The patient began treatment with vancomycin on (b) (6) (Study Day 1). Baseline (Study Day 1) serum creatinine

was 0.3 mg/dL (reference range 0.4-1.4 mg/dL). On Study Day 4, a respiratory culture was positive for MRSA. Serum creatinine was 1.6 mg/dL on Study Day 7, increasing to 2.8 mg/dL on Study Day 8. Renal insufficiency was diagnosed and study medication was discontinued. End-of-therapy clinical response was assessed as indeterminate due to SAE-related early withdrawal. Per the SAE form, the patient was transferred to a state hospital (b) (6). She experienced a slow but progressive recovery from the HAP and renal insufficiency with relatively normal potassium. The patient's last recorded serum creatinine level was 4.8 mg/dL on Study Day 15 (local laboratory value, reference range not provided). Serum creatinine values are presented in the table below.

| Study Day | Serum Creatinine (mg/dL) |
|-----------|--------------------------|
| 1 | 0.3 |
| 4 | 0.4 |
| 7 | 1.6* |
| 8 | 2.8* |
| 15 | 4.8 [†] |

*Above reference range (central lab reference range 0.5-1.3 mg/dL)

[†]Local laboratory value. Local lab reference ranges unknown.

FDA Medical Officer Comments: In each of the three cases above, there was a temporal association between study drug exposure and the onset of progressive renal insufficiency. All had complicated medical conditions prior to or concomitant with the onset of the event. There was no information provided regarding intercurrent events that could have contributed to the onset of renal impairment, such as prolonged hypotension. There was no information as to whether a diagnostic evaluation was conducted to determine the etiology of the renal impairment. None of the patients appeared to have been treated with diuretics, such as furosemide, that could have caused prerenal azotemia. The renal impairment resolved in the telavancin-treated patients, whereas there was insufficient follow-up data provided with respect to the vancomycin-treated patient to determine that patient's outcome.

RIFLE Categorization of Acute Kidney Injury

Acute kidney injury (AKI) is a serious complication for critically ill patients that may underpin the need for dialysis. A classification scheme has been published based on the acronym RIFLE: Risk, Injury, Failure, Loss, and End stage kidney disease, and separate criteria have been established for each stratum based on changes in glomerular filtration rate or changes in urine output (15). The following table summarizes the categorization based on changes in glomerular filtration rate and urine output:

Table 134: Summary Table of the RIFLE Classification of Acute Kidney Injury*

| RIFLE Category | RIFLE Class | GFR Criteria | Urine Output Criteria |
|----------------|-------------|---|---|
| Severity | Risk | 1.5 fold-↑ serum Creatinine or GFR↓>25% | Urine output < 0.5 ml/kg/h X 6 hr |
| | Injury | 2 fold-↑ serum Creatinine or GFR↓>50% | Urine output < 0.5 ml/kg/h X 12 hr |
| | Failure | 3 fold-↑ serum Creatinine or Serum Creatinine ≥4 with acute rise >0.5 mg/dl | Urine output < 0.3 ml/kg/h X 24 hr or anuria x 12 hr |
| Outcome | Loss | Persistent ARF (>4 weeks) | |
| | ESRD | ESRD > 3 months | |

*adapted from *Critical Care* 2004;8:R204-R212.

GFR=glomerular filtration rate; ARF=acute renal failure; ESRD=end stage renal disease

Published studies have suggested that there is an increased risk of mortality associated with each progressive level in the classification system (16).

Using the RIFLE categorization, the following table depicts the FDA Medical Officer’s classification of the patients in Studies 0015 and 0019 who developed AKI. Of note, the FDA Medical Officer identified patients who were misclassified by the Applicant in their analysis. Based on the RIFLE-F criteria, which includes patients in whom the serum creatinine is greater than or equal to 4.0 mg/dL in the setting of an acute increase of at least 0.5 mg/dL in serum creatinine despite a <3-fold increase in creatinine from baseline, 12 patients in Study 0015 and 11 patients in Study 0019 were reclassified by this FDA Medical Officer from “none”, “injury”, “min risk”, or “risk” according to the Applicant’s analysis to the RIFLE-F (Failure) category.

Table 135: FDA Medical Officer Table of Patient Counts for RIFLE Severity Categories, Studies 0015 and 0019, AT Population

| Study | Treatment Group | RIFLE Severity Categories | | |
|-------|-----------------|---------------------------|-------------|--------------|
| | | Risk n | Injury n | Failure n |
| 0015 | Telavancin | 44 | 28 | 30 |
| | Vancomycin | 31 | 20 | 20 |
| 0019 | Telavancin | 39 | 27 | 26 |
| | Vancomycin | 35 | 20 | 19 |

n = patient count

As depicted in the table above, for each of the RIFLE severity categories of Risk, Injury, and Failure, there was a higher number of patients in the telavancin treatment group compared to the vancomycin treatment group of both trials. Although the differences were not statistically significant, the imbalances in patient counts raise concern about the potential nephrotoxicity of telavancin.

Pulmonary Embolism

There were a total of 10 patients who experienced pulmonary embolism as a TEAE in the two telavancin NP studies, including two patients in Study 0015 and eight patients in Study 0019. Eight of the 10 patients were telavancin-treated (two from Study 0015 and six from Study 0019) and two were vancomycin-treated (both from Study 0019). The following table summarizes various characteristics of the patients who developed a pulmonary embolism:

Table 136: FDA Medical Officer Summary Table of Patients with Pulmonary Embolism as a TEAE, Studies 0015 and 0019, AT Population

| Study | Subject # | Age/Race/Gender | Treatment | I.V. Study Drug Duration | AE Study Day | Serious | Severity | Action taken | Related Category* | Outcome |
|------------|------------|-----------------|-----------|--------------------------|--------------|---------|-------------|--------------|-------------------|---------------------|
| Study 15 | 01014-4037 | 81/F/W | TLV | 16 | (b) (6) | YES | Severe | None | Not related | Death |
| | 18000-4505 | 79/M/W | TLV | 6 | | no | Moderate | DC | Not related | Present & unchanged |
| Study 19 | 02019-6007 | 77/F/W | VAN | 14 | | no | Moderate | None | Not related | Improving |
| | 25023-6422 | 55/M/W | TLV | 3 | | YES | Severe | None | Not related | Death |
| | 25024-6479 | 77/M/W | TLV | 3 | | YES | Severe | None | Not related | Death |
| | 38051-6374 | 69/M/W | TLV | 4 | | YES | Severe | None | Not related | Recovered |
| | 38051-6374 | 69/M/W | TLV | 4 | | YES | Severe | None | Not related | Recovered |
| | 40001-6098 | 76/F/AIA | TLV | 4 | | YES | Severe | None | Not related | Death |
| | 47001-6601 | 85/M/W | TLV | 11 | | YES | Severe | None | Not related | Death |
| | 47002-6845 | 31/M/W | VAN | 15 | | YES | Severe | None | Not related | Death |
| 50001-6410 | 80/M/W | TLV | 2 | YES | Severe | None | Not related | Death | | |

*investigator's assessment; W=White, AIA=American Indian/Alaskan; M=male, F=female; AE=adverse event
 TLV=telavancin; VAN=vancomycin

Eight patients experienced a pulmonary embolism (PE) that was assessed as a serious TEAE by investigators; seven were telavancin-treated and one was vancomycin treated. Seven of the eight

patients who experienced a PE as a SAE subsequently died. In some cases, there was a temporal association between telavancin administration and the development of a PE; in three other cases, the onset of the event was ≥ 8 days post-EOT. There were also important concurrent factors and underlying medical conditions that may have affected the likelihood for this complication to occur and confounded causality assessment in some patients.

The Applicant's narratives for the eight patients who experienced pulmonary embolism as a serious TEAE are provided below. Some of the narratives provided by the Applicant did not provide sufficient detail to assess causality.

1) Patient 0015-01014-4037 was an 81-year-old Hispanic female enrolled in Study 0015 and randomly assigned to telavancin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-susceptible *S. aureus* (MSSA). Telavancin therapy ended [REDACTED] (b) (6), for a total exposure of 16 days.

Significant medical history included anemia, arrhythmia, cholecystectomy, CHF, high alkaline phosphatase, high serum lactic dehydrogenase (LDH), left carotid artery obstruction, low serum albumin, and overweight.

Recent medical conditions included anemia (2005-cont), dehydration (17 August 2005-cont), HAP ([REDACTED] (b) (6)-cont), hypokalemia (23 August-24 August 2005), shoulder fracture [REDACTED] (w) (u)-cont), and UTI (16 August-23 August 2005).

Concomitant medications included furosemide, ranitidine, heparin, atenolol, amiodarone, triflusal, midazolam, dopamine, diclofenac, metoclopramide, and haloperidol.

Eight days prior to study entry, the patient was treated with ciprofloxacin for a UTI. Treatment ceased on Study Day -2. The patient was hospitalized on [REDACTED] (b) (6) for HAP and started telavancin and aztreonam on that day. At that time, the patient had a PaO₂ 64 mmHg (FiO₂ 21%), PaCO₂ 35 mmHg, and an arterial pH of 7.43. Baseline serum creatinine was 0.9 mg/dL (reference range 0.4-1.4 mg/dL). Aztreonam was discontinued on Study Day 7. On Study Day 8, the patient was reported to have mild renal impairment although her serum creatinine was stable (1.0 mg/dL). On Study Day 15, the patient had improvement in signs and symptoms of pneumonia. Per the SAE form, on that same day, the patient complained of sudden dyspnea and tachypnea and had an oxygen saturation of 70% (decreased from 83% as of 05 September 2005), PaO₂ 37 mmHg, PaCO₂ 31 mmHg with FiO₂ 21% requiring mechanical ventilatory support. A helical CT scan was performed which showed a pulmonary embolus (information per the SAE form); pulmonary embolism and respiratory arrest were diagnosed. The patient was treated with heparin, sodium bicarbonate, and salbutamol. Per the SAE form, hypotension developed and dopamine was started. An ECG showed no significant changes. The respiratory arrest resolved the same day. On Study Day 16, D-dimer results were 1000 (local lab result; reference range 0-250). Telavancin therapy was completed on Study Day 16 due to resolution of signs and symptoms of pneumonia. End-of-therapy clinical response was assessed as cured. On [REDACTED] (b) (6)

the patient expired due to the pulmonary embolus. No autopsy was performed. The renal impairment was continuing at the time of the patient's death.

FDA Medical Officer Comments: The patient was diagnosed with a PE by CT scan on Day 15, one day prior to completion of the course of study drug. Although prolonged bedrest secondary to pneumonia may have been a contributory factor, there was a temporal association with telavancin exposure. There was insufficient information as to whether other predisposing factors existed for the development of a PE.

2) Patient 0019-25023-6422, a 55-year-old white male, was enrolled in Study 0019 and randomly assigned to telavancin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found due to methicillin-susceptible *S. aureus* (MSSA) and *Haemophilus influenzae*. Telavancin therapy ended on [REDACTED] (b) (6), for a total exposure of three days.

Significant medical history included COPD, smoking, tuberculosis with left pneumonectomy, and nursing home resident. No recent medical condition was reported. Concomitant medications included clonazepam, dextran, ipratropium bromide/fenoterol hydrobromide, heparin-fraction, methylprednisolone, potassium, spironolactone, and theophylline.

[REDACTED] (b) (6) prior to study entry, the patient was hospitalized for HAP with symptoms of dyspnea and mild peripheral cyanosis per the SAE form. The patient's oxygenation status indicated potential respiratory failure, and he was treated with oxygen therapy and showed improvement. On Study Day -1, the patient was diagnosed with pneumonia, subsequently found to be due to MSSA and *H. influenzae* pneumonia. The patient started telavancin on [REDACTED] (b) (6) (Study Day 1). On [REDACTED] (b) (6), the patient experienced sudden shortness of breath with cyanosis, followed by loss of consciousness and convulsions. Despite resuscitation procedures, the patient died on [REDACTED] (b) (6) due to a pulmonary embolism. Per the SAE form, the patient died from cardiac arrest and based on the sudden onset, pulmonary embolism was diagnosed. No evidence of coronary attack, or stroke was found in the macroscopic examination during the autopsy. A written report of the autopsy confirmed the pulmonary embolism and included findings of pulmonary edema, pneumonia, right pulmonary hemorrhage/infarction, enlargement of the left ventricle, cicatrixes of the myocardium, and cerebral, liver, spleen, and kidney congestion. End-of-therapy clinical response was assessed as indeterminate due to the death.

FDA Medical Officer Comments: The patient was diagnosed with a PE on [REDACTED] (b) (6) of the course of study drug and died. Although prolonged bedrest may have been a contributory factor, there was a temporal association with telavancin exposure. There was insufficient information as to whether other predisposing factors existed for the development of a PE.

3) Patient 0019-25024-6479, a 77-year-old white male, was enrolled in Study 0019 and randomly assigned to telavancin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found due to methicillin-resistant *S. aureus* (MRSA) and *Proteus vulgaris*. Telavancin therapy ended on [REDACTED] (b) (6), for a total exposure of three days.

Significant medical history included COPD, gastrectomy due to perforation (M Hoffmeister-Finsterer), smoking, and obliterative atheromatosis. An additional medical history per the SAE form was cachexia. Recent medical conditions included circulatory failure (28 September 2006-cont), laryngeal carcinoma (--September 2006-cont), total laryngectomy (29 September 2006), arterial hypertension (03 October 2006-cont), and MRSA surgical wound with purulent infiltration due to total laryngectomy (b) (6). Concomitant medications included aminophylline, bromhexine, furosemide, heparin-fraction, losartan, paracetamol, pentoxifylline, potassium, spironolactone, theophylline, and verapamil.

The patient had been hospitalized for total laryngectomy (b) (6) prior to study entry, and was previously treated with cefuroxime for surgical wound infection from (b) (6) to (b) (6). On (b) (6) the patient was hospitalized with a diagnosis of pneumonia (later found to be due to MRSA and *P. vulgaris*) and was treated with telavancin. On Study Day 1, the patient had a fever of 38.2 °C, and his laboratory values included potassium 3.23 mmol/L (local laboratory value [reference range 3.59-5.53 mmol/L]), serum creatinine 0.9 mg/dL (central laboratory reference range 0.5-1.6 mg/dL), and pH 7.41 (local laboratory value [reference range 7.35-7.45]). On Study Day 2, the patient had a fever of 38.0 °C and was stable. Blood cultures grew *Staphylococcus hominis* (central laboratory) and *Staphylococcus epidermidis* (local laboratory) on Study Day 2. On (b) (6) the patient died suddenly from a pulmonary embolism. No autopsy was performed. Cause of death per the Death Report was suspicion of pulmonary embolism. End-of-therapy clinical response was assessed as indeterminate due to death.

FDA Medical Officer Comments: The patient was diagnosed with a PE on (b) (6) of the course of study drug and died. Despite the temporal association of telavancin administration, the patient had predisposing risk factors for the development of PE that confounded causality assessment (prolonged bedrest and carcinoma).

4) Patient 0019-38051-6374, a 69-year-old white male, was enrolled in Study 0019 and randomly assigned to telavancin on (b) (6) for the treatment of HAP, subsequently found to be due to *Klebsiella oxytoca*. Telavancin therapy ended on (b) (6) for a total exposure of four days.

Significant medical history included abdominal aortic aneurysm, anemia, depression, gastroesophageal reflux disease, hearing loss, hypertension, mesenteric artery rupture, Parkinson's disease, squamous cell cancer of the tonsil with chemotherapy and radiation, and smoking. Recent medical conditions included coronary disease (13 September 2006-cont), left hip fracture (b) (6) elevated creatine phosphokinase (07 November 2006-cont), aspiration pneumonia (07 November 2006-cont), respiratory alkalosis (07 November 2006-cont), heparin-induced thrombocytopenia (07 November 2006-cont), open reduction internal fixation left hip fracture (b) (6) post-op pain (b) (6) cont), agitation (08 November 2006-

cont), anxiety (08 November 2006-cont), constipation secondary to Parkinson's disease (08 November 2006-cont), electrolyte imbalance (08 November 2006-cont), and malnutrition (08 November 2006-cont). Concomitant medications included paracetamol, acetylcysteine, salbutamol, argatroban, bisacodyl, bupivacaine, carbidopa/levodopa, sodium amidotrizoate and meglumine amidotrizoate, diphenhydramine, docusate, heparin-fraction, entacapone, other anti-anemic preparation, felodipine, fentanyl, haloperidol, ipratropium, lansoprazole, lisinopril, lorazepam, magnesium oxide, metoclopramide, metoprolol, midazolam, magnesium hydroxide, morphine, norepinephrine, nystatin, omeprazole, oxycodone hydrochloride/acetaminophen, RBCs, phenylephrine, phytomenadione, potassium, pramipexole, propofol, plantago afra, quetiapine, ranitidine, risperidone, and warfarin.

(b) (6) prior to study entry, the patient was hospitalized with a fractured left hip and underwent surgical repair via open reduction with internal fixation. (b) (6) prior to study entry, he was diagnosed with *K. oxytoca* pneumonia. On 08 November 2006 (Study Day 1), treatment with telavancin and piperacillin/tazobactam were started. On Study Day 2, a CT scan of the thorax showed a pulmonary embolism in the left upper lobe of undetermined age. He was treated with argatroban. Aztreonam was added to the antimicrobial regimen on Study Day 2 and he was noted to be fluid overloaded, which resolved the same day. On Study Day 4, telavancin was discontinued because consent was withdrawn and the patient was treated with vancomycin from Study Day 5 through Study Day 20. Additional antimicrobial treatment included erythromycin from Study Day 12 to Study Day 25 and ciprofloxacin on Study Day 18. On Study Day 23, a repeat CT scan showed the left pulmonary embolism had completely resolved; however, a new pulmonary embolism in the right lower lobe was present, which completely resolved on Study Day 47. End-of-therapy (Study Day 4) and TOC (Study Day 29) clinical responses were assessed as indeterminate due to consent withdrawal after 4 days.

FDA Medical Officer Comments: A PE was diagnosed on Day 2 of telavancin therapy, and a second PE was diagnosed 21 days after EOT. Despite the temporal association of telavancin administration, the patient had predisposing risk factors for the development of PE that confounded causality assessment (recent open reduction internal fixation of the left hip).

5) Patient 0019-40001-6098, a 76-year-old American Indian/Hispanic female, was enrolled in Study 0019 and randomly assigned to telavancin on (b) (6) for the treatment of HAP (organism not specified). Telavancin therapy ended on (b) (6), for a total exposure of four days.

Significant medical history included abdominal hernioplasty and diabetes mellitus (Type 2). Recent medical condition was intertrochanteric fracture of left hip (b) (6)-cont). Concomitant medications included heparin-fraction, paracetamol, and tramadol. Additional concomitant medications per the SAE form included dobutamine and insulin.

(b) (6) prior to study entry, the patient was hospitalized due to left hip intratrochanteric fracture. Prior to study entry, the patient received ceftriaxone from Study Day -2 to Study

Day -1 and trimethoprim/sulfamethoxazole from Study Day -1 to Study Day 1 for pneumonia. On [REDACTED] (b) (6) [REDACTED] (b) (6) the patient began treatment with telavancin. On [REDACTED] (b) (6), the patient experienced a massive pulmonary embolism that led to her death. An autopsy was not performed. End-of-therapy clinical response was assessed as indeterminate due to death.

FDA Medical Officer Comments: Despite the temporal association of telavancin administration, the patient had predisposing risk factors for the development of PE that confounded causality assessment (left hip intratrochanteric fracture).

6) Patient 0019-47001-6601, an 85-year-old white male, was enrolled in Study 0019 and randomly assigned to telavancin on [REDACTED] (b) (6) for treatment of HAP, subsequently found due to methicillin-resistant *S. aureus* (MRSA), *Pseudomonas aeruginosa*, and *Escherichia coli*. Telavancin therapy ended on [REDACTED] (b) (6), for a total exposure of 11 days.

Significant medical history included prostatic adenoma. Recent medical conditions included hemorrhagic stroke of right hemisphere [REDACTED] (b) (6)-cont), hemorrhagic vasculitis (Henoch-Schonlein like; [REDACTED] (b) (6)-cont), and UTI (04 January 2007-cont). Per the SAE form, an additional medical condition was left side hemiparesis. Concomitant medications included epinephrine, atropine, dexamethasone, diclofenac, dopamine, ferrous sulfate/folic acid/vitamin C/vitamin B12, ferric hydroxide polymalt, fluconazole, heparin-fraction, heparin, chloropyramine, and sucralfate.

[REDACTED] (b) (6) the patient was hospitalized with a hemorrhagic stroke in the right hemisphere. On Study Day -12, the patient began treatment with amikacin (Study Day -12 to Study Day -1) for UTI. On Study Day -11, he started treatment for HAP with ciprofloxacin [REDACTED] (b) (6) and piperimic acid (Study Day -11 to Study Day -1). On Study Day -1, respiratory cultures were obtained (subsequently positive for MRSA, *Pseudomonas aeruginosa*, and *Escherichia coli*.) and blood cultures taken on the same day showed no growth. On [REDACTED] (b) (6) (Study Day 1), the patient began treatment with telavancin. On [REDACTED] (b) (6), per the SAE form, he had a femoral catheter inserted for intravenous administration, which resulted in an ileofemoral venous thrombosis of the right leg (confirmed by Doppler ultrasound), and the patient was started on enoxaparin and piperacillin/tazobactam (Study Day 7 to Study Day 11). Platelet count on Study Day 7 was 322,000/mm³. On [REDACTED] (b) (6), the patient developed a pulmonary artery thrombosis and died despite treatment with dopamine, adrenaline, and atropine. No autopsy was performed. End-of-therapy clinical response was assessed as failure due to persistence or progression of signs and symptoms.

FDA Medical Officer Comments: Despite the temporal association of telavancin administration, the patient had predisposing risk factors for the development of PE that confounded causality assessment (ileofemoral venous thrombosis of the right leg).

7) Patient 0019-47002-6845, a 31-year-old white male, was enrolled in Study 0019 and randomly assigned to vancomycin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found due to *Acinetobacter calcoaceticus*. Vancomycin therapy ended on [REDACTED] (b) (6), for a total exposure of 15 days.

Significant medical history included smoking. Recent medical conditions included open head trauma [REDACTED] (b) (6), brain contusion [REDACTED] (b) (6), fracture of occipital bone [REDACTED] (b) (6), decompressive trepanation [REDACTED] (b) (6), evacuation of subdural hematoma [REDACTED] (b) (6) and traumatic subdural hematoma of right fronto-temporal area [REDACTED] (b) (6).

Concomitant medications included epinephrine, atropine, bisacodyl, carbamazepine, choline alfoscerate, citicoline, dexamethasone, diclofenac, dopamine, heparin-fraction, plasma protein fraction, furosemide, hydrotalcite, lactulose, levodopa, mannitol, metamizole, phenylephrine, piracetam, and RBCs.

On [REDACTED] (b) (6) the patient was hospitalized for open head trauma, brain contusion, and fracture of occipital bone. On Study Day -2, the patient began treatment with ceftriaxone (Study Day -2 to Study Day 1) and amikacin (Study Day -2 to Study Day -1). On [REDACTED] (b) (6) (Study Day 1), respiratory cultures were obtained (subsequently positive for *Acinetobacter calcoaceticus*), and the patient began therapy with vancomycin and aztreonam (Study Day 1 to Study Day 8). On Study Day 8, respiratory cultures were positive for methicillin-resistant *S. aureus* (MRSA) and *Escherichia coli*. On Study Day 8, the dosing for aztreonam was changed from 1 g twice daily to 2 g twice daily (Study Day 8 to Study Day 15). On Study Day 15, respiratory cultures were positive for *Acinetobacter calcoaceticus* and *Klebsiella pneumoniae*, and he began therapy with moxifloxacin (Study Day 15 to Study Day 27) and cefepime (Study Day 15 to Study Day 21). On Study Day 15, vancomycin therapy ended due to an unsatisfactory therapeutic response. On Study Day 22, he began therapy with amikacin (Study Day 22 to Study Day 26). On [REDACTED] (b) (6) the patient had a pulmonary embolism and died as a result of the event. No autopsy was performed. End-of-therapy clinical response was assessed as failure due to persistence or progression of signs and symptoms of pneumonia.

FDA Medical Officer Comments: The patient was diagnosed with a PE 12 days following completion of vancomycin therapy. The patient had predisposing risk factors for the development of PE that confounded causality assessment (recent trauma and prolonged bedrest for treatment of head trauma/subdural hematoma and NP).

8) Patient 0019-50001-6410, an 80-year-old white male, was enrolled in Study 0019 and randomly assigned to telavancin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found due to *Proteus mirabilis*. Telavancin therapy ended on [REDACTED] (b) (6), for a total exposure of 2 days.

Significant medical history included hypertension and smoking. Recent medical conditions included thoracic injury [REDACTED] (b) (6), chronic compensated cardiomyopathy (28 September 2006-cont), gastrointestinal ulcer (19 October 2006-cont), anemia (24 October

2006-cont), inguinal hernia (24 October 2006- cont), and acute renal insufficiency ((b) (6) -cont). Concomitant medications included human albumin, aminophylline, blood and related products, fenoterol with ipratropium, oxygen, and pantoprazole.

On (b) (6), the patient was hospitalized for pneumonia. Prior to study enrollment, the patient experienced acute renal insufficiency, anemia, gastric ulcer, HAP, stool positive for blood, and an elevated serum creatinine. Prior to study entry, the patient received cefuroxime (Study Day -1 to Study Day 1) and amikacin (Study Day -1 to Study Day 1). On (b) (6) (Study Day 1), the patient began treatment with telavancin. However, since Study Day 1 respiratory and blood cultures were positive for Gram-negative bacteria, *Proteus mirabilis* (susceptible to aztreonam), study medication was discontinued because Gram-positive coverage was no longer indicated. Study Day 1 serum creatinine was 10.3 mg/dL (reference range 0.5-1.6 mg/dL). On Study Day 2, the patient started treatment with aztreonam (Study Day 2 to Study Day 3). On Study Day 3, serum creatinine was 9.9 mg/dL and hemodialysis was started. He was treated with cefepime (Study Day 3 only). On Study Day 4, treatment with ceftazidime (Study Day 4 to Study Day 10) was started. Per the SAE form, on Study Day 4, his D-dimer test was 6864 ng/mL (local laboratory reference range < 250 ng/mL), and serum albumin was 18 g/L (local laboratory reference range 36-53 g/L). On Study Day 8, treatment with meropenem (Study Day 8 to Study Day 10) was started. On Study Day 10, serum creatinine remained elevated (5.26 mg/dL) and hemoglobin was 73 g/L (reference range 125-170 g/L). On Study Day 10, the patient developed pain and swelling of the left leg, dyspnea, tachypnea, and severe hypoxia. On (b) (6) the patient died due to a pulmonary embolus. No autopsy was performed. End-of-therapy clinical response was assessed as indeterminate since cultures only revealed Gram-negative pathogens.

FDA Medical Officer Comments: PE developed eight days post-therapy in this patient. Causality assessment was confounded by prolonged bedrest and multiple medical conditions.

Serious Cardiac Adverse Events

The two tables below summarize the serious cardiac adverse events by preferred term in Studies 0015 and 0019. There were 18 telavancin-treated and 21 vancomycin-treated patients in Study 0015 who experienced serious cardiac adverse events. In Study 0019, 12 telavancin-treated and 20 vancomycin-treated patients experienced such events. Of note, no patients treated with either study medication experienced Torsades de pointes, although there was an imbalance in the number of patients who experienced a cardiac arrest in Study 0019 (5 telavancin-treated compared to no vancomycin-treated patients) .

Table 137: FDA Medical Officer Table of Patient Count* with Serious Cardiac TEAE stratified by Preferred Term, Study 0015, AT Population

| Preferred term | Study 0015 | |
|------------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
| ACUTE CORONARY SYNDROME | 1 (0.27%) | 0 (0.00%) |
| ANGINA UNSTABLE | 1 (0.27%) | 0 (0.00%) |
| ATRIAL FIBRILLATION | 2 (0.54%) | 3 (0.80%) |
| ATRIOVENTRICULAR BLOCK COMPLETE | 1 (0.27%) | 0 (0.00%) |
| BRADYCARDIA | 2 (0.54%) | 1 (0.27%) |
| CARDIAC ARREST | 2 (0.54%) | 4 (1.07%) |
| CARDIAC FAILURE | 1 (0.27%) | 2 (0.53%) |
| CARDIAC FAILURE CONGESTIVE | 4 (1.08%) | 3 (0.80%) |
| CARDIOGENIC SHOCK | 1 (0.27%) | 0 (0.00%) |
| CARDIO-RESPIRATORY ARREST | 1 (0.27%) | 0 (0.00%) |
| CORONARY ARTERY DISEASE | 0 (0.00%) | 1 (0.27%) |
| LEFT VENTRICULAR FAILURE | 0 (0.00%) | 1 (0.27%) |
| MYOCARDIAL INFARCTION | 1 (0.27%) | 1 (0.27%) |
| MYOCARDIAL ISCHAEMIA | 2 (0.54%) | 1 (0.27%) |
| SUPRAVENTRICULAR TACHYCARDIA | 0 (0.00%) | 1 (0.27%) |
| VENTRICULAR FIBRILLATION | 0 (0.00%) | 2 (0.53%) |
| VENTRICULAR TACHYCARDIA | 1 (0.27%) | 3 (0.80%) |
| Subjects(total) | 18 (4.84%) | 21 (5.61%) |

* Patients could be counted more than once.

Table 138: FDA Medical Officer Table of Subject Count with Serious Cardiac TEAE stratified by Preferred Term, Study 0019, AT Population

| Preferred term | Study 0019 | |
|-----------------------------|------------------------------|------------------------------|
| | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| ACUTE CORONARY SYNDROME | 0 (0.00%) | 1 (0.26%) |
| ACUTE MYOCARDIAL INFARCTION | 0 (0.00%) | 2 (0.53%) |
| ATRIAL FIBRILLATION | 2 (0.53%) | 2 (0.53%) |
| BRADYCARDIA | 0 (0.00%) | 2 (0.53%) |
| CARDIAC ARREST | 5 (1.32%) | 0 (0.00%) |
| CARDIAC FAILURE | 1 (0.26%) | 3 (0.79%) |
| CARDIAC FAILURE ACUTE | 1 (0.26%) | 0 (0.00%) |
| CARDIAC FAILURE CONGESTIVE | 0 (0.00%) | 7 (1.85%) |
| CARDIOGENIC SHOCK | 1 (0.26%) | 2 (0.53%) |
| CARDIOPULMONARY FAILURE | 0 (0.00%) | 1 (0.26%) |
| CARDIOVASCULAR DISORDER | 0 (0.00%) | 1 (0.26%) |
| ISCHAEMIC CARDIOMYOPATHY | 1 (0.26%) | 0 (0.00%) |
| MYOCARDIAL INFARCTION | 1 (0.26%) | 0 (0.00%) |
| PERICARDIAL EFFUSION | 1 (0.26%) | 0 (0.00%) |
| VENTRICULAR FIBRILLATION | 1 (0.26%) | 0 (0.00%) |
| WANDERING PACEMAKER | 1 (0.26%) | 0 (0.00%) |
| Subjects(total) | 12 (3.17%) | 20 (5.29%) |

* Patients could be counted more than once.

Hy's Rule for Hepatotoxicity

Evidence of presumed hepatocellular injury (i.e., increased serum ALT or AST levels) with no concomitant increase in alkaline phosphatase levels) plus reduced liver function (increased total serum bilirubin levels) occurring simultaneously may indicate drug induced hepatotoxicity. Hy's Law refers to the concurrent findings of ALT $\geq 3 \times$ ULN and total bilirubin $>2 \times$ ULN with alkaline phosphatase $<2 \times$ ULN as indicative of potential drug-related hepatotoxicity.

Table 139: FDA Medical Officer Summary Table of Subject Count who met Hy's Rule for Hepatotoxicity, Studies 0015 and 0019, AT Population

| | Study 0015 | | Study 0019 | |
|---|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| fulfilled Hy's Rule | 6 (1.6%) | 7 (1.9%) | 5 (1.3%) | 5 (1.3%) |
| fulfilled Hy's Rule at baseline | 3 (0.8%) | 2 (0.5%) | 2 (0.5%) | 2 (0.5%) |
| fulfilled Hy's Rule and experienced a 2-grade toxicity increase | 2 (0.5%) | 4 (1.1%) | 2 (0.5%) | 1 (0.3%) |

*Hy's Rule: ALT $\geq 3 \times$ ULN and Total Bilirubin $>2 \times$ ULN with Alkaline Phosphatase $<2 \times$ ULN

As depicted in the table above, a total of 23 patients fulfilled Hy’s Rule, including 13 patients in Study 0015 and 10 patients in Study 0019. Nine patients (five of the 13 patients in Study 0015 and four of the 10 patients in Study 0019) fulfilled Hy’s Rule at baseline prior to exposure to study medication, whereas 14 patients (eight in Study 0015 and six in Study 0019) fulfilled Hy’s Rule post-baseline. Some patients fulfilled Hy’s Rule and experienced a 2-grade toxicity increase. The following table summarizes the affected patients:

Table 140: FDA Medical Officer Summary Table of all Subjects who fulfilled Hy's Rule, Studies 0015 and 0019 (pooled total subject count, n=23)

| Subject # | Treatment | Fulfilled Hy’s Rule at Baseline | 2-grade toxicity increase |
|-----------------|------------|---------------------------------|---------------------------|
| 0015-33402-4714 | TELAVANCIN | X | |
| 0015-38024-4772 | VANCOMYCIN | X | AST |
| 0015-38348-4251 | VANCOMYCIN | X | |
| 0015-41009-4504 | TELAVANCIN | X | |
| 0015-41016-4683 | TELAVANCIN | X | |
| 0019-18004-6140 | VANCOMYCIN | X | |
| 0019-20002-6562 | TELAVANCIN | X | |
| 0019-34003-6237 | VANCOMYCIN | X | |
| 0019-44001-6513 | TELAVANCIN | X | |
| 0015-01012-4133 | TELAVANCIN | | AST |
| 0015-02011-4057 | VANCOMYCIN | | |
| 0015-18000-4117 | VANCOMYCIN | | |
| 0015-38020-4244 | TELAVANCIN | | ALT |
| 0015-38024-4496 | VANCOMYCIN | | T BILI |
| 0015-41000-4416 | VANCOMYCIN | | ALT, T BILI |
| 0015-41001-4542 | VANCOMYCIN | | ALT, T BILI |
| 0015-41009-4501 | TELAVANCIN | | |
| 0019-01021-6340 | TELAVANCIN | | |
| 0019-02028-6613 | VANCOMYCIN | | |
| 0019-18004-6197 | VANCOMYCIN | | T BILI |
| 0019-38341-6384 | TELAVANCIN | | AST |
| 0019-40001-6396 | VANCOMYCIN | | |
| 0019-44009-6485 | TELAVANCIN | | AST, ALT |

ALT=alanine aminotransferase, AST=aspartate aminotransferase
 T BILI=total bilirubin

The Applicant’s narratives for the patients who fulfilled Hy’s Rule post-baseline are provided below for completeness. In general, despite a temporal association with study drug administration, some of the narratives lacked sufficient detail regarding the patients’ hepatic impairment to permit an assessment of causality.

1) Patient 0015-01012-4133, a 23-year-old Hispanic male, was enrolled in Study 0015 and randomized to telavancin on (b) (6) for the treatment of HAP. Telavancin therapy ended on (b) (6), for a total exposure of eight days.

Medical history is significant for altered coagulation parameters (b) (6)-cont), anemia (01 January 2006-cont), excitatory episodes brain injury (b) (6)-cont), hyperbilirubinemia (06 January 2006-cont), traumatic brain injury (b) (6)-cont), and traumatic cranium bone fractures (b) (6)-cont).

Concomitant medications included plasma protein fraction (altered coagulation parameter), haloperidol (excitatory episodes controlled), ibuprofen (prevent pain due to trauma), magnesium (supplementation), metoclopramide (gastroprorest prophylaxis), midazolam (sedation for mechanical ventilation), morphine (analgesia for brain traumatic), pancuronium (neuromuscular blockage for med), red blood cells (anemia), heparin (deep venous thrombosis prophylaxis), and phytomenadione (altered coagulation parameters).

On (b) (6) (Day -6), the patient was hospitalized for traumatic brain injury and was transferred to the ICU from (b) (6). The patient had a Grade III pneumothorax on (b) (6) (Day 2). The patient's bilirubin was abnormal at baseline and continued to increase until (b) (6) (Day 7). The other liver function tests were normal at baseline but increased over time. On Day 7, the patient was diagnosed with cholestatic hepatitis. By the follow-up visit on Day 18, the bilirubin level had decreased to less than the baseline value but was still abnormal. The AST, ALT, and alkaline phosphatase levels remained elevated at the follow-up visit. See the table below for LFT values:

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 30 | 36 | 31 | 43 | 46 | 21 | 89 | 129 |
| Days 3-5 | 4 | 46 | 36 | 51 | 43 | 56 | 21 | 147 | 129 |
| EOT | 7 | 75 | 36 | 66 | 43 | 113 | 21 | 168 | 129 |
| EOT | 10 | 143 | 36 | 111 | 43 | 97 | 21 | 227 | 129 |
| FU/TOC | 18 | 87 | 36 | 118 | 43 | 38 | 21 | 234 | 129 |

ULN = upper limit of normal

EOT clinical response was assessed as a failure due to persistence or progression of signs and symptoms of pneumonia.

FDA Medical Officer Comments: Concomitant with telavancin exposure, the patient developed increases in AST, ALT, alkaline phosphatase, and bilirubin. No information was provided in terms of a diagnostic evaluation for cholestatic hepatitis and hyperbilirubinemia, such as infectious hepatitis serology and hepatic ultrasound. Additionally, no follow-up laboratory test results were provided beyond Day 18 to assess whether the trend of increasing liver function tests was improving. Although there is a temporal association of telavancin exposure with the hepatic test abnormalities, there was insufficient information to assess causality.

2) Patient 0015-02011-4057, a 70-year-old white female, was enrolled in Study 0015 and randomized to vancomycin on (b) (6) for the treatment of HAP. Vancomycin therapy ended on (b) (6), for a total exposure of seven days.

Medical history is significant for acute ischaemic hepatitis (b) (6) -cont), cecal polyps (2003-cont), chronic constipation (2003-cont), colonoscopy (b) (6), diverticular disease (2003-cont), eye edema (b) (6) -cont), hypercholesterolemia (1985-cont), hypertension (1985-cont), hypotension (b) (6) -cont), laparoscopy (b) (6), oliguria (b) (6) cont), osteoarthritis (1995-cont), polymyalgia rheumatica (1995-cont), right hip hemiarthroplasty (b) (6), right leg edema (b) (6) -cont), septic shock (b) (6) -cont), and sinus ventricular tachycardia (intermittent) (b) (6) -cont).

Concomitant medications included acetazolamide (eye edema), insulin huma (high blood sugar level), adenosine (sinus ventricular tachycardia), epinephrine (hypotension), amiodarone (sinus ventricular tachycardia), ipratropium (decreased air entry to lungs), chloramphenicol (eye oedema), heparin-fraction (deep vein thrombosis prophylaxis), heparin-fraction (thrombosis prophylaxis), clonidine (hypertension), dobutamine (hypotension), fentanyl (pain from fractured neck of femor), furosemide (edema), hydrocortisone (sepsis), metoclopramide (gastrointestinal prophylaxis), metoprolol (hypertension), midazolam (sedation while ventilated), norepinephrine (hypotension), pantoprazole (gut prophylaxis), acetylcysteine (ischaemic hepatitis), prednisolone (polymyalgia rheumatica), propofol (sedation while ventilated), ramipril (hypertension), salbutamol (decreased air entry to lungs), spironolactone (edema), and temazepam (insomnia).

On (b) (6) (Day -7), the patient was hospitalized for fractured neck of the femur and was transferred to the ICU (b) (6) (Day -2) - (b) (6) (Day 14). She experienced elevated blood sugar level on (b) (6) (Day1) - continuing, eye edema from (b) (6) (Day 3) to (b) (6) (Day 12), arm edema (both arms) on (b) (6) (Day 5) - continuing, anemia on (b) (6) (Day 6) - continuing, and insomnia on (b) (6) (Day 12) - continuing. The patient's liver function test levels were elevated at baseline consistent with her existing acute ischaemic hepatitis. The levels decreased while on study treatment. By (b) (6) (Day 15), all values were improved from baseline and approaching normal ranges. See the table below for LFT values.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 1168 | 34 | 704 | 32 | 122 | 21 | 342 | 135 |
| EOT | 5 | 84 | 34 | 213 | 32 | 75 | 21 | 280 | 135 |
| EOT | 7 | 53 | 34 | 119 | 32 | 72 | 21 | 239 | 135 |
| FU/TOC | 15 | 44 | 34 | 58 | 32 | 63 | 21 | 213 | 135 |

ULN = upper limit of normal

End of treatment (Day 7) and TOC (Day 14) clinical responses were assessed as cured.

FDA Medical Officer Comments: The patient had markedly abnormal baseline liver function tests attributed to ischemic hepatitis, which improved during the course of study drug

administration. This resolution of laboratory abnormalities despite study drug exposure makes the diagnosis of drug-induced hepatitis from vancomycin exposure unlikely.

3) Patient 0015-18000-4117, a 69-year-old white male, was enrolled in Study 0015 and randomly assigned to vancomycin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-susceptible *S. aureus* (MSSA). Vancomycin therapy ended on [REDACTED] (b) (6), for a study medication exposure of two days (total vancomycin exposure of five days).

Significant medical history included angina pectoris, CVA, chronic renal failure, diabetes (type unknown), diaphragmatic hernia, hyperlipidemia, hypertension, ischemic heart disease, MI x 2, peripheral neuropathy, peptic ulcer, peripheral vascular disease, esophageal reflux, percutaneous transluminal coronary angioplasty x 4, smoking, and weight loss. Recent medical conditions included decubitus ulcer ([REDACTED] (b) (6)-cont), elevated hepatic enzymes ([REDACTED] (b) (6)-cont), gait problem (October 2005-cont), macroalbuminuria (October 2005-cont), rapid atrial fibrillation ([REDACTED] (b) (6)), and right-sided weakness (October 2005-cont).

Concomitant medications included epinephrine (septic shock treatment), atenolol (hypertension), enalapril (hypertension), heparin-fraction (deep vein thrombosis prevention), heparin-fraction (pulmonary embolism prevention), etomidate (anesthesia induction), fentanyl (adjunct to general anesthesia), furosemide (oliguria due to renal insufficiency), heparin (pulmonary embolism prevention), hydrocortisone (bronchospasm), hydrocortisone (septic shock), insulin (diabetes mellitus), ipratropium (bronchospasm), metformin (diabetes), metoprolol (rapid atrial fibrillation), midazolam (induction and maintenance of anesthesia), glyceryl trinitrate (microcirculation alterations in sepsis), norepinephrine (blood pressure control), nystatin (mouth fungal prevention), omeprazole (ulcer disease), pentoxifylline (peripheral vascular disease), ranitidine (gastrointestinal bleeding), simvastatin (hyperlipidemia), tramadol (pain), vecuronium (muscle relaxation for mechanical ventilation), and verapamil (rapid atrial fibrillation).

[REDACTED] (b) (6) prior to study entry, the patient was hospitalized for a right femur fracture. Prior to study entry, the patient received vancomycin and ciprofloxacin for bacteremia on Study Day -1 and from Study Day -1 to Study Day 1, respectively. The patient began treatment with vancomycin and aztreonam on [REDACTED] (b) (6) (Study Day 1). Baseline (Study Day 1) serum creatinine was 2.7 mg/dL (reference range 0.5-1.3 mg/dL). The patient was alert and hemodynamically stable upon recruitment; however, on Study Day 2, the patient experienced septic shock and multi-organ failure. That day, serum creatinine was 2.4 mg/dL. Blood cultures continued to be positive for MSSA. On Study Day 2, the study medication was discontinued due to multi-organ failure. End-of-therapy clinical response was assessed as indeterminate due to study medication discontinuation related to multi-organ failure. The patient began treatment for bacteremia with vancomycin from Study Day 3 to Study Day 4 and cloxacillin from Study Day 4 to Study Day 10. The patient's condition continued to deteriorate. On [REDACTED] (b) (6), the patient died due to multi-organ

failure. The Investigator assessed the septic shock, multi-organ failure and subsequent patient death to be not related to study medication. The Sponsor agrees with this assessment, and notes that the patient entered the study with a medical history of disease in multiple major organs. Study medication was administered only 2 days before withdrawal, so the anti-infective effects of study medication in this patient are indeterminate. The patient's medical history included elevated hepatic enzymes (Day -1). LFT values during the study are displayed in the table below. While the lab values on Day 2 fulfill the criteria for Hy's Law, they are consistent with multi-organ failure (Days 2-10).

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | | | | | | | 164 | 125 |
| EOT | 2 | 207 | 36 | 552 | 35 | 46 | 21 | 159 | 125 |

ULN = upper limit of normal

FDA Medical Officer Comments: Although the baseline LFT values were not provided, the laboratory results from Day 2 fulfilled Hy's Rule. However, the abnormal Day 2 results coincided with the onset of septic shock and multi-organ failure associated with a staphylococcal bacteremia. In view of the short duration of vancomycin exposure and the deterioration in clinical status on Day 2 from sepsis, it is unlikely that the LFT abnormalities could be attributed to vancomycin exposure.

4) Patient 0015-38020-4244, a 31-year-old white male, was enrolled in Study 0015 and randomized to telavancin on (b) (6) for the treatment of HAP. Telavancin therapy ended on (b) (6), for a total exposure of 10 days.

Medical history is significant for acute central hypoventilation ((b) (6)-cont), agitation ((b) (6)-cont), aspiration ((b) (6)-cont), hyperglycemia (not diabetes mellitus) ((b) (6)-cont), hypokalemia ((b) (6)-cont), hypomagnesemia ((b) (6)-cont), respiratory failure ((b) (6)-cont), tracheal edema ((b) (6)-cont), tracheal resection ((b) (6)-cont), tracheal stenosis ((b) (6)-cont), and tracheostomy ((b) (6)).

Concomitant medications included galenic/paracetamol/codeine (pain), salbutamol (pneumonia), ipratropium (pneumonia), darbepoetinalfa (prophylaxis for anemia), dexamethasone (tracheal edema), racepinefrine (tracheal edema), fentanyl (sedation secondary to ventilation), haloperidol (ICU psychosis), magnesium sulfate (hypoPatient magnesium), acetylcysteine (secretions from respiratory tract), nystatin (rash to shoulder), neotracin (wound infection prophylaxis), famotidine (prophylaxis for acidity), potassium (hypokalemia), propofol (sedation secondary to ventilation), metoclopramide (nausea due to HAP secretions), insulin (hyperglycemia), and midazolam (sedation secondary to ventilation).

On (b) (6) (Day -5), the patient was hospitalized for tracheal stenosis and was transferred

to the ICU on the same date through (b) (6) (Day 10). He experienced edema of the upper extremities (b) (6) (Day 3) – (b) (6) (Day 4), re-intubation due to tracheal edema on (b) (6) (Day 4), shoulder rash (b) (6) (Day 5) – (b) (6) (Day 25), pain due to pulling out the Foley catheter on (b) (6) (Day 8) and nausea on (b) (6) (Day 10). The patient was discharged on (b) (6) (Day 12).

The patient’s bilirubin was elevated at baseline. Other liver function test values increased during study drug administration. The cholestatic picture (elevated alkaline phosphatase) occurred prior to the decrease in alkaline phosphatase; criteria lab values were met 2 days prior to study medication discontinuation and had returned to normal ranges by the follow-up visit (Day 25). Additional lab tests were performed (Day 40) that showed these values remained in the normal ranges and all had returned to baseline values or below.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 25 | 36 | 25 | 43 | 65 | 21 | 98 | 129 |
| Days 3-5 | 4 | 44 | 36 | 59 | 43 | 121 | 21 | 145 | 129 |
| EOT | 8 | 101 | 36 | 217 | 43 | 67 | 21 | 300 | 129 |
| EOT | 10 | 78 | 36 | 247 | 43 | 46 | 21 | 253 | 129 |
| FU/TOC | 25 | 21 | 36 | 27 | 43 | 21 | 21 | 123 | 129 |
| All other | 40 | 21 | 36 | 18 | 43 | 17 | 21 | 101 | 129 |

ULN = upper limit of normal

End of treatment (Day 10) and TOC (Day 40) clinical responses were assessed as cured.

FDA Medical Officer Comments: Concomitant with telavancin exposure, the patient developed increases in AST, ALT, alkaline phosphatase, and bilirubin. No information was provided in terms of a diagnostic evaluation for cholestatic hepatitis and hyperbilirubinemia, such as infectious hepatitis serology and hepatic ultrasound. Follow-up laboratory test results revealed a trend of decreasing liver function tests post-therapy. Although there is a temporal association of telavancin exposure with the hepatic test abnormalities, there was insufficient information to assess causality.

5) Patient 0015-38024-4496, a 65-year-old white male, was enrolled in Study 0015 and randomized to vancomycin on (b) (6) for the treatment of HAP. Vancomycin therapy ended on (b) (6), for a total exposure of 11 days.

Medical history is significant for acute renal failure ((b) (6)), anal cyst removal, anemia (b) (6)-cont), anxiety, appendectomy, atherosclerosis, benign prostatic hypertrophy, colectomy, constipation ((b) (6)), elevated ALT ((b) (6)-cont), elevated AST (b) (6)-cont), elevated BUN (b) (6)-cont), generalized edema ((b) (6)-cont), generalized leg pain secondary to claudication (b) (6) 006-cont), hypercholesterolemia, hypercoagulopathy ((b) (6)), hypertension, intermittent hyperglycemia ((b) (6)-cont), intermittent hypokalemia (b) (6)-

cont), intermittent rapid atrial fibrillation (b) (6) -cont), intraoperative hemorrhagic shock (b) (6), left femoral venous bypass (b) (6), left iliac angioplasty (b) (6), nasal cauterization, oral surgery (b) (6), peripheral vascular disease (b) (6) -cont), supraventricular tachycardia (16 (b) (6)), thrombocytopenia (b) (6) -cont), and tobacco use.

Concomitant medications included paracetamol (intermittent fevers), acetazolamide (hypertension), acetylcysteine (hospital acquired pneumonia), acetylsalicylic acid (prophylaxis coronary artery disease), atenolol (hypertension), atorvastatin (hypercholesterolemia), clonidine (hypertension), esomeprazole (prophylaxis stress ulcer), ezetimibe (hypercholesterolemia), furosemide (generalized edema), heparin (prophylaxis deep vein thrombosis), ibuprofen (intermittent fevers), insulin human (intermittent hyperglycemia), labetalol (hypertension), lisinopril (hypertension), magnesium hydroxide (constipation), metoclopramide (prophylaxis of gastrointestinal immobility), metoprolol (hypertension/sinus tachycardia), morphine (generalized leg pain secondary), oxycodone (generalized leg pain secondary), potassium (intermittent hypokalemia), propofol (sedation secondary to ventilation), quetiapine (anxiety), and terazosin (hypertension).

On (b) (6) (Day -4), the patient was hospitalized for leg pain atherosclerosis and was transferred to the ICU on (b) (6) (Day -3) through (b) (6) (Day 4). He experienced intermittent liquid stools (b) (6) (Day 1) - (b) (6) (Day 8), hypotension on (b) (6) (Day 1), penile and scrotal edema on (b) (6) (Day 1) - continuing, tongue ecchymosis (due to an injury) (b) (6) (Day 1) - (b) (6) (Day 3), sinus tachycardia (b) (6) (Day 5) - (b) (6) (Day 10), maculopapular rash on back and scrotum and mouth sores on (b) (6) (Day 6) - continuing, and *E. coli* urinary tract infection (b) (6) (Day 9) - (b) (6) (Day 12). The patient was discharged on (b) (6) (Day 12).

The patient's AST/ALT results were highest at baseline and improved while on treatment, during which elevations in bilirubin occurred. See the table below for LFT values.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | -1 | 121 | 36 | 269 | 43 | 15 | 21 | 62 | 125 |
| Days 3-5 | 4 | 49 | 36 | 73 | 43 | 70 | 21 | 155 | 125 |
| EOT | 6 | 55 | 36 | 72 | 43 | 84 | 21 | 153 | 125 |
| EOT | 11 | | | 202 | 43 | 39 | 21 | 345 | 125 |
| FU/TOC | 15 | 53 | 36 | 140 | 43 | 26 | 21 | 355 | 125 |

ULN = upper limit of normal

End of treatment (Day 10) clinical response was assessed as cured and TOC clinical response (Day 15) was indeterminate.

FDA Medical Officer Comments: The patient had markedly abnormal baseline liver function tests (AST, ALT) of uncertain etiology, which improved during the course of study drug administration. The bilirubin levels increased concomitantly for uncertain reasons. There was insufficient information to assess causality.

6) Patient 0015-41000-4416, a 21-year-old Asian female, was enrolled in Study 0015 and randomized to vancomycin on (b) (6) for the treatment of HAP. Vancomycin therapy ended on (b) (6), for a total exposure of 12 days. Concomitant medications included famotidine (prophylaxis for gastric ulcer) (b) (6) (Day -2) – (b) (6) (Day 12), and paracetamol (fever) (b) (6) (Day 2) – (b) (6) (Day 12).

On (b) (6) (Day -5), the patient was hospitalized for lower respiratory tract infection. She was treated with the following antimicrobials: ampicillin on (b) (6) (Day -5) - (b) (6) (Day -4), cefotaxime on (b) (6) (Day -5) – (b) (6) (Day 5), Augmentin (b) (6) (Day -4) – (b) (6) (Day 3), and amikacin (b) (6) (Day -2) – (b) (6) (Day 5). The patient was discharged on (b) (6) (Day 13). No adverse events were reported.

At baseline, the patient’s bilirubin was approaching the upper limit of normal and her alkaline phosphatase level was slightly above the upper limit of normal. The bilirubin level returned to baseline by Day 10, during study treatment. See the table below for LFT values.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 21 | 34 | 18 | 34 | 20 | 21 | 109 | 106 |
| Days 3-5 | 4 | | | | | | | 44 | 106 |
| Days 6-8 | 7 | | | 144 | 34 | 42 | 21 | 200 | 106 |
| EOT | 10 | 61 | 34 | 160 | 34 | 20 | 21 | 284 | 106 |
| EOT | 12 | | | | | | | 108 | 106 |
| FU/TOC | 19 | 64 | 34 | 23 | 34 | 16 | 21 | 34 | 106 |

ULN = upper limit of normal

End of treatment (10) and TOC (19) clinical responses were assessed as cured.

FDA Medical Officer Comments: The patient experienced concurrent elevations of ALT and bilirubin with an alkaline phosphatase less than 2 x ULN on Day 7 to fulfill Hy’s Rule. The bilirubin elevation resolved by Day 10. The etiology of this finding is uncertain; although there was a temporal association with vancomycin administration, the patient had received other prior and concomitant drugs (such as paracetamol, Augmentin, and cefotaxime) that could have had some contributory effect on the development of abnormalities in liver function. No information was provided as to whether a diagnostic evaluation for non-drug related causes was conducted by the investigator.

7) Patient 0015- 41001-4542, a 51-year-old Asian female, was enrolled in Study 0015 and randomly assigned to vancomycin on (b) (6) for the treatment of HAP (organism

not specified). Vancomycin therapy ended on (b) (6), for a total exposure of 10 days.

Significant medical history included hypertension and post menopausal. Recent medical conditions included diabetes mellitus (type unknown; (b) (6)), explorative laparotomy (b) (6), hollow viscus intestinal perforation (b) (6), hypokalemia (b) (6)-cont), peritonitis (b) (6), pulmonary edema ((b) (6) cont), and sepsis (b) (6).

Concomitant medications included cimetidine, epinephrine, atropine, butorphanol, bisoprolol, diclofenac, dobutamine, dopamine, fentanyl, fluconazole, heparin-fraction, human insulin, hydrocortisone, furosemide, all other therapeutic prophylaxis, acetylcysteine, octreotide, potassium, tramadol, and phytomenadione.

(b) (6) prior to study entry, the patient experienced hollow viscus perforation with peritonitis and was hospitalized. The following day, a laparotomy was performed, and metronidazole and piperacillin/tazobactam were started for peritonitis. Fluconazole was started on Study Day -1 for peritonitis. On (b) (6) (Study Day 1), a chest x-ray showed new lung infiltrates, and the patient began treatment with vancomycin, linezolid, and aztreonam. Piperacillin/tazobactam and linezolid were discontinued on Study Day 1. Baseline (Study Day 1) serum creatinine was 0.6 mg/dL (reference range 0.4-1.1 mg/dL), and baseline platelet count was 111×10^9 cells/L (reference range $140-400 \times 10^9$ cells/L). Per the SAE form, on Study Day 2 the patient's oxygen saturation levels decreased and mechanical ventilation was required. Dopamine was administered for hypotension and dobutamine was started later in the day. The patient was diagnosed with multi-organ failure. Local laboratory values on Study Day 2 included serum creatinine 1.9 mg/dL (reference range 0.4-1.4 mg/dL), potassium 3.3 mmol/L (reference range 3.5-5.3 mmol/L), and magnesium 1.8 mg/dL (reference range 1.8-3.0 mg/dL). Per the SAE form, renal failure was suspected due to the patient's increase in serum creatinine. The dose of study medication was adjusted on Study Day 2 to Study Day 5 based on serum creatinine level. Blood cultures obtained on Day 1, 2 and 3, were all negative. On Study Day 5, serum creatinine was 0.7 mg/dL and respiratory cultures revealed *Acinetobacter* species. On Study Day 6, the patient was diagnosed with gangrene of both hands and hypoglycemia. Relevant local laboratory values on that day included a serum creatinine of 0.8 mg/dL and prothrombin time of 25.1 seconds. Per the SAE form, dalteparin was started for disseminated intravascular coagulation. On Study Day 7, local laboratory platelet count was $32,000 \times 10^9$ cells/L (reference range $150,000- 400,000 \times 10^9$ cells/L). Laboratory values on Study Day 8 showed a serum creatinine of 0.7 mg/dL and a platelet count of 107×10^9 cells/L. Octreotide was started on that day. On Study Day 9, aztreonam, octreotide, and dalteparin were discontinued. On (b) (6), the patient experienced bradycardia and cardiac arrest and subsequently expired. No autopsy was performed.

The liver function test results improved while on study treatment but did not return to baseline levels. The probable cause for the abnormal liver function test levels was the patient's concurrent multiorgan failure and sepsis.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | | | 26 | 34 | 10 | 21 | 68 | 123 |
| Days 3-5 | 5 | 1661 | 34 | 362 | 34 | 75 | 21 | 138 | 123 |
| EOT | 8 | 62 | 34 | 64 | 34 | 68 | 21 | 119 | 123 |

ULN = upper limit of normal

The Investigator assessed all events as not related to the study medication. End of Therapy clinical response was assessed as indeterminate, as the patient's lung lesions showed partial improvement as evidenced by radiographs, and the patient showed partial improvement in signs and symptoms of pneumonia.

FDA Medical Officer Comments: The patient developed a flux in ALT, AST, and bilirubin levels that appeared to coincide with sepsis and peritonitis following hollow viscus perforation. Improvement in liver function tests despite continued exposure to study drug provides evidence of a negative rechallenge.

8) Patient 0015-41009-4501, a 40-year-old Asian male, was enrolled in Study 0015 and randomly assigned to telavancin on [REDACTED] (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-resistant *S. aureus* (MRSA). Telavancin therapy ended on [REDACTED] (b) (6) for a total exposure of seven days.

Significant medical history included alcoholic hepatitis. Per the SAE form, additional medical history included liver cirrhosis. Recent medical conditions included Grade 1 oesophageal varices [REDACTED] (b) (6), obstructive uropathy [REDACTED] (b) (6), and altered sensorium [REDACTED] (b) (6) cont).

Concomitant medications included ondansetron (nausea), pantoprazole (gastric stress ulcer), trihexyphenidyl (prophylaxis mania), risperidone (prophylaxis mania), and thiamine (alcohol withdrawal).

On Study Day -4, the patient was hospitalized for acute hepatitis with pneumonia and septicemia. Prior to study entry, he received amikacin (Study Day -4 to Study Day 7) and piperacillin/tazobactam (Study Day -4 to Study Day 1) for pneumonitis. He also received metronidazole (Study Day -4 to Study Day 1) for anaerobic coverage. Respiratory cultures obtained on Study Day -1 were positive for MRSA; blood cultures were negative. On [REDACTED] (b) (6) (Study Day 1), he began treatment with telavancin. Study Day 1 serum creatinine was 0.9 mg/dL (reference range 0.5-1.2 mg/dL). On Study Day 2, treatment with aztreonam was started (Study Day 2 to ongoing). Due to the presence of yeast, fluconazole was added on Study Day 5. Initially, he showed a positive response per chest x-ray. After 4 days; however, he began to deteriorate showing signs of acute respiratory arrest

syndrome. On Study Day 4, serum creatinine increased to 1.6 mg/dL and it was 2.0 mg/dL on Study Day 7. A chest x-ray showed bilateral haziness in the lungs. Arterial blood gases showed respiratory acidosis with pH of 7.29 (local laboratory reference range 7.35-7.45) and CO₂ of 51 mEq/L (local laboratory reference range 35-45 mEq/L).

The patient's AST and bilirubin were elevated at baseline. He had a history of alcoholic hepatitis and liver cirrhosis and was hospitalized initially for acute hepatitis. The table below provides the relevant values during study.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 101 | 36 | 41 | 43 | 251 | 21 | 59 | 129 |
| Days 3-5 | 4 | 127 | 36 | 43 | 43 | 270 | 21 | 70 | 129 |
| EOT | 7 | 150 | 36 | 52 | 43 | 289 | 21 | 93 | 129 |

ULN = upper limit of normal

On (b) (6) he became severely bradycardic and died. No autopsy was performed. The Investigator assessed the bradycardia and subsequent patient death as not related to study medication. End-of-therapy clinical response was assessed as indeterminate due to death of the patient.

FDA Medical Officer Comments: The patient had abnormal AST and bilirubin at baseline with normal ALT and alkaline phosphatase, a pattern of liver function tests abnormalities that could be consistent with alcoholic hepatitis. He did not develop any substantial laboratory tests changes during study drug administration (despite concomitant exposure to metronidazole and fluconazole), but it was unclear if his functional capacity to exhibit such changes was limited by his underlying hepatic cirrhosis.

9) Patient 0019-01021-6340, a 69-year-old Hispanic male, was enrolled in Study 0019 and randomly assigned to telavancin on (b) (6) for the treatment of HAP, subsequently found to be due to *Streptococcus* species and *Staphylococcus* species. Telavancin therapy ended on (b) (6), for a total exposure of 14 days.

Significant medical history included ankle fracture, duodenal ulcer, and tonsillectomy. Recent medical conditions included renal failure ((b) (6)), lower limb edema ((b) (6)), duodenopancreatectomy ((b) (6)), hyperglycemia ((b) (6)-cont), pancreatic cancer ((b) (6)), and septic shock ((b) (6)-cont). An additional medical condition per the SAE form was jaundice due to pancreatic head tumor.

Concomitant medications included amphotericin B, folic acid with vitamin B, dobutamine, dopamine, fentanyl, furosemide, heparin, hydrocortisone, insulin, ipratropium, lorazepam, midazolam, norepinephrine, omeprazole, phytomenadione, ranitidine, remifentanyl, and salbutamol.

(b) (6) prior to study entry, the patient was hospitalized to undergo a duodenopancreatectomy for pancreatic cancer. He received prophylaxis with clindamycin and gentamycin from Study Day -4 through Study Day -3. On Study Day -1, he went into septic shock and was diagnosed with *Streptococcus* species pneumonia. He was treated with cefepime and vancomycin through Study Day 1. On (b) (6) (Study Day 1), he was diagnosed with *Staphylococcus* species pneumonia and started treatment with telavancin and piperacillin/tazobactam. His baseline (Study Day 4) serum creatinine was 2.9 mg/dL (central laboratory reference range 0.5-1.3 mg/dL) and it remained elevated throughout the study. Per the SAE form, on Study Day 4, the patient became hypotensive and had a decreased hematocrit. He did not respond to volume expanders and required high doses of norepinephrine. An abdominal ultrasound confirmed the presence of an abdominal collection. Pancreatic artery rupture was diagnosed that required surgical ligation of the artery. He recovered with sequelae on Study Day 5. On Study Day 6, he was diagnosed with a pancreatic fistula. His peak serum creatinine value was 3.8 mg/dL on Study Day 8. Telavancin was completed on Study Day 14 with resolution of signs and symptoms of pneumonia.

On Study Day 15, the patient required increasing doses of norepinephrine. Local laboratory values included increased C-reactive protein of 16.3 mg/dL (reference range < 0.5 mg/dL) and increased leukocyte count of $17.2 \times 10^9/L$ (reference range $4.5-9.4 \times 10^9/L$). *Candida albicans* (*C. albicans*) sepsis was diagnosed after an abdominal culture was positive for *C. albicans* and his shock became worse. He started treatment with amphotericin B. His condition continued to deteriorate as he required high doses of epinephrine and he appeared to not be responding to the antimycotic therapy per the SAE form. He died on (b) (6) from *Candida* sepsis.

Baseline liver function test were not available. Lab values from Day 8 fulfill the Hy's Law criteria. By Day 11, AST and ALT levels decreased while on study treatment, but bilirubin and alkaline phosphatase levels remained elevated at End-of Therapy (14).

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (μmol/L) | Bilirubin ULN (μmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Days 3-5 | 4 | | | | | | | 142 | 125 |
| Days 6-8 | 8 | 132 | 36 | 170 | 35 | 152 | 21 | 178 | 125 |
| Days 9-12 | 11 | 68 | 36 | 89 | 35 | 162 | 21 | 317 | 125 |
| EOT | 14 | 64 | 36 | 58 | 35 | 202 | 21 | 335 | 125 |
| EOT | 18 | | | | | | | 402 | 125 |
| FU/TOC | 21 | | | | | | | 469 | 125 |

ULN = upper limit of normal

The Investigator assessed the arterial rupture, septic shock, and *Candida* sepsis with subsequent patient death after the TOC visit as not related to study medication. End-of-therapy (Study Day 14) and TOC (Study Day 21) clinical responses were assessed as cured.

FDA Medical Officer Comments: In the absence of baseline liver function test results, it is impossible to determine if the patient had abnormalities that fulfilled Hy's Rule prior to exposure to study drug. However, the improvement noted in those tests despite continued exposure to telavancin suggest a negative rechallenge.

10) Patient 0019-02028-6613, a 32-year-old white female, was enrolled in Study 0019 and randomly assigned to vancomycin on (b) (6) for the treatment of HAP, subsequently found to be due to *Citrobacter freundii*. Vancomycin therapy ended on (b) (6), for a total exposure of 16 days.

Significant medical history included asthma, excessive alcohol abuse, chronic pancreatitis, duodenal ulcer, and hepatitis. Recent medical conditions included tachycardia (b) (6) cont), hematemesis ((b) (6)), Grade A Mallory-Weiss tear (b) (6) -cont), ARDS (b) (6) -cont), aspiration pneumonia (b) (6) -cont), decompensated liver failure ((b) (6) -cont), gastritis ((b) (6) -cont), hemorrhoids ((b) (6) -cont), hypernatremia (b) (6) cont), perineal thrush ((b) (6) -cont), head lice ((b) (6) -cont), and acute renal failure (b) (6) -cont).

Concomitant medications included acetazolamide, human insulin, human albumin, clotrimazole, fentanyl, fluconazole, furosemide, hydrocortisone, lactulose, metaraminol, metoclopramide, midazolam, morphine, nystatin, norepinephrine, oxycodone, pantoprazole, paracetamol, permethrin, propofol, cinchocaine hydrochloride hydrocortisone, salbutamol, spironolactone, and vasopressin injection.

On Study Day -13, the patient was hospitalized with chronic pancreatitis and peritonitis. Per the SAE form, the patient developed pulmonary infiltrates and respiratory failure consistent with aspiration pneumonitis. On Study Day -9, the patient required mechanical ventilation and developed acute renal failure. On Study Day -7, the patient began treatment with ceftriaxone (Study Day -7 to Study Day 6) for aspiration pneumonia. Although her condition improved, her respiratory status deteriorated and a sputum culture was positive for mixed organisms consistent with VAP. Respiratory cultures obtained on (b) (6) (Study Day 1), were positive for *C. freundii* complex and the patient began treatment with vancomycin and erythromycin (Study Day 1 to Study Day 23). On Study Day 2, the patient experienced peritonitis that remained ongoing and treatment with metronidazole was added (Study Day 2 to Study Day 11). On Study Day 3, study medication was unblinded since laboratory results (presumably vancomycin levels) were mistakenly sent to the ward. On Study Day 7, treatment with meropenem began (Study Day 7 to Study Day 24). On Study Day 8, treatment with azithromycin began (Study Day 8 to Study Day 19). On Study Day 9, treatment with trimethoprim (Study Day 9 to Study Day 11) and ciprofloxacin (Study Day 9 to Study Day 23) were started. Per the SAE form, on Study Day 10, chest drains were inserted due to subcutaneous emphysema and there was clinical evidence of pneumothorax that was not visible on the chest x-ray. No adverse sequelae occurred secondary to the pneumothorax. The event of pneumothorax was considered to be improving but remained

ongoing. On Study Day 16, the patient completed study medication due to resolution of signs and symptoms of pneumonia. However, the patient's clinical condition deteriorated with hemodynamic compromise consistent with sepsis. On Study Day 17, she started treatment with piperacillin/tazobactam (Study Day 17 to Study Day 23). On Study Day 18, treatment with vancomycin was started (Study Day 18 to Study Day 24). On Study Day 23, the patient's ascites had worsened. Her hemodynamic and respiratory compromise, along with the results from the peritoneal fluid microscopy, led to the diagnosis of spontaneous bacterial peritonitis. On [REDACTED] (b) (6), she died as a result of bacterial peritonitis. The Investigator assessed the pneumothorax and bacterial peritonitis and subsequent patient death as not related to the study medication.

The patient's liver enzyme tests and bilirubin level were abnormal at baseline consistent with the patient's medical history and hospital course. All values began to decrease while on study treatment but then increased on Day 10. Lab values on Days 14 and 16 continued to increase consistent with the patient's worsening clinical condition due to sepsis and peritonitis.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 78 | 34 | 98 | 34 | 98 | 21 | 87 | 106 |
| Days 3-5 | 4 | 56 | 34 | 74 | 34 | 75 | 21 | 108 | 106 |
| Days 6-8 | 7 | 37 | 34 | 39 | 34 | 78 | 21 | 90 | 106 |
| Days 9-12 | 10 | 76 | 34 | 76 | 34 | 70 | 21 | 140 | 106 |
| EOT | 14 | 101 | 34 | 108 | 34 | 107 | 21 | 159 | 106 |
| EOT | 16 | 119 | 34 | 109 | 34 | 111 | 21 | 197 | 106 |

ULN = upper limit of normal

End-of-therapy clinical response was assessed as cured since pneumonia-associated signs and symptoms resolved. The patient died before the TOC assessment.

FDA Medical Officer Comments: The patient had abnormal liver function tests at baseline that improved initially, but later increased by Day 10. Despite the temporal association with study drug exposure, there were multiple concurrent medical events (sepsis, peritonitis) and medication exposures (ceftriaxone, macrolides, carbapenems) that confounded causality assessment.

11) Patient 0019-18004-6197, a 77-year-old white male, was enrolled in Study 0019 and randomly assigned to vancomycin on [REDACTED] (b) (6) for the treatment of HAP (organism not specified). Vancomycin therapy ended on [REDACTED] (b) (6), for a study medication exposure of eight days (total vancomycin exposure of nine days).

Significant medical history included CHF, hyperlipidemia, hypertension, ischemic heart disease, inferior wall MI, infero-posterior wall MI, paroxysmal atrial fibrillation, prostatectomy, smoking, and coronary artery bypass graft surgery. Recent medical conditions included aortic stenosis and valve replacement (start date unknown- [REDACTED] (b) (6)), elevated liver enzymes [REDACTED] (b) (6).

(b) (6)-cont), mechanical ventilation (b) (6)-cont), hypoalbuminemia (b) (6)-cont), oliguria (b) (6)-cont), leukocytosis (b) (6)-cont), lymphocytopenia (b) (6)-cont), hyperbilirubinemia (b) (6)-cont), acute and chronic renal failure (b) (6)-cont), and anemia (b) (6)-cont).

Concomitant medications included ipratropium, acetylsalicylic acid, blood and related products, warfarin, dopamine, levothyroxine, fentanyl, fluconazole, furosemide, insulin, sodium polystyrene sulfonate, all other therapeutic prophylaxis, domperidone, norepinephrine, human packed blood cells, vasopressin injection, metoclopramide, milrinone, propofol, methylprednisolone, atracurium, salbutamol, and ranitidine.

On Study Day -13, the patient was hospitalized for severe aortic stenosis. On Study Day -6, he underwent cardiac catheterization (with contrast) and subsequent aortic valve replacement. Per the SAE form narrative, he developed acute renal failure after catheterization and surgery. On Study Day -1, he developed nosocomial pneumonia and leukocytosis with Gram-positive bacteria in his sputum. The patient received treatment with piperacillin/tazobactam and vancomycin on Study Day -1. On (b) (6) (Study Day 1), he began treatment with vancomycin and aztreonam (Study Day 1 to Study Day 8). His Study Day 1 serum creatinine value was 3.3 mg/dL (reference range 0.5-1.5 mg/dL). Despite treatment, his condition continued to deteriorate with more infiltrates in his lungs and leukocytosis. Hemodialysis was started. His Study Day 6 serum creatinine value was 6.7 mg/dL. On Study Day 8, the patient was felt to be septic. As a result, study medication was discontinued and he began treatment with imipenem (Study Day 8 to cont) and fluconazole. On Study Day 10 and Study Day 17, serum creatinine values were 6.7 mg/dL and 4.3 mg/dL, respectively. On Study Day 13, metronidazole was started (Study Day 13 to cont). Per the SAE form, local laboratory results included WBC count of 22,850/μL (local laboratory reference range 4000-10,800/μL), serum creatinine of 4.34 mg/dL (local laboratory reference range 0.8-1.4 mg/dL), and urea of 286 mg/dL (local laboratory reference range 15-45 mg/dL).

The patient's liver enzymes were elevated at baseline. On Day 10, while the enzyme levels decreased from baseline, his bilirubin level increased. These laboratory abnormalities may have been consistent with sepsis. At the follow-up visit (Day 17) his enzymes were well below baseline levels and bilirubin was approaching the baseline level.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (μmol/L) | Bilirubin ULN (μmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 253 | 36 | 272 | 35 | 31 | 21 | 60 | 130 |
| EOT | 6 | | | 134 | 35 | 32 | 21 | 88 | 130 |
| EOT | 10 | 178 | 36 | 164 | 35 | 84 | 21 | 119 | 130 |
| FU/TOC | 17 | 134 | 36 | 62 | 35 | 34 | 21 | 127 | 130 |

ULN = upper limit of normal

The patient's condition continued to deteriorate. On (b) (6), the patient died as a result of multi-organ failure. No autopsy was performed. End-of-therapy clinical response was assessed as

a failure due to persistence or progression of signs and symptoms of pneumonia. The Investigator assessed the sepsis and subsequent patient death after the follow-up visit as not related to study medication.

FDA Medical Officer Comments: The patient had abnormal baseline liver function tests (AST and ALT) whose etiology was not characterized in the narrative. Although the AST and ALT declined by Day 10, they remained elevated and were associated with an increase in bilirubin such that Hy' Rule was fulfilled at that time. Causality assessment was confounded by ongoing sepsis and concomitant medications (carbapenems, fluconazole, and metronidazole).

12) Patient 0019-38341-6384, a 59-year-old black male, was enrolled in Study 0019 and randomly assigned to telavancin on (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-susceptible *S. aureus* (MSSA). Telavancin therapy ended on (b) (6), for a total exposure of eight days.

No significant medical history was reported. Recent medical conditions included gastric serosal repair (b) (6), hemobronchorrhea (b) (6)-cont), hemoperitoneum ((b) (6) -cont), hypotension ((b) (6) -cont), kidney laceration ((b) (6) -cont), left diaphragmatic tear and repair ((b) (6) -cont), left hemopneumothorax (b) (6) cont), liver laceration ((b) (6) -cont), lumbar transverse process fracture ((b) (6) -cont), mesenteric hematomas and tears ((b) (6) -cont), multiple bilateral rib fractures ((b) (6) -cont), open abdomen ((b) (6) -cont), pneumomediastinum ((b) (6) -cont), pubic fracture ((b) (6) -cont), respiratory distress ((b) (6) -cont), right adrenal hemorrhage ((b) (6) -cont), sacral fracture (b) (6) -cont), splenectomy for splenic rupture (b) (6) -cont), anemia (b) (6) -cont), hypokalemia (b) (6) -cont), hyperglycemia (b) (6) -cont), atrial fibrillation ((b) (6) -cont), bilateral lower extremity DVT (b) (6) -cont), hypertension (b) (6) -cont), edema ((b) (6)), and alkalosis ((b) (6)).

Concomitant medications included human albumin, salbutamol, amiodarone, ipratropium, calcium gluconate, docusate, tetracosactide, warfarin, dextromethorphan, acetazolamide, dobutamine, factor VII, fentanyl, iron, folic acid, gastrografin, heparin, haemophilus influenzae B, hydrocortisone, insulin, Ringer's lactate solution, furosemide, metoprolol, heparin-fraction, magnesium hydroxide, acetylcysteine, norepinephrine, oxycodone, famotidine, potassium, electrolyte solutions, hemodialytics/hemofiltrates, propofol, and sodium bicarbonate.

(b) (6) prior to study entry, the patient was hospitalized with abdominal pain secondary to a motor vehicle accident. Per the SAE form, injuries included a left hemopneumothorax, pneumomediastinum, multiple rib fractures, right adrenal hemorrhage, left superior pole kidney laceration, bilateral superior/inferior pubic rami fracture, right zone II sacral fracture, and lumbar transverse fracture. He underwent surgical repairs, intubation, and received packed-RBCs, fresh frozen plasma transfusions, albumin, cryoprecipitate, and platelets. He

was admitted to the surgical ICU on a ventilator in critical condition.

(b) (6) prior to study entry, he went into atrial fibrillation which was controlled with medication. On Study Day -1, the patient respiratory cultures revealed MSSA and he was treated with imipenem. On (b) (6) (Study Day 1), he started treatment with telavancin, tobramycin, and piperacillin/tazobactam. His baseline (Study Day 1) serum creatinine was 0.7 mg/dL (central laboratory reference range 0.5-1.3 mg/dL). Telavancin was completed on Study Day 8 due to resolution of signs and symptoms of pneumonia. Thick secretions were still present, but his ventilation requirements and leukocytosis had decreased. Per the SAE form, throughout the hospitalization, the patient was extubated and re-intubated several times, and received several blood transfusions. On Study Day 11, he was diagnosed with a Gram-negative UTI, developed septic shock, abdominal compartment syndrome, and a coagulopathy. He had an exploratory laparotomy and was found to be bleeding from the left lower lobe of the liver, which was repaired. He became acidotic and hypernatremic, and dialysis was started due to acute renal failure. Local laboratory values on Study Day 12 included serum creatinine 2.3 mg/dL (reference range 0.8-1.5 mg/dL), PT 25.1 seconds (reference range 9.1-11.8 seconds), and PTTs ranging from 53.8 to 94.2 seconds (reference range 21.1-35.2 seconds). The patient was diagnosed with multi-organ failure and was treated with levofloxacin, imipenem, metronidazole, and linezolid. Serum creatinine value on Study Day 16 was 1.9 mg/dL. On Study Day 20, the patient had an acute episode of decompensation and desaturation and at the request of the family the he was made a DNR. The patient died from multi-organ failure on (b) (6). End-of-therapy (Study Day 9) and TOC (Study Day 16) clinical responses were assessed as indeterminate due to thick secretions, decreased leukocytosis, and need for additional antibiotics.

With the exception of an elevated bilirubin at baseline, the patient's liver function values were normal throughout study treatment. At the follow-up visit (16), the patient's liver enzymes and bilirubin levels were abnormal but were consistent with the patient's deteriorating condition (multi-organ failure).

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 25 | 36 | 31 | 43 | 72 | 21 | 117 | 131 |
| EOT | 6 | 49 | 36 | 53 | 43 | 22 | 21 | 154 | 131 |
| EOT | 9 | 31 | 36 | 37 | 43 | 21 | 21 | 167 | 131 |
| FU/TOC | 16 | 260 | 36 | 111 | 43 | 140 | 21 | 124 | 131 |

ULN = upper limit of normal

The Investigator assessed the multi-organ failure and subsequent patient death after the follow-up visit as not related to study medication.

FDA Medical Officer Comments: The patient had normal AST and ALT at baseline with an elevated bilirubin. During telavancin administration, no repeat liver function tests were reported except for those at EOT. At Day 6, the AST and ALT were elevated, while the bilirubin was just

above normal. He developed abnormalities in ALT, AST, and bilirubin post-treatment, but causality assessment was confounded by multiple concomitant medications and multi-organ failure.

13) Patient 0019-40001-6396, a 74-year-old American Indian male, was enrolled in Study 0019 and randomly assigned to vancomycin on (b) (6) (Study Day 1) for the treatment of HAP. Vancomycin therapy ended on (b) (6) for a total exposure of 12 days.

Medical history is significant for abdominal surgery (1996), anemia (b) (6)-cont), cubital-radio fracture left (b) (6)-cont), interhemispheric hemorrhage (b) (6)-cont), peritonitis (1996), and traumatic severe head injury (b) (6)-cont). Concomitant medications included clonixin (adjuvant treatment of head trauma), omeprazole (upper gastrointestinal bleeding), phenytoin (prophylaxis for seizures), and ranitidine (prophylaxis for gastritis).

The patient was hospitalized on (b) (6) (Study Day -6) for severe traumatic head injury/ interhemispheric hemorrhage. He was diagnosed with HAP on (b) (6) (Study Day 1). His liver enzymes and bilirubin were abnormal at baseline. Bilirubin levels decreased over the course of study treatment while the enzyme levels fluctuated.

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (µmol/L) | Bilirubin ULN (µmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 103 | 36 | 56 | 35 | 41 | 21 | 105 | 130 |
| Days 3-5 | 4 | 74 | 36 | 60 | 35 | 80 | 21 | 95 | 130 |
| Days 6-8 | 6 | 121 | 36 | 65 | 35 | 58 | 21 | 83 | 130 |
| EOT | 10 | 117 | 36 | 75 | 35 | 34 | 21 | 145 | 130 |
| EOT | 13 | | | | | 7 | 21 | | |

ULN = upper limit of normal

End-of-therapy (Study Day 12) clinical response was assessed as a failure due to persistence or progression of signs and symptoms of pneumonia. The patient was discharged from hospital on (b) (6) (Study Day 13) and subsequently died, date unknown.

FDA Medical Officer Comments: The patient had abnormal baseline liver function tests, but the etiology was not characterized in the narrative. By Day 10 (EOT), AST, ALT, bilirubin, and alkaline phosphatase were elevated, but no diagnostic evaluation was described. Repeat ALT and AST were not reported post-EOT. He received multiple concomitant medications that could have affected liver function, but there was insufficient information to assess causality with respect to study drug.

14) Patient 0019-44009-6485, a 58-year-old white male, was enrolled in Study 0019 and randomly assigned to telavancin on (b) (6) for the treatment of HAP, subsequently found to be due to methicillin-resistant *S. aureus* (MRSA). Telavancin therapy ended on (b) (6), for a total exposure of 16 days.

Significant medical history included smoking. Recent medical conditions included chest trauma (b) (6) -cont), face burn (b) (6) -cont), hypertension (b) (6) -cont), lung contusion (b) (6) -cont), severe brain trauma (b) (6) -cont), and smoke inhalation (b) (6) -cont).

Concomitant medications included metamizole, clonidine, heparin-fraction, midazolam, all other therapeutic prophylaxis, enalapril, fentanyl, furosemide, mannitol, esomeprazole, terlipressin, somatostatin, and ademetionine.

On Study Day -7, the patient was hospitalized for severe head injury and smoke inhalation. He received ceftriaxone (Study Day -7 to Study Day -6) and imipenem/cilastatin (Study Day -6 to Study Day -1) for infection prophylaxis. On (b) (6) (Study Day 1), respiratory cultures were positive for MRSA and he began telavancin and aztreonam therapy (Study Day 1). On that day, his serum creatinine was 1.2 mg/dL (reference range 0.5-1.3 mg/dL). On Study Day 4, respiratory cultures grew *Enterobacter cloacae*. On Study Day 13, he was diagnosed with hemorrhage and shock from a gastric ulcer, and treatment with terlipressin, esomeprazole, and etamsylate were started. Per the SAE form, hemoglobin values were as follows on Study Day 13, 4.5 g/dL (local laboratory reference range 14.0-18.0 g/dL) and on Study Day 14, 9.4 g/dL. On Study Day 15, the patient developed acute renal failure after a 36 hour period of hemorrhagic shock and treatment with terlipressin. Etamsylate was discontinued and furosemide was started for oliguria on that day. Per the SAE form, Study Day 15 serum creatinine value was elevated at 2.44 mg/dL (local laboratory reference range not provided). On Study Day 16, terlipressin was discontinued and the event of shock was considered recovered with sequelae. On Study Day 16, telavancin therapy was discontinued since Gram-positive coverage was no longer required. Study Day 16 hemoglobin was 12.1 g/dL. On Study Day 17, treatment with imipenem/cilastatin was started (Study Day 17 to Study Day 27) for pneumonia. Also, on Study Day 17, he had a lung injury. The patient was dialyzed on Study Day 17 and Study Day 18 by continuous venovenous hemodialysis. On Study Day 18, furosemide was discontinued. Dialysis was again scheduled for Study Day 20; however, was not attempted due to a new stomach hemorrhage, and etamsylate and somatostatin were started. Per the SAE form, Study Day 20 hemoglobin values were 6.2 g/dL and 6.8 g/dL, and Study Day 21 hemoglobin value was 6.3 g/dL. On Study Day 28, sulperazone treatment began after completion of imipenem/cilastatin on Study Day 27.

The patient's bilirubin was abnormal at baseline and improved while receiving study treatment. His liver enzymes and alkaline phosphatase were elevated on Study Day 10, but improved before discontinuation of study treatment.

Clinical Review
 Alfred Sorbello, DO, MPH
 NDA 22-407/N-000
 Theravance for injection (VIBATIV™)

| Analysis Window | Study Day | AST/SGOT (U/L) | AST/SGOT ULN (U/L) | ALT/SGPT (U/L) | ALT/SGPT ULN (U/L) | Bilirubin (μmol/L) | Bilirubin ULN (μmol/L) | Alk Phos (U/L) | Alk Phos ULN (U/L) |
|-----------------|-----------|----------------|--------------------|----------------|--------------------|--------------------|------------------------|----------------|--------------------|
| Baseline | 1 | 27 | 36 | 20 | 43 | 75 | 21 | 56 | 131 |
| Days 3-5 | 4 | 16 | 36 | 21 | 43 | 42 | 21 | 68 | 131 |
| Days 6-8 | 7 | 21 | 36 | 33 | 43 | 37 | 21 | 90 | 131 |
| Days 9-12 | 10 | 217 | 36 | 175 | 43 | 43 | 21 | 180 | 131 |
| EOT | 14 | 44 | 36 | 91 | 43 | 31.2 | 21 | 82 | 131 |
| EOT | 20 | 23 | 36 | 29 | 43 | 26 | 21 | 120 | 131 |
| FU/TOC | 37 | 11 | 36 | 10 | 43 | 21 | 21 | 45 | 131 |

ULN = upper limit of normal

Per the SAE form on [REDACTED] (b) (6) after the last dose of study medication, he experienced a sudden decrease in blood pressure and heart rate, followed by cardiac arrest. Resuscitation was unsuccessful and the patient died as a result of the cardiac arrest. The events of gastric ulcer hemorrhage and shock were considered to be improving but remained ongoing. No autopsy was performed. The Investigator assessed the gastric ulcer hemorrhage, renal failure, and shock as not related to study medication.

End-of-therapy clinical response was assessed as indeterminate since the study medication eradicated MRSA but the patient developed nosocomial pneumonia due to polyresistant *Klebsiella pneumoniae*.

FDA Medical Officer Comments: The patient had normal AST and ALT with elevated bilirubin at baseline. The liver function tests were essentially normal during the initial seven days of study drug, but increased to reach a peak on Day 10 and then declined to normal range by Day 20. Causality assessment was confounded by multiple medications and episodes of shock that developed beginning on Day 13. There was insufficient information provided regarding the diagnostic evaluation of the Day 10 liver function test elevations prior to the first episode of shock.

Hypersensitivity Reactions

Three patients in Study 0015 and four patients in Study 0019 experienced hypersensitivity reactions to study drug. None of the events were serious, and all of the events were mild or moderate in severity. The following table summarizes relevant information for each patient, including concomitant medications:

Table 141: FDA Medical Officer Summary Table of Patients who experienced Hypersensitivity Reactions, Studies 0015 and 0019, AT Safety Population

| Subject # | Study | Treatment | Duration Of Study Drug | Study Day of AE Onset | Description | Severity | Serious | Action Taken | Outcome | Related | Concomitant medications |
|-----------------|-------|-----------|------------------------|-----------------------|--|----------|---------|--------------|---------------------------------------|---------------------------|-------------------------------------|
| 0015-14003-4162 | 0015 | TLV | 8 | 3 | ALLERGIC SKIN REACTION DUE TO AZACTAM IV | MILD | NO | NONE | COMPLETELY RECOVERED | NOT RELATED | DIMETINDENE MALEATE |
| 0015-33007-4645 | 0015 | VAN | 8 | 8 | CHEST TIGHTNESS (DUE TO ALLERGIC REACTION) | MILD | NO | NONE | COMPLETELY RECOVERED | POSSIBLY/PROBABLY RELATED | GLYCERYL TRINITRATE, HYDROCORTISONE |
| 0015-33009-4236 | 0015 | VAN | 11 | 3 | DRUG ALLERGY (not further described) | MOD | NO | NONE | COMPLETELY RECOVERED | POSSIBLY/PROBABLY RELATED | BETAMETHASONE, DIPHENHYDRAMINE |
| 0019-18004-6172 | 0019 | TLV | 11 | 5 | SUSPECTED ENVIRONMENTAL ALLERGY | MILD | NO | NONE | COMPLETELY RECOVERED | NOT RELATED | PREDNISONE |
| 0019-22005-6644 | 0019 | VAN | 15 | 8 | FLUSH OF SKIN IN THE PLACE OF CATHETER (ALLERGIC TOSILICON CATHETER) | MOD | NO | NONE | CONDITION STILL PRESENT AND UNCHANGED | NOT RELATED | |
| 0019-34003-6608 | 0019 | TLV | 17 | 1 | DRUG ALLERGY (not further described) | MOD | NO | NONE | CONDITION IMPROVING | POSSIBLY/PROBABLY RELATED | CHLORPHENAMINE DEXA ATARAX |
| 0019-44001-6577 | 0019 | VAN | 14 | 14 | UNKNOWN ALLERGY | MILD | NO | NONE | CONDITION STILL PRESENT AND UNCHANGED | NOT RELATED | |

TLV=telavancin; VAN=vancomycin; MOD=moderate; AE=adverse event

FDA Medical Officer Note: There was one telavancin-treated patient in Study 0015 (Patient # 0015-18001-4246) who developed red man syndrome as a TEAE that was assessed as possibly/probably related to study drug exposure by the Investigator. The event was non-serious and mild in intensity. The patient completely recovered from the event. There were no other similarly affected patients in the study populations for Studies 0015 and 0019.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

According to Section 4.1 Adverse Event Methods of the Applicant's Integrated Summary of Safety, adverse events were to be monitored throughout the study period of the Phase 3 HAP studies. An adverse event or adverse experience (AE) was defined as any untoward medical occurrence in a patient administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing events, which increased in frequency or severity or changed in nature during or as a consequence of use of a drug in human clinical trials, were also to be considered adverse events. Adverse events also were to include pre- or post-treatment complications that occurred as a result of protocol-mandated procedures (e.g., invasive procedures such as biopsies). Any AE (i.e., a new event or an exacerbation of a pre-existing condition) with an onset date after study drug administration, and up to the last day on study (including the off-study medication period of the study before the Follow-up Visit), was to be recorded as an AE on the appropriate CRF page(s) and would be considered treatment-emergent.

The following two tables summarize the distribution of all TEAEs by System Organ Class (SOC) designation. In Study 0015, the Infections and Infestations SOC had the highest frequency of TEAEs in both treatment groups. In contrast, in Study 0019, the Gastrointestinal Disorders SOC had the highest frequency of TEAEs in both treatment groups.

Table 142: FDA Medical Officer Table of all TEAE stratified by System Organ Class, Study 0015, AT Safety Population

| SYSTEM ORGAN CLASS (SOC) | Telavancin N=372 | Vancomycin N=374 |
|---|---------------------|---------------------|
| INFECTIONS AND INFESTATIONS | 103 (27.69%) | 104 (27.81%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 81 (21.77%) | 58 (15.51%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 74 (19.89%) | 82 (21.93%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 72 (19.35%) | 80 (21.39%) |
| CARDIAC DISORDERS | 62 (16.67%) | 71 (18.98%) |
| INVESTIGATIONS | 55 (14.78%) | 45 (12.03%) |
| VASCULAR DISORDERS | 54 (14.52%) | 53 (14.17%) |
| PSYCHIATRIC DISORDERS | 48 (12.90%) | 67 (17.91%) |
| RENAL AND URINARY DISORDERS | 47 (12.63%) | 49 (13.10%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 46 (12.37%) | 59 (15.78%) |
| NERVOUS SYSTEM DISORDERS | 45 (12.10%) | 36 (9.63%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 35 (9.41%) | 33 (8.82%) |
| HEPATOBIILIARY DISORDERS | 15 (4.03%) | 10 (2.67%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 12 (3.23%) | 21 (5.61%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 10 (2.69%) | 7 (1.87%) |
| EYE DISORDERS | 6 (1.61%) | 7 (1.87%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 3 (0.81%) | 1 (0.27%) |
| ENDOCRINE DISORDERS | 3 (0.81%) | 0 (0.00%) |
| IMMUNE SYSTEM DISORDERS | 1 (0.27%) | 2 (0.53%) |
| EAR AND LABYRINTH DISORDERS | 0 (0.00%) | 1 (0.27%) |

Table 143: FDA Medical Officer Table of all TEAE stratified by System Organ Class, Study 0019, AT Safety Population

| SYSTEM ORGAN CLASS (SOC) | Telavancin N=379 | Vancomycin N=378 |
|---|---------------------|---------------------|
| GASTROINTESTINAL DISORDERS | 130 (34.30%) | 127 (33.60%) |
| INFECTIONS AND INFESTATIONS | 96 (25.33%) | 88 (23.28%) |
| METABOLISM AND NUTRITION DISORDERS | 94 (24.80%) | 93 (24.60%) |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | 70 (18.47%) | 62 (16.40%) |
| CARDIAC DISORDERS | 62 (16.36%) | 72 (19.05%) |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | 58 (15.30%) | 59 (15.61%) |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | 56 (14.78%) | 55 (14.55%) |
| VASCULAR DISORDERS | 55 (14.51%) | 52 (13.76%) |
| INVESTIGATIONS | 52 (13.72%) | 54 (14.29%) |
| PSYCHIATRIC DISORDERS | 51 (13.46%) | 46 (12.17%) |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | 49 (12.93%) | 63 (16.67%) |
| NERVOUS SYSTEM DISORDERS | 44 (11.61%) | 45 (11.90%) |
| RENAL AND URINARY DISORDERS | 39 (10.29%) | 41 (10.85%) |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | 30 (7.92%) | 36 (9.52%) |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | 19 (5.01%) | 13 (3.44%) |
| EYE DISORDERS | 8 (2.11%) | 10 (2.65%) |
| ENDOCRINE DISORDERS | 6 (1.58%) | 6 (1.59%) |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS | 5 (1.32%) | 1 (0.26%) |
| EAR AND LABYRINTH DISORDERS | 4 (1.06%) | 3 (0.79%) |
| HEPATOBIILIARY DISORDERS | 3 (0.79%) | 9 (2.38%) |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) | 3 (0.79%) | 2 (0.53%) |
| IMMUNE SYSTEM DISORDERS | 2 (0.53%) | 2 (0.53%) |
| CONGENITAL, FAMILIAL AND GENETIC DISORDERS | 1 (0.26%) | 0 (0.00%) |
| SURGICAL AND MEDICAL PROCEDURES | 0 (0.00%) | 1 (0.26%) |

In terms of individual TEAEs by preferred term, the most commonly reported events in the telavancin group of Study 0015 were diarrhea (12.6%), constipation (8.6%), anemia (8.1%), and hypokalemia (8.1%). The frequency of each of these events in the telavancin treatment group was within the range of the comparator group (14.4%, 9.6%, 13.1%, and 11.0%, respectively). In Study 0019, diarrhea (10.0%) and constipation (10.0%) were the most commonly reported events in the telavancin group, whereas diarrhea (10.0%) and hypokalemia (10.3%) were the most commonly reported events in the vancomycin group. Nausea and rash were more commonly reported in telavancin- compared to vancomycin-treated patients in Study 0015, but there was no marked disparity in the frequency of those events in the two treatment groups in Study 0019.

Table 144: FDA Medical Officer Table of Subject Count for all TEAE with frequency $\geq 5\%$ in telavancin and comparator treatment groups stratified by Preferred Term, Studies 0015 and 0019, AT Population

| Preferred Term | Study 0015 | | Study 0019 | |
|-------------------------|------------------------------|------------------------------|------------------------------|------------------------------|
| | Telavancin N=372 n (%) | Vancomycin N=374 n (%) | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
| Diarrhea | 47 (12.63) | 54 (14.44) | 38 (10.03) | 38 (10.05) |
| Constipation | 32 (8.60) | 36 (9.63) | 38 (10.03) | 35 (9.26) |
| Anemia | 30 (8.06) | 49 (13.10) | 34 (8.97) | 36 (9.52) |
| Hypokalemia | 30 (8.06) | 41 (10.96) | 31 (8.18) | 39 (10.32) |
| Nausea | 27 (7.26) | 19 (5.08) | 13 (3.43) | 12 (3.17) |
| Hypotension | 23 (6.18) | 26 (6.95) | 25 (6.60) | 26 (6.88) |
| Decubitus ulcer | 22 (5.91) | 26 (6.95) | 17 (4.49) | 18 (4.76) |
| Vomiting | 21 (5.65) | 19 (5.08) | 15 (3.96) | 12 (3.17) |
| Rash | 21 (5.65) | 10 (2.67) | 12 (3.17) | 16 (4.23) |
| Peripheral edema | 20 (5.38) | 26 (6.95) | 14 (3.69) | 12 (3.17) |
| Urinary tract infection | 19 (5.11) | 21 (5.61) | 14 (3.69) | 9 (2.38) |
| Insomnia | 16 (4.30) | 32 (8.56) | 18 (4.75) | 15 (3.97) |
| Hypertension | 11 (2.96) | 14 (3.74) | 21 (5.54) | 12 (3.17) |
| Anxiety | 10 (2.69) | 20 (5.35) | 12 (3.17) | 12 (3.17) |

n=number of subjects (patients) with the specified TEAE

The following table depicts the comparative frequency of TEAEs in the treatment groups in Study 0015 with a frequency of $\geq 2\%$. As depicted in the table, the most frequent TEAEs in the telavancin group were diarrhea (12.6%), constipation (8.6%), hypokalemia (8%), and anemia (8%), whereas the most common TEAEs in the vancomycin group were diarrhea (14.4%), anemia (13.1%), and hypokalemia (11.0%). It is noteworthy that the rate of acute renal failure as a TEAE in the telavancin group was $>1.8\%$ higher than that reported in the comparator group (2.7%).

Table 145: FDA Medical Officer Summary Table of Incidence (%) of TEAE reported with frequency of $\geq 2\%$ for patients treated with telavancin, Study 0015, AT Population

| Preferred term | Telavancin N=372 n (%) | Vancomycin N=374 n (%) |
|----------------------------|------------------------------|------------------------------|
| DIARRHOEA | 47 (12.63%) | 54 (14.44%) |
| CONSTIPATION | 32 (8.60%) | 36 (9.63%) |
| ANAEMIA | 30 (8.06%) | 49 (13.10%) |
| HYPOKALAEMIA | 30 (8.06%) | 41 (10.96%) |
| NAUSEA | 27 (7.26%) | 19 (5.08%) |
| HYPOTENSION | 23 (6.18%) | 26 (6.95%) |
| DECUBITUS ULCER | 22 (5.91%) | 26 (6.95%) |
| RASH | 21 (5.65%) | 10 (2.67%) |
| VOMITING | 21 (5.65%) | 19 (5.08%) |
| OEDEMA PERIPHERAL | 20 (5.38%) | 26 (6.95%) |
| URINARY TRACT INFECTION | 19 (5.11%) | 21 (5.61%) |
| RENAL FAILURE ACUTE | 18 (4.84%) | 10 (2.67%) |
| ATRIAL FIBRILLATION | 16 (4.30%) | 18 (4.81%) |
| RESPIRATORY FAILURE | 16 (4.30%) | 15 (4.01%) |
| INSOMNIA | 16 (4.30%) | 32 (8.56%) |
| SEPTIC SHOCK | 15 (4.03%) | 13 (3.48%) |
| MULTI-ORGAN FAILURE | 12 (3.23%) | 8 (2.14%) |
| HYPOGLYCAEMIA | 12 (3.23%) | 9 (2.41%) |
| HYPERKALAEMIA | 11 (2.96%) | 9 (2.41%) |
| BLOOD CREATININE INCREASED | 11 (2.96%) | 6 (1.60%) |
| HYPERTENSION | 11 (2.96%) | 14 (3.74%) |
| HYPOALBUMINAEMIA | 11 (2.96%) | 16 (4.28%) |
| HYPERGLYCAEMIA | 10 (2.69%) | 11 (2.94%) |
| AGITATION | 10 (2.69%) | 12 (3.21%) |
| FLUID OVERLOAD | 10 (2.69%) | 9 (2.41%) |
| ANXIETY | 10 (2.69%) | 20 (5.35%) |
| CARDIAC FAILURE CONGESTIVE | 10 (2.69%) | 12 (3.21%) |
| HEADACHE | 10 (2.69%) | 13 (3.48%) |
| SEPSIS | 9 (2.42%) | 10 (2.67%) |
| ORAL CANDIDIASIS | 9 (2.42%) | 5 (1.34%) |
| NON-CARDIAC CHEST PAIN | 8 (2.15%) | 7 (1.87%) |
| HAEMATURIA | 8 (2.15%) | 7 (1.87%) |
| PAIN | 8 (2.15%) | 7 (1.87%) |
| METABOLIC ACIDOSIS | 8 (2.15%) | 3 (0.80%) |
| PNEUMONIA | 8 (2.15%) | 8 (2.14%) |
| HYPONATRAEMIA | 8 (2.15%) | 11 (2.94%) |

The following table depicts the comparative frequency of TEAEs in the treatment groups in Study 0019 with a frequency of $\geq 2\%$. As depicted in the table, the most frequent TEAEs in the telavancin group were diarrhea (10.0%), constipation (10.0%), hypokalemia (8%), and anemia (9.0%), whereas the most common TEAEs in the vancomycin group were diarrhea (10.1%), anemia (9.5%), and hypokalemia (10.3%). It is noteworthy that the rate of acute renal failure as a TEAE in the telavancin group and vancomycin groups were comparable.

Table 146: FDA Medical Officer Summary Table of TEAE with incidence of ≥ 2 in patients treated with telavancin, Study 0019, AT Population

| Preferred term | Telavancin N=379 n (%) | Vancomycin N=378 n (%) |
|--------------------------------------|------------------------------|------------------------------|
| DIARRHOEA | 38 (10.03%) | 38 (10.05%) |
| CONSTIPATION | 38 (10.03%) | 35 (9.26%) |
| ANAEMIA | 34 (8.97%) | 36 (9.52%) |
| HYPOKALAEMIA | 31 (8.18%) | 39 (10.32%) |
| HYPOTENSION | 25 (6.60%) | 26 (6.88%) |
| HYPERTENSION | 21 (5.54%) | 12 (3.17%) |
| INSOMNIA | 18 (4.75%) | 15 (3.97%) |
| SEPTIC SHOCK | 17 (4.49%) | 16 (4.23%) |
| DECUBITUS ULCER | 17 (4.49%) | 18 (4.76%) |
| SEPSIS | 17 (4.49%) | 7 (1.85%) |
| RENAL FAILURE ACUTE | 16 (4.22%) | 18 (4.76%) |
| HYPERGLYCAEMIA | 16 (4.22%) | 17 (4.50%) |
| ATRIAL FIBRILLATION | 15 (3.96%) | 18 (4.76%) |
| VOMITING | 15 (3.96%) | 12 (3.17%) |
| OEDEMA PERIPHERAL | 14 (3.69%) | 12 (3.17%) |
| HYPOGLYCAEMIA | 14 (3.69%) | 9 (2.38%) |
| URINARY TRACT INFECTION | 14 (3.69%) | 9 (2.38%) |
| HYPERKALAEMIA | 13 (3.43%) | 10 (2.65%) |
| HEADACHE | 13 (3.43%) | 10 (2.65%) |
| MULTI-ORGAN FAILURE | 13 (3.43%) | 6 (1.59%) |
| NAUSEA | 13 (3.43%) | 12 (3.17%) |
| TACHYCARDIA | 12 (3.17%) | 7 (1.85%) |
| ANXIETY | 12 (3.17%) | 12 (3.17%) |
| RASH | 12 (3.17%) | 16 (4.23%) |
| HYPOALBUMINAEMIA | 11 (2.90%) | 3 (0.79%) |
| LEUKOCYTOSIS | 11 (2.90%) | 9 (2.38%) |
| HYPOMAGNESAEMIA | 10 (2.64%) | 7 (1.85%) |
| ALANINE AMINOTRANSFERASE INCREASED | 10 (2.64%) | 17 (4.50%) |
| RESPIRATORY FAILURE | 10 (2.64%) | 12 (3.17%) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 10 (2.64%) | 13 (3.44%) |
| CARDIAC FAILURE CONGESTIVE | 9 (2.37%) | 12 (3.17%) |
| DEPRESSION | 9 (2.37%) | 3 (0.79%) |
| THROMBOCYTOPENIA | 9 (2.37%) | 7 (1.85%) |
| AGITATION | 8 (2.11%) | 11 (2.91%) |
| HYPONATRAEMIA | 8 (2.11%) | 11 (2.91%) |
| PNEUMOTHORAX | 8 (2.11%) | 4 (1.06%) |
| PNEUMONIA | 8 (2.11%) | 7 (1.85%) |
| GASTROINTESTINAL HAEMORRHAGE | 8 (2.11%) | 12 (3.17%) |

Designated Medical Events

The following table summarizes the frequency of various TEAEs as designated medical events in the two telavancin NP studies by treatment group. The most frequently reported designated medical event was acute renal failure, which was reported in a higher percentage of telavancin treated compared to vancomycin treated patients in Study 0015. A similar imbalance was not observed in Study 0019.

Table 147: FDA Medical Officer Table of Subject Count who experienced Designated Medical Events by Treatment Group and Study, Studies 0015 and 0019, AT Population

| Designated Medical Event | Study 0015 | | Study 0019 | |
|--|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 |
| Acute pancreatitis | 0 (0.0%) | 1 (0.3%) | 0 (0.0%) | 0 (0.0%) |
| Acute respiratory failure | 1 (0.3%) | 4 (1.1%) | 4 (1.1%) | 4 (1.1%) |
| Agranulocytosis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Anaphylaxis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Aplastic anemia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Blindness | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Bone marrow depression | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Deafness | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Disseminated intravascular coagulation | 0 (0.0%) | 0 (0.0%) | 2 (0.5%) | 2 (0.5%) |
| Hemolytic anemia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Liver/hepatic failure | 0 (0.0%) | 1 (0.3%) | 1 (0.3) | 2 (0.5%) |
| Liver necrosis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Liver transplant | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Pancytopenia | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (0.3%) |
| Renal failure (acute) | 18 (4.8%) | 10 (2.7%) | 16 (4.2%) | 18 (4.8%) |
| Seizure | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Stevens Johnson Syndrome | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Torsades de pointes | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Toxic Epidermal Necrolysis | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Thrombotic thrombocytopenic purpura | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |
| Ventricular fibrillation | 0 (0.0%) | 2 (0.5%) | 1 (0.3%) | 0 (0.0%) |

There were four patients who developed hepatic failure: one vancomycin-treated patient in Study 0015, two vancomycin-treated patients in Study 0019, and one telavancin-treated patient in Study 0019. In three patients, the events were severe, but the events were considered to have been serious in only two patients by the investigators. There were two deaths, both involving vancomycin-treated subjects. In only one patient, a patient treated with vancomycin, was the event considered to have been possibly or probably related to study drug. The patients are summarized in the table below:

Table 148: FDA Medical Officer Summary Table of Patients who had hepatic failure as a designated medical event, Studies 0015 and 0019, AT Population

| Subject # | Study # | Treatment | Severity | Serious | Action Taken | Outcome | Relation to Study Drug |
|------------|---------|------------|----------|---------|--------------|---------------------------------------|---------------------------|
| 38045-4279 | 0015 | VANCOMYCIN | SEVERE | YES | NONE | PATIENT DIED | NOT RELATED |
| 08000-6257 | 0019 | VANCOMYCIN | MILD | NO | NONE | COMPLETELY RECOVERED | POSSIBLY/PROBABLY RELATED |
| 38069-6174 | 0019 | VANCOMYCIN | SEVERE | YES | NONE | PATIENT DIED | NOT RELATED |
| 38357-6534 | 0019 | TELAVANCIN | SEVERE | NO | NONE | CONDITION STILL PRESENT AND UNCHANGED | NOT RELATED |

As described in the Applicant’s narrative in the 0019 Clinical Study Report, the single telavancin patient (0019-38357-6534) reported with hepatic failure was a 79 year old male who had MRSA and *S. epidermidis* isolated from blood cultures and MRSA and *K. pneumoniae* isolated from respiratory cultures. The patient began treatment with telavancin and aztreonam. Baseline (Study Day 1) serum creatinine was 4.2 mg/dL (central laboratory reference range 0.5-1.5 mg/dL). On Study Day 4, aztreonam was discontinued and the patient was started on imipenem/cilastatin. Tobramycin was started on Study Day 7 for *Klebsiella pneumoniae*. On Study Day 8, the patient had disseminated intravascular coagulation along with a pneumothorax and worsening of renal failure. Prior to Study Day 8, he had anemia, hyperkalemia (resolved on Study Day 6), hypocalcemia, malnutrition, increased blood bilirubin, hepatic failure, and ventricular arrhythmia. All of the previously mentioned events except hyperkalemia were continuing at the time of death. Blood cultures obtained on Study Days 7 and 17 were negative. On Study Day 18, the sepsis worsened and on Study Day 19, his pneumonia had gotten worse. Study medication was discontinued on Study Day 19 due to consent withdrawal. The patient died on (b) (6) due to worsening disseminated intravascular coagulation. It is unknown if an autopsy was performed. End-of-therapy clinical response was assessed as indeterminate due to incomplete course of treatment.

Patient 0015-23003-4099 was an additional patient treated in the vancomycin arm of Study 0015 who developed acute liver failure and acute renal failure in association with *Candida parapsilosis* fungemia and later died.

7.4.2 Laboratory Findings

In the Phase 3 HAP trials (0015 and 0019), hematology, serum chemistry, and urinalysis were performed at Baseline, end of first infusion on Day 1, after the end of the first infusion on every third day (Days 1, 4, 7, 10, 13), at the EOT and at the TOC evaluation. All laboratory tests were performed at a central laboratory. The focus of the analysis of clinical laboratory assessments in this document is to initially review potentially clinically significant changes and then compare mean changes from Baseline for hematology and serum chemistry parameters within each treatment group and to determine whether there are clinically meaningful differences between treatment with telavancin and vancomycin in the frequency of such changes.

It is noteworthy that determinations of serum calcium, glucose, sodium, and uric acid were not performed as part of the central laboratory chemistry panel. In the Applicant's response to an information request from the Division dated February 25, 2009, the Applicant stated that "the choice of analytes for the safety laboratory panel was based on data from the preclinical and Phase 1 and 2 studies, which did not detect signals in any of these parameters".

Chemistry Shift Tables

The Applicant provided multiple shift tables in the 0015 and 0019 Clinical Study Reports. The data in the tables was verified by the FDA Medical Officer based on information in the electronic datasets provided by the Applicant. Selected chemistry shift tables are reproduced here for completeness (and the remainder are in the Appendix at the end of this report). Most subjects had normal baseline serum chemistry parameters, and they were maintained throughout the study.

For serum creatinine, however, there was a marked imbalance with a greater number of shifts from normal and low values at baseline to high values at EOT in the telavancin group (13.8%) compared to the vancomycin group (5.8%) for Study 0015, and the difference (telavancin – vancomycin) was statistically significant [95% CI = (3.1, 12.9)]. A similar imbalance for serum creatinine was not observed in Study 0019. Additionally, for BUN, there was a marked imbalance with a greater number of shifts to high values at EOT in the telavancin group (21.7%) compared to the vancomycin group (13.0%) in Study 0015, and the difference (telavancin – vancomycin) was statistically significant [95% CI = (1.8, 15.5)]. A similar imbalance with respect to BUN was not evident in Study 0019. Shifts in serum creatinine and BUN from normal and low values at baseline to high values at Follow-up/TOC were more frequent in the telavancin group compared to the vancomycin group in Study 0015, but the differences were not statistically significant.

In Study 0019, shifts in alkaline phosphatase levels from normal and low values at baseline to high levels at EOT were most notable in the vancomycin treatment group (23.8%) compared to the telavancin group (16.7%), and the difference (telavancin – vancomycin) was statistically significant [95% CI = (-14.2, -0.005)]. A similar imbalance was not observed in Study 0015.

Table 149: Chemistry Shift Tables - Study 0015, AT Population (from Applicant's Supporting Table 192)

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015

| Lab test name: ALKALINE PHOSPHATASE (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 62 | 46 | 0 | 68 | 54 | 1 |
| Normal | 29 | 185 | 0 | 23 | 182 | 1 |
| Low | 0 | 0 | 1 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 40 | 37 | 0 | 51 | 45 | 1 |
| Normal | 33 | 143 | 1 | 28 | 139 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: ALT (SGPT) (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 59 | 44 | 0 | 72 | 45 | 0 |
| Normal | 41 | 150 | 1 | 42 | 145 | 1 |
| Low | 0 | 3 | 2 | 0 | 2 | 2 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 36 | 28 | 0 | 32 | 33 | 0 |
| Normal | 43 | 132 | 2 | 53 | 123 | 3 |
| Low | 1 | 0 | 1 | 0 | 2 | 0 |

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: AST (SGOT) (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 65 | 36 | 0 | 76 | 35 | 0 |
| Normal | 40 | 142 | 0 | 49 | 125 | 1 |
| Low | 0 | 8 | 0 | 1 | 5 | 1 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 32 | 25 | 0 | 39 | 19 | 0 |
| Normal | 51 | 125 | 0 | 55 | 118 | 1 |
| Low | 0 | 2 | 0 | 0 | 3 | 0 |

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Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: CREATININE (UMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 56 | 38 | 0 | 41 | 15 | 2 |
| Normal | 15 | 214 | 3 | 24 | 239 | 8 |
| Low | 0 | 10 | 10 | 0 | 19 | 8 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 40 | 22 | 0 | 36 | 15 | 0 |
| Normal | 12 | 182 | 4 | 21 | 188 | 6 |
| Low | 0 | 3 | 8 | 0 | 11 | 8 |

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: TOTAL BILIRUBIN (UMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 22 | 8 | 0 | 24 | 12 | 0 |
| Normal | 20 | 215 | 11 | 22 | 211 | 8 |
| Low | 0 | 27 | 5 | 0 | 31 | 6 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 9 | 8 | 0 | 13 | 5 | 0 |
| Normal | 20 | 183 | 11 | 24 | 183 | 6 |
| Low | 0 | 14 | 3 | 0 | 13 | 5 |

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: UREA NITROGEN (MMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 76 | 49 | 0 | 62 | 31 | 0 |
| Normal | 31 | 173 | 2 | 45 | 206 | 1 |
| Low | 1 | 1 | 1 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 45 | 23 | 0 | 46 | 25 | 1 |
| Normal | 31 | 161 | 2 | 35 | 169 | 0 |
| Low | 0 | 0 | 0 | 0 | 1 | 0 |

Table 150: Chemistry Shift Tables - Study 0019, AT Population, (from Applicant's Supporting Table 193)

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019

| Lab test name: ALKALINE PHOSPHATASE (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 81 | 38 | 0 | 55 | 62 | 0 |
| Normal | 27 | 187 | 1 | 21 | 194 | 3 |
| Low | 1 | 0 | 1 | 0 | 1 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 51 | 38 | 1 | 41 | 46 | 0 |
| Normal | 28 | 142 | 0 | 19 | 144 | 2 |
| Low | 0 | 0 | 1 | 0 | 0 | 0 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: ALT (SGPT) (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 70 | 46 | 1 | 72 | 54 | 0 |
| Normal | 45 | 140 | 4 | 36 | 149 | 3 |
| Low | 0 | 3 | 0 | 0 | 0 | 1 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 43 | 34 | 1 | 38 | 29 | 0 |
| Normal | 49 | 107 | 3 | 37 | 126 | 1 |
| Low | 0 | 1 | 0 | 0 | 1 | 0 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: AST (SGOT) (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 80 | 38 | 0 | 76 | 46 | 0 |
| Normal | 58 | 122 | 3 | 47 | 133 | 2 |
| Low | 0 | 2 | 0 | 0 | 1 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 46 | 18 | 0 | 31 | 24 | 0 |
| Normal | 57 | 103 | 2 | 51 | 110 | 1 |
| Low | 0 | 4 | 0 | 0 | 3 | 0 |

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Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: CREATININE (UMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 31 | 25 | 3 | 20 | 23 | 1 |
| Normal | 12 | 247 | 11 | 31 | 240 | 8 |
| Low | 0 | 12 | 13 | 0 | 16 | 19 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 18 | 22 | 2 | 19 | 20 | 1 |
| Normal | 10 | 199 | 11 | 21 | 176 | 11 |
| Low | 0 | 5 | 9 | 0 | 12 | 7 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: TOTAL BILIRUBIN (UMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 25 | 7 | 0 | 22 | 5 | 0 |
| Normal | 20 | 231 | 9 | 21 | 240 | 3 |
| Low | 0 | 12 | 8 | 0 | 24 | 4 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 8 | 5 | 0 | 8 | 5 | 0 |
| Normal | 28 | 170 | 14 | 23 | 173 | 4 |
| Low | 0 | 11 | 2 | 0 | 21 | 2 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: UREA NITROGEN (MMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 70 | 39 | 0 | 52 | 33 | 0 |
| Normal | 41 | 192 | 1 | 55 | 206 | 0 |
| Low | 0 | 2 | 0 | 0 | 2 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 32 | 31 | 0 | 31 | 28 | 0 |
| Normal | 44 | 161 | 1 | 42 | 158 | 0 |
| Low | 0 | 0 | 0 | 0 | 1 | 0 |

Hematology Shift Tables

The Applicant provided multiple shift tables in the 0015 and 0019 Clinical Study Reports. The data in the tables was verified by the FDA Medical Officer. Selected hematology shift tables are reproduced here for completeness (and the remainder are in the Appendix at the end of this report). Most subjects had normal baseline hematology parameters, and they were maintained throughout the study.

For WBC count, however, there was a marked imbalance with a greater number of shifts from normal and low values at baseline to high values at TOC in the vancomycin group (24.2%) compared to the telavancin group (12.6%) for Study 0015, and the difference (telavancin – vancomycin) was statistically significant [95% CI = (-22.5, -0.7)]. A similar imbalance for WBC was not observed at EOT in Study 0015 nor was an imbalance observed in Study 0019 at either study visit.

Table 151: Hematology Shift Tables - Study 0015, AT Population (from Applicant's Supporting Table 190)

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: EOSINOPHILS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 3 | 8 | 0 | 0 | 10 | 0 |
| Normal | 2 | 259 | 0 | 4 | 251 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 14 | 0 | 0 | 16 | 0 |
| Normal | 2 | 209 | 0 | 4 | 190 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: HEMATOCRIT (L/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 1 | 1 |
| Normal | 1 | 62 | 19 | 1 | 50 | 26 |
| Low | 0 | 45 | 138 | 0 | 41 | 137 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 1 | 0 |
| Normal | 0 | 57 | 24 | 1 | 46 | 37 |
| Low | 0 | 35 | 95 | 0 | 28 | 89 |

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 NDA 22-407/N-000
 Theravance for injection (VIBATIV™)

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: HEMOGLOBIN (G/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 34 | 11 | 0 | 22 | 13 |
| Low | 0 | 36 | 209 | 0 | 36 | 209 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 34 | 24 | 0 | 26 | 25 |
| Low | 0 | 25 | 152 | 0 | 21 | 147 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: PLATELETS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 31 | 45 | 4 | 24 | 43 | 4 |
| Normal | 20 | 115 | 15 | 6 | 126 | 20 |
| Low | 0 | 8 | 11 | 1 | 9 | 11 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 28 | 34 | 3 | 16 | 39 | 3 |
| Normal | 16 | 95 | 17 | 13 | 96 | 11 |
| Low | 0 | 8 | 6 | 0 | 8 | 7 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: WBC (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 107 | 39 | 0 | 94 | 30 | 2 |
| Normal | 69 | 69 | 2 | 72 | 73 | 3 |
| Low | 1 | 2 | 1 | 0 | 5 | 2 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 61 | 12 | 0 | 47 | 22 | 1 |
| Normal | 79 | 77 | 1 | 77 | 70 | 1 |
| Low | 0 | 4 | 1 | 2 | 0 | 1 |

Table 152: Hematology Shift Tables - Study 0019, AT Population (from Applicant's Supporting Table 191)

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: EOSINOPHILS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 4 | 8 | 0 | 1 | 10 | 0 |
| Normal | 5 | 254 | 0 | 5 | 257 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 3 | 6 | 0 | 0 | 10 | 0 |
| Normal | 3 | 200 | 0 | 4 | 183 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: HEMATOCRIT (L/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 1 | 0 | 0 | 0 | 1 |
| Normal | 1 | 44 | 19 | 1 | 66 | 24 |
| Low | 0 | 31 | 170 | 0 | 32 | 158 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 1 | 0 |
| Normal | 2 | 49 | 39 | 1 | 47 | 33 |
| Low | 0 | 24 | 91 | 0 | 24 | 96 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: HEMOGLOBIN (G/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 34 | 19 | 1 | 38 | 11 |
| Low | 0 | 22 | 208 | 0 | 33 | 213 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 32 | 31 | 1 | 30 | 24 |
| Low | 0 | 23 | 133 | 0 | 24 | 138 |

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Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: PLATELETS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 28 | 49 | 2 | 26 | 64 | 3 |
| Normal | 17 | 122 | 16 | 14 | 136 | 12 |
| Low | 1 | 10 | 10 | 0 | 8 | 12 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 18 | 47 | 2 | 18 | 46 | 4 |
| Normal | 16 | 88 | 7 | 17 | 98 | 9 |
| Low | 0 | 6 | 3 | 0 | 5 | 4 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: WBC (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 96 | 36 | 0 | 94 | 38 | 2 |
| Normal | 53 | 93 | 2 | 71 | 86 | 3 |
| Low | 1 | 1 | 3 | 0 | 3 | 1 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 52 | 16 | 0 | 46 | 18 | 1 |
| Normal | 66 | 80 | 2 | 72 | 75 | 2 |
| Low | 1 | 2 | 1 | 2 | 2 | 1 |

Analysis of Measures of Central Tendency

The following tables provide the mean (\pm standard deviation) and the median changes from baseline to EOT for various selected hematology and chemistry parameters:

Table 153: FDA Medical Officer Table of Measures of Central Tendency for Changes from Baseline to EOT for Serum Hematology Tests, Studies 0015 and 0019, AT Safety Population

| Parameter (units) | Study 0015 | | | | | | Study 0019 | | | | | |
|-------------------------------|------------|---------------|--------|------------|---------------|--------|------------|---------------|--------|------------|---------------|--------|
| | Telavancin | | | Vancomycin | | | Telavancin | | | Vancomycin | | |
| | n | Mean (SD) | Median |
| Hematocrit (L/L) | 265 | -0.01 (0.05) | -0.01 | 257 | -0.01 (0.05) | -0.01 | 267 | -0.01 (0.05) | -0.01 | 282 | -0.005 (0.05) | -0.01 |
| Hemoglobin (G/L) | 290 | -4.71 (15.5) | -5.00 | 280 | -3.91 (15.72) | -4.00 | 283 | -2.34 (15.02) | -2.00 | 296 | -2.64 (15.16) | -2.00 |
| WBC ($\times 10^9/L$) | 290 | -1.53 (6.27) | -1.15 | 281 | -1.83 (6.34) | -1.23 | 285 | -0.96 (6.38) | -0.72 | 298 | -1.17 (5.82) | -1.16 |
| RBC ($\times 10^{12}/L$) | 290 | -0.13 (0.52) | -0.10 | 275 | -0.11 (0.53) | -0.10 | 280 | -0.07 (0.51) | -0.10 | 293 | -0.07 (0.52) | -0.10 |
| Platelets ($\times 10^9/L$) | 249 | 64.77 (172.3) | 50.0 | 244 | 84.26 (162.5) | 56.5 | 255 | 45.09 (154.3) | 36.0 | 275 | 93.37 (205.9) | 59.0 |
| Eosinophils (%) | 272 | 0.72 (2.09) | 0.40 | 265 | 1.00 (2.24) | 0.75 | 271 | 0.59 (2.27) | 0.30 | 273 | 0.72 (2.14) | 0.50 |

n = number of patients with baseline and EOT measurements

Overall, the measures of central tendency for the changes from baseline to EOT were comparable across treatment groups within each trial and across the two trials for the selected hematology parameters. However, there were greater increases in the mean and median changes from baseline for platelet counts in the vancomycin treatment groups compared to the telavancin treatment groups in both trials.

Table 154: FDA Medical Officer Table of Measures of Central Tendency for Changes from Baseline to EOT for Serum Chemistry Tests, Studies 0015 and 0019, AT Safety Population

| Parameter (units) | Study 0015 | | | | | | Study 0019 | | | | | |
|---------------------------------------|------------|---------------|--------|------------|----------------|--------|------------|---------------|--------|------------|---------------|--------|
| | Telavancin | | | Vancomycin | | | Telavancin | | | Vancomycin | | |
| | n | Mean (SD) | Median | n | Mean (SD) | Median | n | Mean (SD) | Median | n | Mean (SD) | Median |
| ALT (U/L) | 300 | -2.52 (127.6) | 1.00 | 309 | -2.79 (119.2) | 0.00 | 309 | 0.55 (131.0) | 1.00 | 315 | 1.55 (73.84) | 2.00 |
| AST (U/L) | 291 | -1.92 (74.47) | -2.00 | 293 | -14.16 (123.8) | -4.00 | 303 | 16.37 (302.9) | -2.00 | 305 | -3.76 (81.65) | -1.00 |
| Creatinine ($\mu\text{mol}/L$) | 346 | 13.28 (74.91) | 0.00 | 356 | -6.45 (91.50) | -5.00 | 354 | 8.48 (52.88) | 0.00 | 358 | -0.58 (67.98) | -4.00 |
| Creatinine clearance (ml/min) | 337 | -1.71 (32.51) | 0.00 | 346 | 4.02 (36.93) | 4.30 | 347 | -4.65 (38.43) | 0.00 | 352 | 6.33 (43.00) | 3.30 |
| Magnesium (mmol/L) | 333 | 0.00 (0.16) | 0.00 | 336 | 0.00 (0.18) | 0.00 | 337 | -0.02 (0.18) | -0.02 | 337 | -0.02 (0.18) | 0.00 |
| Potassium (mmol/L) | 323 | -0.01 (0.80) | 0.00 | 332 | 0.12 (0.84) | 0.10 | 338 | -0.05 (0.87) | 0.00 | 340 | 0.12 (0.85) | 0.10 |
| Total bilirubin ($\mu\text{mol}/L$) | 308 | -2.67 (22.05) | -1.1 | 314 | -3.06 (12.65) | -2.00 | 312 | -3.40 (14.34) | -1.10 | 319 | -1.97 (13.92) | -1.10 |

n = number of patients with baseline and EOT measurements

Overall, the measures of central tendency for the changes from baseline to EOT were comparable across treatment groups within each trial and across the two trials for the selected chemistry parameters. 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 of both trials compared to concomitant mean decreases in serum creatinine and

mean increases in creatinine clearance in the vancomycin groups of both trials. The median serum creatinine declined in the vancomycin groups of both trials compared to no change in the telavancin groups. These findings provide additional evidence of the potential for nephrotoxicity from telavancin use.

Two-grade Post-baseline Toxicity Increases

In response to an information request from the Division dated February 25, 2009, the Applicant provided electronic datasets that included flags for patients who experienced at least a two-fold post-baseline increase in toxicity grade. The data stratified by study and treatment arm are provided in the table below:

Table 155: FDA Medical Officer Summary Table of Patient Count who experienced a Two-grade Toxicity Increase stratified by Laboratory Test and Treatment Group, Studies 0015 and 0019, AT Safety Population

| Lab Test | Study 0015 | | | Study 0019 | | |
|----------------------|-----------------------|-----------------------|--|-----------------------|-----------------------|--|
| | TLV N=372 n (%) | VAN N=374 n (%) | 95% CI for risk difference (TLV-VAN) | TLV N=379 n (%) | VAN N=378 n (%) | 95% CI for risk difference (TLV-VAN) |
| Alkaline phosphatase | 7 (1.9) | 16 (4.3) | -2.4 (-4.9, 0.1) | 9 (2.4) | 9 (2.4) | -0.006 (-2.2, 2.2) |
| ALT (SGPT) | 21 (5.6) | 29 (7.8) | -2.1 (-5.7, 1.5) | 30 (7.9) | 29 (7.7) | 0.2 (-3.6, 4.1) |
| AST (SGOT) | 19 (5.1) | 19 (5.1) | 0.03 (-3.1, 3.2) | 25 (6.6) | 24 (6.3) | 0.2 (-3.3, 3.8) |
| Creatinine | 35 (9.4) | 14 (3.7) | 5.7 (2.1, 9.2)* | 24 (6.3) | 19 (5.0) | 1.3 (-2.0, 4.6) |
| Hemoglobin | 24 (6.5) | 21 (5.6) | 0.8 (-2.6, 4.3) | 20 (5.3) | 20 (5.3) | -0.01 (-3.2, 3.2) |
| Lymphocytes | 39 (10.5) | 43 (11.5) | -1.0 (-5.5, 3.5) | 37 (9.8) | 36 (9.5) | 0.3 (-3.9, 4.6) |
| Magnesium | 18 (4.8) | 20 (5.3) | -0.5 (-3.7, 2.6) | 22 (5.8) | 18 (4.8) | 1.0 (-2.1, 4.2) |
| Neutrophils | 2 (0.5) | 2 (0.5) | 0.003 (-1.0, 1.0) | 2 (0.5) | 6 (1.6) | -1.1 (-2.5, 0.4) |
| Platelets | 1 (0.3) | 6 (1.6) | -1.3 (-2.7, 0.04) | 7 (1.8) | 9 (2.4) | -0.5 (-2.6, 1.5) |
| Serum potassium | 42 (11.3) | 39 (10.4) | 0.9 (-3.6, 5.3) | 54 (14.2) | 42 (11.1) | 3.1 (-1.6, 7.9) |
| Total bilirubin | 9 (2.4) | 9 (2.4) | 0.01 (-2.2, 2.2) | 7 (1.8) | 8 (2.1) | -0.26 (-2.3, 1.8) |
| WBC | 2 (0.5) | 8 (2.1) | -1.6 (-3.2, 0.04) | 2 (0.5) | 3 (0.8) | -0.3 (-1.4, 0.9) |
| TOTAL Subject Count | 219 (58.9) | 226 (60.4) | 1.1 (-6.0, 8.2) | 239 (63.1) | 223 (59.0) | 4.1 (-2.9, 11.0) |

*statistically significant difference; TLV=telavancin, VAN=vancomycin

As depicted in the table above, there is a higher frequency of two-grade toxicity increases in creatinine in the telavancin group compared to the vancomycin group of Study 0015, and the difference is statistically significant. A similar finding was not evident in Study 0019 for telavancin-treated patients. In relation to the other laboratory tests listed in the table, there were no statistically significant within-study differences in the frequency of two-grade toxicity increases.

The Applicant also provided a similar table of patient count with at least a two-grade increase in toxicity. However, the Applicant's table included pooled telavancin and pooled vancomycin data without comment on whether any of the cross-treatment differences were statistically significant. The following table from the FDA Medical Officer provides the 95% CI for the risk difference.

Table 156: FDA Medical Officer Table of Patient Count who experienced a Two-grade Toxicity Increase stratified by Laboratory Test and Treatment Group in the pooled telavancin and pooled vancomycin groups, Studies 0015 and 0019, AT Safety Population

| Lab Test | Pooled TLV N=751 n (%) | Pooled VAN N=752 n (%) | 95% CI for risk difference (TLV-VAN) |
|----------------------|------------------------------|------------------------------|--|
| Alkaline phosphatase | 16 (2.1) | 25 (3.3) | -1.2 (-2.8, 0.5) |
| ALT (SGPT) | 51 (6.8) | 58 (7.7) | -0.9 (-3.5, 1.7) |
| AST (SGOT) | 44 (5.9) | 43 (5.7) | 0.1 (-2.2, 2.5) |
| Creatinine | 59 (7.9) | 33 (4.4) | 3.5 (1.0, 5.9)* |
| Hemoglobin | 44 (5.9) | 41 (5.5) | 0.4 (-1.9, 2.7) |
| Lymphocytes | 76 (10.1) | 79 (10.5) | -0.4 (-3.5, 2.7) |
| Magnesium | 40 (5.3) | 38 (5.1) | 0.3 (-2.0, 2.5) |
| Neutrophils | 4 (0.5) | 8 (1.1) | -0.5 (-1.4, 0.4) |
| Platelets | 8 (1.1) | 15 (2.0) | -0.9 (-2.2, 0.3) |
| Serum potassium | 96 (12.8) | 81 (10.8) | 2.0 (-1.2, 5.3) |
| Total bilirubin | 16 (2.1) | 17 (2.3) | -0.1 (-1.6, 1.4) |
| WBC | 4 (0.5) | 11 (1.5) | -0.9 (-1.9, 0.1) |
| TOTAL Subject Count | 458 (61.0) | 449 (59.7) | 1.2 (-3.7, 6.2) |

*statistically significant difference; TLV=telavancin, VAN=vancomycin

As depicted in the table above, there is a higher frequency of two-grade toxicity increases in serum creatinine in the pooled telavancin group compared to the pooled vancomycin group, and the difference is statistically significant.

In order to assess for a potential association between a two-grade toxicity increase in creatinine and baseline renal impairment, the number of patients in the telavancin arm who had a baseline serum creatinine >1.2 mg/dL was compared to the number of patients with similar baseline findings in the vancomycin arm of Study 0015. Among the 35 telavancin-treated patients with a two-grade toxicity increase in creatinine, 12 (34.2%) had a baseline serum creatinine >1.2 mg/dL. In contrast, only 2 of the 14 (14.3%) vancomycin-treated patients with a two-grade toxicity increase in creatinine had a baseline serum creatinine >1.2 mg/dL. Thus, it appears that telavancin exposure among patients with an abnormal baseline serum creatinine in Study 0015 is associated with a higher risk for a two-grade toxicity increase in creatinine. In contrast, in Study 0019, four patients in each treatment group who had a baseline serum creatinine >1.2 mg/dL experienced a two-grade toxicity increase in creatinine.

In order to assess for a potential association between a two-grade toxicity increase in creatinine and mortality, the number of patients in the telavancin group compared to the vancomycin group of Study 0015 who had a two-grade toxicity increase in creatinine and died between start of study drug and EOT + 28 days was determined. In the telavancin group, 12 of the 85 (14.1%) patients who died in that reporting period had experienced a two-grade toxicity increase in creatinine compared to 2 of the 63 (3.2%) patients in the vancomycin group who died, and the difference was statistically significant. Thus, the above findings collectively suggest a possible association between telavancin exposure in patients with abnormal baseline serum creatinine and

increased risks for two-grade toxicity increases in creatinine and higher mortality. A similar finding was not evident in Study 0019 for the same parameters.

7.4.3 Vital Signs

The vital signs that were measured at the pre-treatment visit for all enrolled patients included temperature, diastolic and systolic blood pressure, heart rate, and respiratory rate. However, the only vital signs measured at subsequent visits were temperature and respiratory rate. As axillary temperatures were utilized for multiple patients at various study visits despite their poor accuracy and reproducibility, an analysis of temperature could not be conducted. A safety analysis could not be performed regarding diastolic and systolic blood pressure and heart rate, since no post-baseline recordings were provided in the datasets for this NDA.

Table 157: FDA Medical Officer Criteria for Abnormal Vital Signs as marked outliers, AT Population

| Vital Sign | Age Group | Gender | Markedly Abnormal Criteria | |
|------------------|-----------|--------|----------------------------|--------------|
| | | | Less Than | Greater Than |
| Oral Temp (°C) | ≥18 | Both | 35.6 | 40.5 |
| Respiratory Rate | ≥18 | Both | 12 | 20 |

The results of analyzing individual vital sign parameters for marked outliers using the criteria above are summarized in the following tables:

Table 158: FDA Medical Officer Summary Table of Subject Count with Respiratory Rate abnormalities as Marked Outliers, AT Population

| Respiratory Rate (breaths/min) | Study Visit | Study 0015 | | Study 0019 | |
|--------------------------------|----------------|---------------|---------------|---------------|---------------|
| | | TLV | VAN | TLV | VAN |
| >25 | Baseline | 216/361 (60%) | 193/365 (53%) | 167/367 (46%) | 168/364 (46%) |
| | Day 2 | 130/343 (38%) | 150/358 (42%) | 121/353 (34%) | 123/345 (36%) |
| | Day 7 | 76/233 (32%) | 63/254 (25%) | 67/260 (26%) | 68/258 (26%) |
| | Day 10 | 29/125 (23%) | 34/136 (25%) | 40/145 (28%) | 45/155 (29%) |
| | Day 14 | 12/46 (26%) | 10/48 (21%) | 17/55 (31%) | 16/58 (28%) |
| | Day 21 | 0 (0%) | 1/3 (33%) | 1/3 (33%) | 6/12 (50%) |
| | End of Therapy | 72/337 (21%) | 79/354 (22%) | 89/354 (25%) | 79/350 (23%) |
| | TOC/ follow-up | 37/263 (14%) | 37/258 (14%) | 35/271 (13%) | 36/258 (14%) |
| <10 | Baseline | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Day 2 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Day 7 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Day 10 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Day 14 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Day 21 | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | End of Therapy | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | TOC/ follow-up | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |

As depicted above, there were comparable frequencies of tachypnea (respiratory rate >25 breaths/min) in the two treatment groups for both of the telavancin NP studies at the various time points assessed. There were no patients with recorded respiratory rates of <10 breaths/min in either study.

7.4.4 Electrocardiograms (ECGs)

According to the Applicant's Clinical Study Reports, the focus of the analysis of ECGs was on the QTcF interval. Other ECG variables, including morphology, PR, HR, and overall interpretation were provided in separate listings. Electrocardiograms were acquired prior to the initial dose of study medication and post-infusion on Study Days 4, 7, 10, 14, 17, and 21 and at the EOT Visit. Machine-read results were submitted to a central facility (eResearch Technology, Inc.) for manual reading.

Table 159: FDA Medical Officer Summary Table of Post-dose Changes from Baseline in QTc Interval (corrected by Fredericia's Correction Formula), adapted from Table 9-20 of the Applicant's 0015 and 0019 Clinical Study Reports, AT population

| | Study 0015 | | | Study 0019 | | |
|-------------------------------------|---------------------|---------------------|---------|---------------------|---------------------|---------|
| | Telavancin N=372 | Vancomycin N=374 | p-value | Telavancin N=379 | Vancomycin N=378 | p-value |
| Post-baseline Average Change (msec) | | | | | | |
| Mean, SD | 5.7, 26.77 | 2.9, 26.73 | 0.197 | 6.3, 22.42 | 1.2, 27.06 | 0.010 |
| Median | 4.7 | 2.6 | | 5.8 | 2.6 | |
| Min, max | -88.3, 86.9 | -84.8, 103.7 | | -53.6, 143.9 | -93.7, 104.3 | |
| n | 309 | 320 | | 322 | 320 | |
| Post-baseline Maximum Change (msec) | | | | | | |
| Mean, SD | 18.3, 30.24 | 16.4, 30.25 | 0.453 | 19.9, 29.27 | 13.7, 30.24 | 0.009 |
| Median | 16.3 | 14.7 | | 16.2 | 11.8 | |
| Min, max | -75.3, 152.3 | -76.3, 173.0 | | -49.7, 246.7 | -93.7, 129.3 | |
| n | 309 | 320 | | 322 | 320 | |
| Post-baseline Maximum Value (n) | | | | | | |
| ≤ 450 msec | 264 (80%) | 293 (84%) | | 294 (87%) | 286 (84%) | |
| >450 – 480 msec | 56 (17%) | 40 (11%) | | 30 (9%) | 43 (13%) | |
| >480 – 500 msec | 6 (2%) | 10 (3%) | | 6 (2%) | 5 (1%) | |
| >500 msec | 4 (1%) | 6 (2%) | | 8 (2%) | 6 (2%) | |
| Total | 330 | 349 | | 338 | 340 | |
| Post-baseline Maximum Change (n) | | | | | | |
| ≤30 msec | 213 (69%) | 242 (76%) | | 226 (70%) | 236 (74%) | |
| >30 – 60 msec | 69 (22%) | 55 (17%) | | 75 (23%) | 63 (20%) | |
| >60 msec | 27 (9%) | 23 (7%) | | 21 (7%) | 21 (7%) | |
| Total | 309 | 320 | | 322 | 320 | |

There was a higher post-baseline average change (msec) in QTcF interval and a higher maximum post-baseline change (msec) in QTcF interval in the patients in the telavancin group compared to the vancomycin group in Study 0019, and the differences were statistically significant. A similar finding was not observed in Study 0015.

Table 160: FDA Medical Officer Summary Table of Post-dose Changes from Baseline in QTc Interval (corrected by Bazett’s Correction Formulas), adapted from Tables 199 and 200 from the Applicant’s 0015 and 0019 Clinical Study Reports, AT population

| | Study 0015 | | | Study 0019 | | |
|-------------------------------------|---------------|--------------|---------|--------------|--------------|---------|
| | Telavancin | Vancomycin | p-value | Telavancin | Vancomycin | p-value |
| Post-baseline Average Change (msec) | | | | | | |
| Mean, SD | 3.8, 26.56 | -0.4, 25.74 | 0.046 | 4.6, 23.92 | -1.5, 26.57 | 0.002 |
| Median | 2.7 | 0.4 | | 4.6 | -1.2 | |
| Min, max | -106.8, 3.3 | -81.7, 87.0 | | -68.3, 154.3 | -98.0, 104.3 | |
| n | 309 | 320 | | 322 | 320 | |
| Post-baseline Maximum Change (msec) | | | | | | |
| Mean, SD | 16.6, 30.77 | 13.3, 28.93 | 0.168 | 18.0, 30.40 | 11.1, 29.0 | 0.003 |
| Median | 14.0 | 13.5 | | 15.8 | 9.5 | |
| Min, max | -106.3, 148.6 | -77.0, 157.3 | | -68.3, 259.9 | -90.3, 135.3 | |
| n | 309 | 320 | | 322 | 320 | |
| Post-baseline Maximum Value (n) | | | | | | |
| ≤ 450 msec | 164 (50%) | 211 (60%) | | 204 (60%) | 216 (64%) | |
| >450 – 480 msec | 110 (33%) | 94 (27%) | | 96 (28%) | 81 (24%) | |
| >480 – 500 msec | 36 (11%) | 21 (6%) | | 21 (6%) | 29 (9%) | |
| >500 msec | 20 (6%) | 23 (7%) | | 17 (5%) | 14 (4%) | |
| Total | 330 | 349 | | 338 | 340 | |
| Post-baseline Maximum Change (n) | | | | | | |
| ≤30 msec | 222 (72%) | 246 (77%) | | 233 (72%) | 253 (79%) | |
| >30 – 60 msec | 62 (20%) | 56 (18%) | | 65 (20%) | 53 (17%) | |
| >60 msec | 25 (8%) | 18 (6%) | | 24 (7%) | 14 (4%) | |
| Total | 309 | 320 | | 322 | 320 | |

There was a higher post-baseline average change (msec) in QTcB interval and a higher maximum post-baseline change (msec) in QTcB interval in the patients in the telavancin group compared to the vancomycin group in Study 0019, and the difference was statistically significant. A similar higher post-baseline average change (msec) in QTcB interval in the patients in the telavancin group compared to the vancomycin group was observed in Study 0015, and the difference was statistically significant.

Table 161: FDA Medical Officer Table of the number of Patients with maximum post-baseline QTcF values >500 msec and maximum increase from baseline in QTcF >60 msec, Studies 0015 and 0019, All treated population

| Clinical Trial | Treatment | Max post-baseline QTcF >500 msec | Max increase from baseline in QTcF >60 msec |
|----------------|------------|----------------------------------|---|
| 0015 | Telavancin | 4 | 27 |
| | Vancomycin | 6 | 23 |
| 0019 | Telavancin | 8 | 21 |
| | Vancomycin | 6 | 21 |

A total of 24 patients exhibited maximum post-baseline QTcF values >500 msec and 92 patients had maximum increases from baseline in QTcF >60 msec as depicted in the table above.

Clinical Review
 Alfred Sorbello, DO, MPH
 NDA 22-407/N-000
 Theravance for injection (VIBATIV™)

Table 162: FDA Medical Officer Summary Table of Patients with Maximum QTc > 500 msec, Studies 0015 and 0019, AT Population

| Subject # | Study | Treatment | Max increase from baseline in QTcF >60 msec | Cardiac SAE | Death | FDA Medical Officer Notes |
|-----------------|-------|-----------|---|---------------------|-------|---|
| 0015-01014-4042 | 0015 | TLV | | | | |
| 0015-01028-4440 | 0015 | TLV | X | | | TLV discontinued due to prolonged QTc |
| 0015-06013-4156 | 0015 | TLV | X | Myocardial ischemia | | |
| 0015-52000-4703 | 0015 | TLV | | | | |
| 0015-01012-4045 | 0015 | VAN | X | | | |
| 0015-05004-4460 | 0015 | VAN | X | Cardiac failure | X | |
| 0015-06026-4508 | 0015 | VAN | | | | |
| 0015-33001-4483 | 0015 | VAN | X | | | |
| 0015-41013-4681 | 0015 | VAN | | | | |
| 0015-41016-4354 | 0015 | VAN | X | | | TEAE: sinus tachycardia, QTc prolongation |
| 0019-01016-6081 | 0019 | TLV | X | | | |
| 0019-08008-6635 | 0019 | TLV | | | | |
| 0019-20013-6406 | 0019 | TLV | X | | | TEAE: bradycardia |
| 0019-20017-6463 | 0019 | TLV | X | | | TEAE: myocardial ischemia and TLV discontinued due to prolonged QTc |
| 0019-34002-6653 | 0019 | TLV | X | | | |
| 0019-34003-6123 | 0019 | TLV | | | | |
| 0019-34003-6541 | 0019 | TLV | X | | | |
| 0019-38357-6534 | 0019 | TLV | X | | | TEAE: ventricular dysrhythmia |
| 0019-01006-6550 | 0019 | VAN | | | | |
| 0019-02028-6613 | 0019 | VAN | X | | | |
| 0019-05000-6067 | 0019 | VAN | X | | | |
| 0019-20010-6324 | 0019 | VAN | X | | | TEAE: acute myocardial infarction and cardiogenic shock |
| 0019-22006-6519 | 0019 | VAN | X | | | |
| 0019-44001-6577 | 0019 | VAN | | Cardiac failure | X | |

TLV = telavancin; VAN = vancomycin

As depicted above, 24 patients exhibited maximum post-baseline QTcF values >500 msec during study participation, including 10 patients in Study 0015 (4 telavancin and 6 vancomycin treated) and 14 patients in Study 0019 (8 telavancin and 6 vancomycin treated). Of the 24 patients, 16 also exhibited a maximum increase from baseline in QTcF >60 msec, including 6 patients in Study 0015 (2 telavancin and 4 vancomycin treated) and 10 patients (6 telavancin and 4 vancomycin treated) in Study 0019. Three patients experienced serious cardiac adverse events and two patients died. Telavancin was discontinued in two patients due to QTc prolongation. One of the vancomycin-treated patients was reported with QTc prolongation as a TEAE.

7.4.5 Special Safety Studies/Clinical Trials

The Applicant performed a thorough QT/QTc study (designed with guidelines as defined in the 2002 FDA-Health Canada Concept paper), which demonstrated that telavancin prolonged the QTc interval >10 msec. Please refer to the original NDA 22-110 for the report of the Interdisciplinary Review Team for QT Studies for details.

7.4.6 Immunogenicity

Telavancin is a low molecular weight compound and was not tested for immunogenicity.

7.5 Other Safety Explorations

C. difficile-associated disease

Eight patients developed *C. difficile*-related diarrhea or colitis while participating in the two telavancin NP studies, including two telavancin-treated and five vancomycin-treated patients in Study 0015 and one telavancin-treated patient in Study 0019. The episodes of *C. difficile* related disease were moderate to severe in intensity, but none of the events were assessed as serious by study investigators. No action was taken with respect to study drug in any of the eight patients. Six of the eight patients recovered completely. The event was assessed as possibly/probably related to study drug in three patients. The following table summarizes the affected patients:

Table 163: FDA Medical Officer Table of Patients who developed *C. difficile* associated diarrhea or colitis as a TEAE, Studies 0015 and 0019, AT Safety Population

| Subject ID # | Study | Treatment | Adverse event | Severity | Serious | Action Taken | Outcome | Relation to study drug |
|--------------|-------|-----------|-----------------------------|----------|---------|--------------|---------------------------------------|---------------------------|
| 38148-4745 | 0015 | TLV | CLOSTRIDIUM COLITIS | SEVERE | NO | NONE | COMPLETELY RECOVERED | POSSIBLY/PROBABLY RELATED |
| 38311-4724 | 0015 | TLV | CLOSTRIDIUM COLITIS | MILD | NO | NONE | CONDITION IMPROVING | NOT RELATED |
| 38024-4568 | 0015 | VAN | CLOSTRIDIUM COLITIS | MODERATE | NO | NONE | COMPLETELY RECOVERED | POSSIBLY/PROBABLY RELATED |
| 38045-4279 | 0015 | VAN | CLOSTRIDIAL INFECTION | MODERATE | NO | NONE | CONDITION STILL PRESENT AND UNCHANGED | NOT RELATED |
| 38070-4748 | 0015 | VAN | CLOSTRIDIUM COLITIS | MODERATE | NO | NONE | COMPLETELY RECOVERED | NOT RELATED |
| 38148-4675 | 0015 | VAN | CLOSTRIDIUM COLITIS | MODERATE | NO | NONE | COMPLETELY RECOVERED | NOT RELATED |
| 38348-4251 | 0015 | VAN | CLOSTRIDIAL INFECTION | SEVERE | NO | NONE | COMPLETELY RECOVERED | POSSIBLY/PROBABLY RELATED |
| 38357-6508 | 0019 | TLV | GASTROENTERITIS CLOSTRIDIAL | MODERATE | NO | NONE | COMPLETELY RECOVERED | NOT RELATED |

TLV = telavancin; VAN = vancomycin

FDA Medical Officer Comment: All of the patients had received prior or concomitant antibacterial drugs that could have contributed to the development of C. difficile diarrhea.

Concomitant procedures for adverse events

The most frequent adverse events that required concomitant procedures were renal-related (renal failure, renal failure acute, renal impairment, renal insufficiency, and anuria). The concomitant procedures for these renal AEs involved hemodialysis and veno venous hemofiltration. Eight telavancin-treated and five vancomycin-treated patients in Study 0015 required concomitant procedures for renal-related AEs, and four patients each in the telavancin and vancomycin treatment groups in Study 0019 required concomitant procedures for renal-related AEs. Two telavancin-treated patients in Study 0015 and three patients in the vancomycin group of Study 0019 required blood transfusion. One patient each in the vancomycin group of Study 0015 and both treatment groups of Study 0019 required cardioversion for various arrhythmias. The following table summarizes the concomitant procedures for adverse events.

Table 164: FDA Medical Officer Table of Concomitant Procedures for Adverse Events, Studies 0015 and 0019, AT Safety Population

| Adverse Event | Concomitant Procedure | N | Study 0015 | | Study 0019 | |
|------------------------------|---|---|------------|-----|------------|-----|
| | | | TLV | VAN | TLV | VAN |
| ACUTE MYOCARDIAL INFARCTION | INCREMENTAL DEFIBRILLATION | 1 | 0 | 0 | 1 | 0 |
| ANAEMIA | BLOOD TRANSFUSION | 2 | 1 | 0 | 0 | 1 |
| ANURIA | VENO VENOUS HEMOFILTRATION | 1 | 1 | 0 | 0 | 0 |
| ATRIAL FIBRILLATION | CARDIOVERSION | 1 | 0 | 0 | 1 | 0 |
| BRADYCARDIA | CARDIOVERSION | 1 | 0 | 0 | 0 | 1 |
| CARDIAC FAILURE | BLOOD TRANSFUSION | 1 | 0 | 0 | 0 | 1 |
| CHOLECYSTITIS | PERCUTANEOUS CHOLECYSTOSTOMY TUBE PLACEMENT | 1 | 0 | 0 | 1 | 0 |
| HEPATORENAL SYNDROME | PARACENTESIS | 1 | 1 | 0 | 0 | 0 |
| HYPOVOLAEMIC SHOCK | 2 UNITS PRBC | 1 | 1 | 0 | 0 | 0 |
| MYOCARDIAL ISCHAEMIA | EXTERNAL PACEMAKER | 1 | 0 | 1 | 0 | 0 |
| RENAL FAILURE | HEMODIALYSIS | 2 | 1 | 0 | 0 | 1 |
| RENAL FAILURE | HEMODIALYSIS RECOMMENDED | 1 | 0 | 0 | 0 | 1 |
| RENAL FAILURE ACUTE | CONTINUOUS VENO VENEUS HEMOFILTRATION | 1 | 0 | 1 | 0 | 0 |
| RENAL FAILURE ACUTE | DIALYSIS | 3 | 1 | 1 | 1 | 0 |
| RENAL FAILURE ACUTE | HEMODIALYSIS | 6 | 2 | 1 | 2 | 1 |
| RENAL FAILURE ACUTE | VASCATH | 1 | 0 | 1 | 0 | 0 |
| RENAL FAILURE ACUTE | VENO VENOUS HEMODIALYSIS | 2 | 1 | 0 | 1 | 0 |
| RENAL IMPAIRMENT | HEMODIALYSIS | 1 | 0 | 0 | 0 | 1 |
| RENAL INSUFFICIENCY | HEMODIALYSIS | 2 | 1 | 1 | 0 | 0 |
| RENAL INSUFFICIENCY | VENO VENOUS HEMOFILTRATION | 1 | 1 | 0 | 0 | 0 |
| SUPRAVENTRICULAR TACHYCARDIA | CARDIOVERTED 5 TIMES | 1 | 0 | 1 | 0 | 0 |
| THROMBOCYTOPENIA | BLOOD TRANSFUSION | 1 | 0 | 0 | 0 | 1 |
| VENTRICULAR FIBRILLATION | INCREMENTAL DEFIBRILLATION | 1 | 0 | 0 | 1 | 0 |
| WANDERING PACEMAKER | PACEMAKER LEAD REPLACEMENT | 1 | 0 | 0 | 1 | 0 |

N=patient count; TLV = telavancin; VAN = vancomycin

7.5.1 Dose Dependency for Adverse Events

The two clinical trials used the identical dose of telavancin 10 mg/kg daily in patients with normal renal function compared to standard dosing of vancomycin. Both drugs required dosage adjustment for renal impairment.

7.5.2 Time Dependency for Adverse Events

The two phase 3 clinical trials for NP used identical dosing regimens (10 mg/kg once daily) for telavancin administration in patients with normal renal function and adjusted dosage regimens for subjects with renal impairment as described previously in this report. There was no new data submitted in the NDA with respect to adverse events associated with variations in dosage or infusion duration time in either study.

7.5.3 Drug-Demographic Interactions

Age

The most frequently reported TEAEs among all patients regardless of age strata in both Studies 0015 and 0019 were gastrointestinal disorders, including nausea, diarrhea, and constipation. Hypokalemia tended to occur more commonly among patients ≥ 65 years old. Acute renal failure was reported as a TEAE with comparable frequency in the patients < 65 years old and patients ≥ 65 years old. The following two tables summarize the TEAEs by preferred term stratified by age that were reported with frequency $\geq 2\%$ in Studies 0015 and 0019.

Table 165: FDA Medical Officer Table of TEAE stratified by age with frequency $\geq 2\%$ in telavancin arm, Study 0015, AT Safety Population

| Preferred term | Telavancin | | Vancomycin | |
|--------------------------------------|---------------|-----------------|---------------|-----------------|
| | <65 years | ≥ 65 years | <65 years | ≥ 65 years |
| Subjects | 170 (100.00%) | 202 (100.00%) | 162 (100.00%) | 212 (100.00%) |
| NAUSEA | 16 (9.41%) | 11 (5.45%) | 8 (4.94%) | 11 (5.19%) |
| DIARRHOEA | 13 (7.65%) | 34 (16.83%) | 17 (10.49%) | 37 (17.45%) |
| RASH | 11 (6.47%) | 10 (4.95%) | 4 (2.47%) | 6 (2.83%) |
| CONSTIPATION | 10 (5.88%) | 22 (10.89%) | 20 (12.35%) | 16 (7.55%) |
| VOMITING | 10 (5.88%) | 11 (5.45%) | 7 (4.32%) | 12 (5.66%) |
| HYPOKALAEMIA | 9 (5.29%) | 21 (10.40%) | 13 (8.02%) | 28 (13.21%) |
| HYPOTENSION | 9 (5.29%) | 14 (6.93%) | 10 (6.17%) | 16 (7.55%) |
| INSOMNIA | 9 (5.29%) | 7 (3.47%) | 17 (10.49%) | 15 (7.08%) |
| ANAEMIA | 8 (4.71%) | 22 (10.89%) | 16 (9.88%) | 33 (15.57%) |
| DECUBITUS ULCER | 8 (4.71%) | 14 (6.93%) | 9 (5.56%) | 17 (8.02%) |
| ATRIAL FIBRILLATION | 7 (4.12%) | 9 (4.46%) | 7 (4.32%) | 11 (5.19%) |
| RENAL FAILURE ACUTE | 7 (4.12%) | 11 (5.45%) | 4 (2.47%) | 6 (2.83%) |
| SEPTIC SHOCK | 7 (4.12%) | 8 (3.96%) | 5 (3.09%) | 8 (3.77%) |
| URINARY TRACT INFECTION | 7 (4.12%) | 12 (5.94%) | 8 (4.94%) | 13 (6.13%) |
| BLOOD ALKALINE PHOSPHATASE INCREASED | 6 (3.53%) | 1 (0.50%) | 4 (2.47%) | 1 (0.47%) |
| BLOOD CREATININE INCREASED | 6 (3.53%) | 5 (2.48%) | 4 (2.47%) | 2 (0.94%) |
| HYPERTENSION | 6 (3.53%) | 5 (2.48%) | 5 (3.09%) | 9 (4.25%) |
| RESPIRATORY FAILURE | 6 (3.53%) | 10 (4.95%) | 7 (4.32%) | 8 (3.77%) |
| AGITATION | 5 (2.94%) | 5 (2.48%) | 7 (4.32%) | 5 (2.36%) |
| ALANINE AMINOTRANSFERASE INCREASED | 5 (2.94%) | 2 (0.99%) | 5 (3.09%) | 4 (1.89%) |
| BRADYCARDIA | 5 (2.94%) | 1 (0.50%) | 5 (3.09%) | 5 (2.36%) |
| HAEMATURIA | 5 (2.94%) | 3 (1.49%) | 1 (0.62%) | 6 (2.83%) |
| HEADACHE | 5 (2.94%) | 5 (2.48%) | 7 (4.32%) | 6 (2.83%) |
| MULTI-ORGAN FAILURE | 5 (2.94%) | 7 (3.47%) | 4 (2.47%) | 4 (1.89%) |
| ORAL CANDIDIASIS | 5 (2.94%) | 4 (1.98%) | 3 (1.85%) | 2 (0.94%) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 4 (2.35%) | 2 (0.99%) | 5 (3.09%) | 3 (1.42%) |
| DYSGEUSIA | 4 (2.35%) | 0 (0.00%) | 1 (0.62%) | 1 (0.47%) |
| GASTROINTESTINAL HAEMORRHAGE | 4 (2.35%) | 3 (1.49%) | 1 (0.62%) | 7 (3.30%) |
| HYPERGLYCAEMIA | 4 (2.35%) | 6 (2.97%) | 5 (3.09%) | 6 (2.83%) |
| HYPOGLYCAEMIA | 4 (2.35%) | 8 (3.96%) | 2 (1.23%) | 7 (3.30%) |
| METABOLIC ACIDOSIS | 4 (2.35%) | 4 (1.98%) | 0 (0.00%) | 3 (1.42%) |
| OEDEMA PERIPHERAL | 4 (2.35%) | 16 (7.92%) | 14 (8.64%) | 12 (5.66%) |
| SEPSIS | 4 (2.35%) | 5 (2.48%) | 3 (1.85%) | 7 (3.30%) |
| THROMBOCYTHAEMIA | 4 (2.35%) | 3 (1.49%) | 0 (0.00%) | 1 (0.47%) |

Table 166: FDA Medical Officer Table of TEAE stratified by age with frequency $\geq 2\%$ in telavancin arm, Study 0019, AT Safety Population

| Preferred term | Telavancin | | Vancomycin | |
|---|-------------|-----------------|-------------|-----------------|
| | <65 years | ≥ 65 years | <65 years | ≥ 65 years |
| CONSTIPATION | 21 (11.54%) | 17 (8.63%) | 17 (9.24%) | 18 (9.28%) |
| DIARRHOEA | 16 (8.79%) | 22 (11.17%) | 16 (8.70%) | 22 (11.34%) |
| ANAEMIA | 14 (7.69%) | 20 (10.15%) | 19 (10.33%) | 17 (8.76%) |
| HYPERTENSION | 14 (7.69%) | 7 (3.55%) | 4 (2.17%) | 8 (4.12%) |
| HYPOKALAEMIA | 13 (7.14%) | 18 (9.14%) | 12 (6.52%) | 27 (13.92%) |
| HEADACHE | 10 (5.49%) | 3 (1.52%) | 4 (2.17%) | 6 (3.09%) |
| HYPERGLYCAEMIA | 10 (5.49%) | 6 (3.05%) | 7 (3.80%) | 10 (5.15%) |
| HYPOMAGNESAEMIA | 9 (4.95%) | 1 (0.51%) | 3 (1.63%) | 4 (2.06%) |
| RENAL FAILURE ACUTE | 9 (4.95%) | 7 (3.55%) | 7 (3.80%) | 11 (5.67%) |
| DECUBITUS ULCER | 8 (4.40%) | 9 (4.57%) | 10 (5.43%) | 8 (4.12%) |
| HYPOTENSION | 8 (4.40%) | 17 (8.63%) | 12 (6.52%) | 14 (7.22%) |
| NAUSEA | 8 (4.40%) | 5 (2.54%) | 7 (3.80%) | 5 (2.58%) |
| SEPSIS | 8 (4.40%) | 9 (4.57%) | 6 (3.26%) | 1 (0.52%) |
| HYPERKALAEMIA | 7 (3.85%) | 6 (3.05%) | 4 (2.17%) | 6 (3.09%) |
| INSOMNIA | 7 (3.85%) | 11 (5.58%) | 3 (1.63%) | 12 (6.19%) |
| URINARY TRACT INFECTION | 6 (3.30%) | 8 (4.06%) | 2 (1.09%) | 7 (3.61%) |
| ANXIETY | 6 (3.30%) | 6 (3.05%) | 5 (2.72%) | 7 (3.61%) |
| HYPOALBUMINAEMIA | 6 (3.30%) | 5 (2.54%) | 3 (1.63%) | 0 (0.00%) |
| RASH | 6 (3.30%) | 6 (3.05%) | 7 (3.80%) | 9 (4.64%) |
| HYPOGLYCAEMIA | 6 (3.30%) | 8 (4.06%) | 4 (2.17%) | 5 (2.58%) |
| TACHYCARDIA | 6 (3.30%) | 6 (3.05%) | 3 (1.63%) | 4 (2.06%) |
| ALANINE AMINOTRANSFERASE INCREASED | 6 (3.30%) | 4 (2.03%) | 10 (5.43%) | 7 (3.61%) |
| PNEUMOTHORAX | 6 (3.30%) | 2 (1.02%) | 2 (1.09%) | 2 (1.03%) |
| AGITATION | 6 (3.30%) | 2 (1.02%) | 3 (1.63%) | 8 (4.12%) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 6 (3.30%) | 4 (2.03%) | 6 (3.26%) | 7 (3.61%) |
| VOMITING | 6 (3.30%) | 9 (4.57%) | 3 (1.63%) | 9 (4.64%) |
| OEDEMA PERIPHERAL | 6 (3.30%) | 8 (4.06%) | 3 (1.63%) | 9 (4.64%) |
| ACUTE RESPIRATORY DISTRESS SYNDROME | 6 (3.30%) | 1 (0.51%) | 3 (1.63%) | 4 (2.06%) |
| CARDIAC FAILURE CONGESTIVE | 5 (2.75%) | 4 (2.03%) | 1 (0.54%) | 11 (5.67%) |
| DEPRESSION | 5 (2.75%) | 4 (2.03%) | 1 (0.54%) | 2 (1.03%) |
| LEUKOCYTOSIS | 5 (2.75%) | 6 (3.05%) | 2 (1.09%) | 7 (3.61%) |
| ANASARCA | 5 (2.75%) | 2 (1.02%) | 5 (2.72%) | 3 (1.55%) |
| INTERNATIONAL NORMALISED RATIO INCREASED | 5 (2.75%) | 0 (0.00%) | 2 (1.09%) | 0 (0.00%) |
| MULTI-ORGAN FAILURE | 5 (2.75%) | 8 (4.06%) | 1 (0.54%) | 5 (2.58%) |
| BLOOD ALKALINE PHOSPHATASE INCREASED | 4 (2.20%) | 1 (0.51%) | 1 (0.54%) | 2 (1.03%) |
| ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED | 4 (2.20%) | 0 (0.00%) | 0 (0.00%) | 1 (0.52%) |
| HYPOPHOSPHATAEMIA | 4 (2.20%) | 0 (0.00%) | 1 (0.54%) | 4 (2.06%) |
| HYPONATRAEMIA | 4 (2.20%) | 4 (2.03%) | 6 (3.26%) | 5 (2.58%) |
| THROMBOCYTHAEMIA | 4 (2.20%) | 0 (0.00%) | 8 (4.35%) | 1 (0.52%) |
| HYPERNATRAEMIA | 4 (2.20%) | 2 (1.02%) | 4 (2.17%) | 0 (0.00%) |

| Preferred term | Telavancin | | Vancomycin | |
|------------------|------------|------------|------------|------------|
| | <65 years | ≥65 years | <65 years | ≥65 years |
| ORAL CANDIDIASIS | 4 (2.20%) | 1 (0.51%) | 3 (1.63%) | 3 (1.55%) |
| PNEUMONIA | 4 (2.20%) | 4 (2.03%) | 2 (1.09%) | 5 (2.58%) |

Patients aged ≥75 years old were enrolled in both clinical trials. In Study 0015, there were 131 (35%) patients in the telavancin group and 124 (33%) patients in the vcancomycin group who were within that age group. In Study 0019, 99 (26%) of patients in the telavancin group and 109 (29%) in the vancomycin group were aged ≥75 years old. Among patients aged ≥75 years old, gastrointestinal disorders (diarrhea), hypokalemia, and anemia were among the most common TEAEs across both trials as depicted in the table below:

Table 167: FDA Medical Officer Table of TEAE in patients aged ≥75 years with frequency ≥2% stratified by study and treatment group, Studies 0015 and 0019, AT Safety Population

| Preferred term | 0015 | | 0019 | |
|-------------------------|---------------------|---------------------|---------------------|---------------------|
| | Telavancin N=372 | Vancomycin N=374 | Telavancin N=379 | Vancomycin N=378 |
| DIARRHOEA | 22 (5.91%) | 16 (4.28%) | 13 (3.43%) | 14 (3.70%) |
| HYPOKALAEMIA | 17 (4.57%) | 13 (3.48%) | 7 (1.85%) | 20 (5.29%) |
| ANAEMIA | 16 (4.30%) | 18 (4.81%) | 11 (2.90%) | 11 (2.91%) |
| OEDEMA PERIPHERAL | 13 (3.49%) | 8 (2.14%) | 4 (1.06%) | 5 (1.32%) |
| HYPOTENSION | 12 (3.23%) | 11 (2.94%) | 7 (1.85%) | 8 (2.12%) |
| DECUBITUS ULCER | 11 (2.96%) | 8 (2.14%) | 6 (1.58%) | 4 (1.06%) |
| CONSTIPATION | 11 (2.96%) | 8 (2.14%) | 10 (2.64%) | 9 (2.38%) |
| RESPIRATORY FAILURE | 10 (2.69%) | 6 (1.60%) | 3 (0.79%) | 4 (1.06%) |
| URINARY TRACT INFECTION | 8 (2.15%) | 7 (1.87%) | 6 (1.58%) | 3 (0.79%) |
| NAUSEA | 8 (2.15%) | 5 (1.34%) | 4 (1.06%) | 3 (0.79%) |
| RASH | 8 (2.15%) | 2 (0.53%) | 4 (1.06%) | 7 (1.85%) |

Gender

The most frequently reported TEAEs among all patients regardless of gender in both Studies 0015 and 0019 were gastrointestinal disorders, including diarrhea and constipation. Hypokalemia tended to occur slightly more commonly among women. Acute renal failure was reported as a TEAE with comparable frequency in men and women. The following two tables summarize the TEAEs by preferred term stratified by gender that were reported with frequency ≥2% in Studies 0015 and 0019.

Table 168: FDA Medical Officer Table of TEAE with frequency $\geq 2\%$ in telavancin arm stratified by gender and treatment group, Study 0015, AT Safety Population

| Preferred term | Telavancin | | Vancomycin | |
|--------------------------------------|---------------|---------------|---------------|---------------|
| | Male | Female | Male | Female |
| Subjects | 235 (100.00%) | 137 (100.00%) | 213 (100.00%) | 161 (100.00%) |
| DIARRHOEA | 29 (12.34%) | 18 (13.14%) | 29 (13.62%) | 25 (15.53%) |
| HYPOTENSION | 17 (7.23%) | 6 (4.38%) | 13 (6.10%) | 13 (8.07%) |
| CONSTIPATION | 17 (7.23%) | 15 (10.95%) | 21 (9.86%) | 15 (9.32%) |
| ANAEMIA | 16 (6.81%) | 14 (10.22%) | 22 (10.33%) | 27 (16.77%) |
| HYPOKALAEMIA | 15 (6.38%) | 15 (10.95%) | 24 (11.27%) | 17 (10.56%) |
| OEDEMA PERIPHERAL | 14 (5.96%) | 6 (4.38%) | 10 (4.69%) | 16 (9.94%) |
| NAUSEA | 14 (5.96%) | 13 (9.49%) | 8 (3.76%) | 11 (6.83%) |
| SEPTIC SHOCK | 12 (5.11%) | 3 (2.19%) | 9 (4.23%) | 4 (2.48%) |
| DECUBITUS ULCER | 12 (5.11%) | 10 (7.30%) | 18 (8.45%) | 8 (4.97%) |
| RASH | 12 (5.11%) | 9 (6.57%) | 4 (1.88%) | 6 (3.73%) |
| RENAL FAILURE ACUTE | 12 (5.11%) | 6 (4.38%) | 8 (3.76%) | 2 (1.24%) |
| HYPOGLYCAEMIA | 11 (4.68%) | 1 (0.73%) | 6 (2.82%) | 3 (1.86%) |
| ATRIAL FIBRILLATION | 11 (4.68%) | 5 (3.65%) | 12 (5.63%) | 6 (3.73%) |
| INSOMNIA | 10 (4.26%) | 6 (4.38%) | 19 (8.92%) | 13 (8.07%) |
| BLOOD CREATININE INCREASED | 9 (3.83%) | 2 (1.46%) | 2 (0.94%) | 4 (2.48%) |
| HYPERTENSION | 9 (3.83%) | 2 (1.46%) | 7 (3.29%) | 7 (4.35%) |
| CARDIAC FAILURE CONGESTIVE | 9 (3.83%) | 1 (0.73%) | 7 (3.29%) | 5 (3.11%) |
| MULTI-ORGAN FAILURE | 9 (3.83%) | 3 (2.19%) | 4 (1.88%) | 4 (2.48%) |
| AGITATION | 8 (3.40%) | 2 (1.46%) | 9 (4.23%) | 3 (1.86%) |
| RESPIRATORY FAILURE | 8 (3.40%) | 8 (5.84%) | 10 (4.69%) | 5 (3.11%) |
| METABOLIC ACIDOSIS | 8 (3.40%) | 0 (0.00%) | 2 (0.94%) | 1 (0.62%) |
| HYPERGLYCAEMIA | 8 (3.40%) | 2 (1.46%) | 8 (3.76%) | 3 (1.86%) |
| VOMITING | 6 (2.55%) | 15 (10.95%) | 13 (6.10%) | 6 (3.73%) |
| EXCORIATION | 6 (2.55%) | 1 (0.73%) | 5 (2.35%) | 3 (1.86%) |
| ORAL CANDIDIASIS | 6 (2.55%) | 3 (2.19%) | 4 (1.88%) | 1 (0.62%) |
| HEADACHE | 6 (2.55%) | 4 (2.92%) | 5 (2.35%) | 8 (4.97%) |
| SEPSIS | 6 (2.55%) | 3 (2.19%) | 5 (2.35%) | 5 (3.11%) |
| URINARY TRACT INFECTION | 6 (2.55%) | 13 (9.49%) | 11 (5.16%) | 10 (6.21%) |
| PNEUMONIA | 6 (2.55%) | 2 (1.46%) | 4 (1.88%) | 4 (2.48%) |
| HYPERKALAEMIA | 6 (2.55%) | 5 (3.65%) | 4 (1.88%) | 5 (3.11%) |
| HAEMATURIA | 6 (2.55%) | 2 (1.46%) | 4 (1.88%) | 3 (1.86%) |
| HYPONATRAEMIA | 6 (2.55%) | 2 (1.46%) | 6 (2.82%) | 5 (3.11%) |
| ALANINE AMINOTRANSFERASE INCREASED | 6 (2.55%) | 1 (0.73%) | 5 (2.35%) | 4 (2.48%) |
| PAIN | 6 (2.55%) | 2 (1.46%) | 5 (2.35%) | 2 (1.24%) |
| HYPOALBUMINAEMIA | 6 (2.55%) | 5 (3.65%) | 10 (4.69%) | 6 (3.73%) |
| BRADYCARDIA | 6 (2.55%) | 0 (0.00%) | 5 (2.35%) | 5 (3.11%) |
| BLOOD ALKALINE PHOSPHATASE INCREASED | 6 (2.55%) | 1 (0.73%) | 4 (1.88%) | 1 (0.62%) |
| ANASARCA | 5 (2.13%) | 1 (0.73%) | 3 (1.41%) | 5 (3.11%) |
| INFUSION SITE PHLEBITIS | 5 (2.13%) | 1 (0.73%) | 4 (1.88%) | 1 (0.62%) |

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| Preferred term | Telavancin | | Vancomycin | |
|--------------------------------------|------------|------------|------------|------------|
| | Male | Female | Male | Female |
| MALNUTRITION | 5 (2.13%) | 1 (0.73%) | 0 (0.00%) | 3 (1.86%) |
| ASPARTATE AMINOTRANSFERASE INCREASED | 5 (2.13%) | 1 (0.73%) | 4 (1.88%) | 4 (2.48%) |
| ERYTHEMA | 5 (2.13%) | 2 (1.46%) | 3 (1.41%) | 3 (1.86%) |
| ABDOMINAL DISTENSION | 5 (2.13%) | 1 (0.73%) | 1 (0.47%) | 1 (0.62%) |
| GASTROINTESTINAL HAEMORRHAGE | 5 (2.13%) | 2 (1.46%) | 5 (2.35%) | 3 (1.86%) |

Table 169: FDA Medical Officer Table of TEAE with frequency $\geq 2\%$ in telavancin arm stratified by gender and treatment group, Study 0019, AT Population

| Preferred term | Telavancin | | Vancomycin | |
|-------------------------|-------------|-------------|-------------|-------------|
| | Male | Female | Male | Female |
| Subjects | 254 (100%) | 125 (100%) | 254 (100%) | 124 (100%) |
| CONSTIPATION | 26 (10.24%) | 12 (9.60%) | 26 (10.24%) | 9 (7.26%) |
| ANAEMIA | 24 (9.45%) | 10 (8.00%) | 23 (9.06%) | 13 (10.48%) |
| DIARRHOEA | 22 (8.66%) | 16 (12.80%) | 26 (10.24%) | 12 (9.68%) |
| HYPOKALAEMIA | 17 (6.69%) | 14 (11.20%) | 22 (8.66%) | 17 (13.71%) |
| HYPOTENSION | 15 (5.91%) | 10 (8.00%) | 13 (5.12%) | 13 (10.48%) |
| SEPSIS | 14 (5.51%) | 3 (2.40%) | 5 (1.97%) | 2 (1.61%) |
| HYPERTENSION | 13 (5.12%) | 8 (6.40%) | 7 (2.76%) | 5 (4.03%) |
| HYPERGLYCAEMIA | 12 (4.72%) | 4 (3.20%) | 11 (4.33%) | 6 (4.84%) |
| SEPTIC SHOCK | 12 (4.72%) | 5 (4.00%) | 9 (3.54%) | 7 (5.65%) |
| INSOMNIA | 10 (3.94%) | 8 (6.40%) | 10 (3.94%) | 5 (4.03%) |
| OEDEMA PERIPHERAL | 10 (3.94%) | 4 (3.20%) | 8 (3.15%) | 4 (3.23%) |
| RENAL FAILURE ACUTE | 10 (3.94%) | 6 (4.80%) | 11 (4.33%) | 7 (5.65%) |
| HEADACHE | 9 (3.54%) | 4 (3.20%) | 9 (3.54%) | 1 (0.81%) |
| ATRIAL FIBRILLATION | 9 (3.54%) | 6 (4.80%) | 9 (3.54%) | 9 (7.26%) |
| VOMITING | 9 (3.54%) | 6 (4.80%) | 5 (1.97%) | 7 (5.65%) |
| URINARY TRACT INFECTION | 9 (3.54%) | 5 (4.00%) | 5 (1.97%) | 4 (3.23%) |
| ANXIETY | 8 (3.15%) | 4 (3.20%) | 6 (2.36%) | 6 (4.84%) |
| DECUBITUS ULCER | 8 (3.15%) | 9 (7.20%) | 10 (3.94%) | 8 (6.45%) |
| MULTI-ORGAN FAILURE | 8 (3.15%) | 5 (4.00%) | 5 (1.97%) | 1 (0.81%) |
| HYPOALBUMINAEMIA | 8 (3.15%) | 3 (2.40%) | 2 (0.79%) | 1 (0.81%) |
| HYPERKALAEMIA | 7 (2.76%) | 6 (4.80%) | 8 (3.15%) | 2 (1.61%) |
| NAUSEA | 7 (2.76%) | 6 (4.80%) | 6 (2.36%) | 6 (4.84%) |
| PNEUMONIA | 7 (2.76%) | 1 (0.80%) | 5 (1.97%) | 2 (1.61%) |
| LEUKOCYTOSIS | 7 (2.76%) | 4 (3.20%) | 5 (1.97%) | 4 (3.23%) |
| HYPOGLYCAEMIA | 7 (2.76%) | 7 (5.60%) | 7 (2.76%) | 2 (1.61%) |
| TACHYCARDIA | 7 (2.76%) | 5 (4.00%) | 6 (2.36%) | 1 (0.81%) |
| HYPOMAGNESAEMIA | 6 (2.36%) | 4 (3.20%) | 4 (1.57%) | 3 (2.42%) |
| RASH | 6 (2.36%) | 6 (4.80%) | 10 (3.94%) | 6 (4.84%) |
| HYPERNATRAEMIA | 6 (2.36%) | 0 (0.00%) | 4 (1.57%) | 0 (0.00%) |
| RENAL INSUFFICIENCY | 6 (2.36%) | 1 (0.80%) | 2 (0.79%) | 1 (0.81%) |
| METABOLIC ACIDOSIS | 6 (2.36%) | 1 (0.80%) | 4 (1.57%) | 0 (0.00%) |

| Preferred term | Telavancin | | Vancomycin | |
|--------------------------------------|------------|------------|-------------|------------|
| | Male | Female | Male | Female |
| ASPARTATE AMINOTRANSFERASE INCREASED | 6 (2.36%) | 4 (3.20%) | 10 (3.94%) | 3 (2.42%) |

7.5.4 Drug-Disease Interactions

Based on the all-cause mortality analysis described in previous sections of this report, there appears to be an imbalance with a higher risk for death in telavancin-treated patients who have renal impairment at baseline compared to similarly renally impaired patients who were treated with vancomycin. Please refer to the previous discussion for details.

7.5.5 Drug-Drug Interactions

According to the Applicant's Integrated Summary of Safety, the inhibitory activity of telavancin against the following cytochrome P450 (CYP) enzymes was evaluated in human liver microsomes: CYP 1A2, 2C9, 2C19, 2D6, and 3A4/5. Telavancin inhibited CYP 3A4/5 at potentially clinically relevant concentrations. An *in vivo* study with the probe substrate midazolam was conducted to further evaluate this effect. Telavancin had no effect on the pharmacokinetic disposition of midazolam. Therefore, telavancin is unlikely to alter the pharmacokinetics of drugs metabolized by the cytochrome P450 system to a clinically significant degree.

Section 7.3 of the Applicant's Integrated Summary of Safety describes drug-drug interaction studies that were performed with telavancin and other antibiotics that are likely to be co-administered:

- Aztreonam: Co-administration of telavancin and aztreonam had no effect on the pharmacokinetics of either antibiotic.
- Piperacillin-tazobactam: Co-administration of telavancin and piperacillin-tazobactam had no effect on the pharmacokinetics of any of the antibiotics.

7.6 Additional Safety Evaluations

Drug-Laboratory Test Interactions / Coagulation Tests

In the Applicant's Integrated Summary of Safety, a drug-laboratory test interaction (coagulation) was described as follows: In the initial clinical study of telavancin (Study 101a), an individual was identified with unexplained prolongation of prothrombin time when sampled shortly after administration of telavancin. A similar effect was observed in the second study (Study 102a), and evaluations conducted in conjunction with that study suggested that prolongations of prothrombin and partial thromboplastin times associated with administration of telavancin did not indicate an effect of the drug on coagulation. In this study and in follow-up, results from a series of *in vitro* and *in vivo* studies confirmed that telavancin interferes with common laboratory tests used to monitor coagulation (prothrombin time [PT], international normalized ratio [INR], activated partial thromboplastin time [aPTT], and in high concentrations, activated clotting time [ACT]) but does not interfere with coagulation per se. The table below lists the coagulation

tests that are affected and those that are not affected by telavancin.

Table 170: Applicant's Table of Coagulation Tests Affected and Unaffected by Telavancin

| Test with Telavancin Interference | Tests without Telavancin Interference |
|---------------------------------------|---|
| Prothrombin Time | Thrombin time |
| International normalized ratio | Whole blood (Lee-White) clotting time |
| Activated partial thromboplastin time | Ex vivo platelet aggregation |
| Activated clotting time | Chromogenic Factor Xa assay |
| Coagulation based factor Xa tests | Functional (chromogenic) Factor X assay |
| | Bleeding time |
| | D-dimer |
| | Fibrin degradation products |

Based on the results of the *in vitro* studies, the increased values for PT and aPTT that were observed in the clinic are false positive findings due to assay interference by telavancin. Furthermore, the normal values observed in the physiologically intact system, the whole blood clotting time (WBCT), and the return toward normal values in assays that use additional platelets or phospholipids as well as in the whole blood recalcification time, which uses platelets present in the blood rather than an added platelet surrogate, are consistent with the prolongation in PT and aPTT representing laboratory artifacts. In patients receiving unfractionated heparin where monitoring is required within 18 hours of a telavancin dose, a chromogenic Factor Xa-based assay (Stachrom® Heparin test) should be performed instead of an aPTT, activated clotting time, or a coagulation-based Factor Xa assay (e.g., Heptest®). The functional Factor X assay should allow accurate monitoring of warfarin in patients receiving telavancin. Results from the *in vivo* setting were consistent with those determined to affect coagulation parameters *in vitro*. For patients receiving telavancin who require monitoring of coagulation tests, anticoagulation tests should be performed at least 18 hours after telavancin dosing and preferably at trough, just before the next dose of telavancin.

7.6.1 Human Carcinogenicity

Telavancin was being assessed for short-term treatment (5-21 days) of an acute infectious process. Therefore, carcinogenicity testing was not indicated at this time.

7.6.2 Human Reproduction and Pregnancy Data

According to the Applicant's Integrated Summary of Safety, the Applicant stated in Section 7.4 that telavancin administered to pregnant animals was associated with reduced fetal weight. Digit and limb malformations were also observed in some animals but a consistent underlying mechanism could not be identified. Administration of telavancin to pregnant women should be avoided unless the benefits of treatment clearly outweigh the potential risks to the fetus. It is not known whether telavancin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when telavancin is administered to a nursing woman.

There have been no adequate and well controlled studies of telavancin in pregnant women with HAP. No pregnancies were reported in patients who participated in the Phase 3 HAP studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

Both of the phase 3 studies for NP excluded patients <18 years of age. In Module 1 of the current NDA submission, Section 1.9.2 Pediatric Assessment, the Applicant provided a request for deferral of pediatric studies pending completion of the FDA review of Studies 0015 and 0019 as conducted in adults.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

According to the Applicant's Integrated Summary of Safety, the Applicant stated in Section 7.5 that there were no reported TEAEs of drug overdose during the Phase 3 HAP studies. One patient (0015-18000-4505) experienced a TEAE of pulmonary toxicity, which was described as "interstitial lung disease presumably due to administration of amiodarone" and was coded to the preferred term of "drug toxicity".

Patients with a creatinine clearance (CrCL) ≤ 50 mL/min were to receive a modified dosing regimen of telavancin. Of the 58 patients who received doses of telavancin in excess of that stipulated by the protocol, 48 received doses 1.1-1.428-fold higher than protocol specified due to a misunderstanding in rounding the dose up to the nearest 25 mg during preparation and the remaining 10 patients received doses ≥ 1.5 -fold higher than the protocol-specified dose. According to the Applicant's Integrated Summary of Safety, none of the patients administered doses in excess of those that were protocol-specified developed significant safety issues except for two patients who developed renal failure as part of multi-organ failure (patient #0019-08016-6817 and patient #0015-38348-4254).

7.7 Additional Submissions / Safety Issues

The Applicant submitted a safety update (report dated July 28, 2009) that included all available information regarding the safety of telavancin available to the Applicant through June 30, 2009. No new, additional non-clinical or clinical study safety data were available at the time of the submission. One clinical study evaluating the effect of telavancin on the gastrointestinal flora was being conducted in Europe.

The Applicant described that during a post data-lock audit of clinical sites, a number of adverse events were identified that did not appear in the listings of adverse events in the clinical database. Four deaths were included among the serious adverse events, and they occurred after patients had completed participation in the study. In addition, the Applicant conducted a literature search, which revealed no new safety data and no new data from epidemiologic studies or from studies of other drugs in the same or similar chemical classes.

Safety Conclusions

The most common TEAE observed among telavancin-treated patients in the two NP clinical trials were gastrointestinal-related (diarrhea and constipation). *C. difficile*-related diarrhea was reported in both treatment arms of Studies 0015 and 0019, but the affected patients had received prior or concomitant antibacterial drugs that could have contributed to the onset of the events. Hypokalemia and anemia were reported more commonly in the elderly, but that patient subgroup had many concomitant illnesses and concomitant medications that could have contributed to the findings.

Telavancin exposure was associated with evidence of nephrotoxicity in Studies 0015 and 0019 based on several types of evidence, including imbalances in the frequency of serious renal-related TEAEs across the telavancin and vancomycin treatment arms, imbalances in the severity of the renal events as categorized using the RIFLE classification scheme for acute kidney injury, and imbalances associated with clinical laboratory abnormalities (such as measures of central tendency, shifts from low or normal baseline serum creatinine levels to high levels at EOT in Study 0015, and two-grade increases in toxicity compared to baseline). The all-cause mortality data indicated a trend of higher death rates for telavancin-treated patients with baseline renal impairment compared to renally impaired patients treated with vancomycin or non-renally impaired patients treated with either drug. However, final data analysis must await the follow-up mortality information to be provided by the Applicant in the future.

Telavancin appeared to prolong the QT interval, but was not associated with clinically apparent life-threatening torsades de pointes in the limited number of patients studied. There were more telavancin-treated patients who were discontinued from study medication due to having two consecutive ECGs with QTc >500 msec and there were higher post-baseline average changes (msec) in QTcB interval and a higher maximum post-baseline change (msec) in QTcB interval in the patients in the telavancin group compared to the vancomycin group.

There was an imbalance with respect to the incidence of pulmonary embolism, which was reported more frequently in the telavancin-treated compared to the vancomycin-treated patients across both trials. Eight patients experienced a pulmonary embolism (PE) that was assessed as a serious TEAE by investigators; seven were telavancin-treated and one was vancomycin treated. Seven of the eight patients who experienced a PE as a SAE subsequently died. In some cases, there was a temporal association between telavancin administration and the development of a PE; in other cases, the onset of the event was ≥ 8 days post-EOT. Some patients had important concurrent factors and underlying medical conditions that may have affected the likelihood for this complication to occur, which confounded causality assessment.

The ability to assess safety signals (especially for rare adverse events) based on the results of the clinical laboratory tests was limited due to the considerable amount of missing data. The missing data exceeded the amount that would be expected based on patient deaths up to the EOT and TOC visits.

The all-cause mortality data described previously in this report suggested a higher risk for death among patients treated with telavancin compared to vancomycin in Study 0015. The higher risk for death was observed particularly in patients with renal impairment who were treated with telavancin. However, due to the considerable amount of censored data provided in the Applicant's most recent submission to the Division, final analysis of the all-cause mortality data will depend on the additional information to be provided by the Applicant in the future.

8 Postmarket Experience

As of the time of this application, telavancin is not marketed anywhere in the world; therefore, no postmarketing data are available.

9 Appendices

9.1 Literature Reviewed/References Cited

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9.2 Labeling Recommendations

This section is not applicable as the NDA is not approvable for the indication being sought by the Applicant.

9.3 Advisory Committee Meeting

Following a discussion between the Applicant and the Division, an Anti-Infective Drug Advisory Committee Meeting tentatively scheduled for October 26-27, 2009 was postponed to allow more time for the Applicant to accrue additional all-cause mortality data following a query of investigative sites and then enable the Division to review the updated information.

9.4 Chemistry Shift Tables

This section includes additional chemistry shift tables for Studies 0015 and 0019 from the Applicant's supporting tables that were not included in Section 7.4.2 of this report:

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: HGB. A1C-HPLCVARIANT(-70)-QT | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 3 | 0 | 0 | 5 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 2 | 0 | 0 | 2 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: LDH (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 103 | 34 | 0 | 101 | 28 | 0 |
| Normal | 50 | 101 | 0 | 54 | 107 | 0 |
| Low | 0 | 0 | 0 | 0 | 1 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 52 | 15 | 0 | 54 | 21 | 0 |
| Normal | 65 | 87 | 0 | 53 | 88 | 0 |
| Low | 0 | 1 | 0 | 0 | 0 | 0 |

Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: MAGNESIUM (MMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 26 | 20 | 0 | 23 | 12 | 1 |
| Normal | 10 | 265 | 3 | 10 | 257 | 18 |
| Low | 0 | 7 | 2 | 0 | 13 | 2 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 15 | 28 | 0 | 11 | 14 | 1 |
| Normal | 7 | 203 | 2 | 11 | 208 | 12 |
| Low | 0 | 3 | 1 | 1 | 5 | 4 |

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Supporting Table 192: Chemistry – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: SERUM POTASSIUM (MMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 2 | 6 | 0 | 0 | 12 | 1 |
| Normal | 9 | 228 | 30 | 5 | 242 | 27 |
| Low | 0 | 38 | 10 | 2 | 22 | 21 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 4 | 0 | 0 | 5 | 0 |
| Normal | 9 | 191 | 31 | 3 | 202 | 27 |
| Low | 0 | 15 | 5 | 1 | 13 | 8 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: HGB. A1C-HPLCVARIANT(-70)-QT | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 3 | 0 | 0 | 4 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 3 | 0 | 0 | 2 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: LDH (U/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 130 | 29 | 0 | 112 | 46 | 0 |
| Normal | 36 | 114 | 0 | 43 | 98 | 0 |
| Low | 0 | 0 | 0 | 0 | 1 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 62 | 17 | 0 | 50 | 30 | 0 |
| Normal | 56 | 95 | 0 | 57 | 84 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

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Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: MAGNESIUM (MMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 10 | 8 | 0 | 18 | 13 | 1 |
| Normal | 17 | 279 | 8 | 13 | 274 | 10 |
| Low | 1 | 10 | 4 | 1 | 5 | 2 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 5 | 4 | 0 | 9 | 14 | 0 |
| Normal | 11 | 227 | 4 | 12 | 200 | 5 |
| Low | 1 | 8 | 2 | 1 | 4 | 1 |

Supporting Table 193: Chemistry – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: SERUM POTASSIUM (MMOL/L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 2 | 8 | 0 | 0 | 8 | 1 |
| Normal | 5 | 248 | 23 | 6 | 256 | 32 |
| Low | 1 | 39 | 12 | 0 | 25 | 12 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 5 | 0 | 0 | 7 | 0 |
| Normal | 4 | 210 | 18 | 4 | 199 | 25 |
| Low | 1 | 18 | 5 | 0 | 11 | 4 |

9.5 Hematology Shift Tables

This section includes additional hematology shift tables for Studies 0015 and 0019 from the Applicant's supporting tables that were not included in Section 7.4.2 of this report:

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015

| Lab test name: ATYPICAL LYMPHOCYTES (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 4 | 0 | 0 | 6 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: ATYPICAL LYMPHOCYTES (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 4 | 0 | 0 | 6 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: BANDS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 7 | 21 | 0 | 5 | 10 | 0 |
| Normal | 22 | 208 | 0 | 32 | 203 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 7 | 0 | 3 | 5 | 0 |
| Normal | 18 | 189 | 0 | 27 | 163 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

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Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: BANDS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 13 | 23 | 0 | 7 | 14 | 0 |
| Normal | 27 | 178 | 0 | 30 | 179 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 5 | 7 | 0 | 5 | 7 | 0 |
| Normal | 21 | 171 | 0 | 25 | 145 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: BASOPHILS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 2 | 0 | 0 | 8 | 0 |
| Normal | 4 | 268 | 0 | 2 | 255 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 4 | 0 | 0 | 8 | 0 |
| Normal | 3 | 220 | 0 | 2 | 200 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: BASOPHILS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 5 | 0 | 0 | 4 | 0 |
| Normal | 9 | 231 | 0 | 5 | 223 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 8 | 0 | 0 | 1 | 0 |
| Normal | 6 | 192 | 0 | 5 | 179 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

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Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: BLASTS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: BLASTS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: EOSINOPHILS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 4 | 15 | 0 | 0 | 7 | 0 |
| Normal | 4 | 223 | 0 | 7 | 218 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 20 | 0 | 0 | 9 | 0 |
| Normal | 4 | 182 | 0 | 6 | 170 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: LYMPHOCYTES (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 3 | 0 | 1 | 4 | 1 |
| Normal | 5 | 145 | 43 | 3 | 133 | 39 |
| Low | 0 | 16 | 34 | 1 | 24 | 26 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 8 | 3 | 0 | 4 | 1 |
| Normal | 3 | 123 | 48 | 4 | 119 | 37 |
| Low | 0 | 6 | 15 | 0 | 8 | 12 |

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Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: MONOCYTES (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 5 | 7 | 1 | 0 | 10 | 1 |
| Normal | 9 | 172 | 43 | 9 | 177 | 28 |
| Low | 0 | 24 | 14 | 0 | 28 | 15 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 2 | 5 | 1 | 0 | 8 | 1 |
| Normal | 8 | 149 | 37 | 3 | 156 | 29 |
| Low | 1 | 14 | 9 | 0 | 10 | 5 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: MONOCYTES (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 8 | 19 | 0 | 7 | 7 | 0 |
| Normal | 35 | 176 | 6 | 27 | 182 | 2 |
| Low | 0 | 1 | 1 | 0 | 5 | 2 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 7 | 8 | 0 | 4 | 9 | 0 |
| Normal | 24 | 181 | 5 | 20 | 148 | 1 |
| Low | 0 | 2 | 0 | 0 | 3 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: NEUTROPHILS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 136 | 22 | 1 | 132 | 22 | 0 |
| Normal | 75 | 39 | 0 | 71 | 41 | 1 |
| Low | 0 | 2 | 1 | 0 | 2 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 71 | 6 | 2 | 72 | 11 | 0 |
| Normal | 99 | 43 | 0 | 84 | 45 | 0 |
| Low | 3 | 4 | 0 | 0 | 1 | 0 |

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Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: NEUTROPHILS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 114 | 28 | 0 | 98 | 21 | 1 |
| Normal | 55 | 47 | 1 | 66 | 42 | 0 |
| Low | 1 | 0 | 0 | 0 | 3 | 1 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 69 | 9 | 1 | 54 | 15 | 0 |
| Normal | 71 | 51 | 0 | 73 | 40 | 0 |
| Low | 3 | 3 | 0 | 2 | 1 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: NUCLEATED RED BLOOD CELLS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 2 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 1 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: LYMPHOCYTES (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 1 | 0 | 0 | 2 | 0 |
| Normal | 0 | 39 | 66 | 1 | 37 | 74 |
| Low | 0 | 20 | 150 | 0 | 19 | 135 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 3 | 1 | 0 | 1 | 0 |
| Normal | 0 | 43 | 93 | 0 | 35 | 89 |
| Low | 0 | 5 | 83 | 0 | 14 | 73 |

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Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: PROMYELOCYTE (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: PROMYELOCYTE (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: RBC (X10 ¹² /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 1 | 0 |
| Normal | 1 | 57 | 16 | 2 | 46 | 17 |
| Low | 0 | 35 | 181 | 0 | 32 | 177 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 1 | 0 |
| Normal | 0 | 52 | 32 | 1 | 41 | 38 |
| Low | 0 | 31 | 119 | 0 | 21 | 113 |

Supporting Table 190: Hematology – Shift Tables – Safety Population, Study 0015 (Cont'd)

| Lab test name: TOTAL ABS. NEUTROPHIL COUNT (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 128 | 27 | 0 | 116 | 24 | 1 |
| Normal | 59 | 50 | 0 | 69 | 44 | 0 |
| Low | 1 | 0 | 1 | 0 | 4 | 1 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 74 | 11 | 0 | 63 | 17 | 0 |
| Normal | 78 | 53 | 1 | 80 | 41 | 0 |
| Low | 3 | 2 | 0 | 2 | 1 | 0 |

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Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019

| Lab test name: ATYPICAL LYMPHOCYTES (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 3 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 2 | 0 | 0 | 2 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: ATYPICAL LYMPHOCYTES (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 3 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 2 | 0 | 0 | 2 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: BANDS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 9 | 17 | 0 | 8 | 13 | 0 |
| Normal | 18 | 197 | 0 | 28 | 206 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 2 | 7 | 0 | 3 | 6 | 0 |
| Normal | 18 | 165 | 0 | 21 | 149 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

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Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: BANDS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 7 | 14 | 0 | 8 | 19 | 0 |
| Normal | 22 | 177 | 0 | 29 | 184 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 2 | 7 | 0 | 1 | 5 | 0 |
| Normal | 21 | 152 | 0 | 24 | 135 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: BASOPHILS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 4 | 0 | 0 | 2 | 0 |
| Normal | 3 | 281 | 0 | 3 | 268 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 3 | 0 | 0 | 6 | 0 |
| Normal | 2 | 205 | 0 | 3 | 188 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: BASOPHILS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 2 | 0 | 0 | 3 | 0 |
| Normal | 4 | 217 | 0 | 6 | 236 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 1 | 1 | 0 |
| Normal | 3 | 183 | 0 | 4 | 162 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

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Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: BLASTS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 1 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: BLASTS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 1 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: EOSINOPHILS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 4 | 15 | 0 | 4 | 13 | 0 |
| Normal | 7 | 197 | 0 | 7 | 221 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 2 | 6 | 0 | 0 | 11 | 0 |
| Normal | 6 | 172 | 0 | 5 | 153 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: LYMPHOCYTES (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 0 | 0 | 0 | 1 | 0 |
| Normal | 0 | 53 | 51 | 1 | 45 | 60 |
| Low | 0 | 14 | 155 | 1 | 20 | 152 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 1 | 2 | 0 | 2 | 0 |
| Normal | 0 | 48 | 79 | 1 | 40 | 72 |
| Low | 0 | 11 | 71 | 0 | 10 | 75 |

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Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: LYMPHOCYTES (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 4 | 0 | 1 | 5 | 0 |
| Normal | 3 | 126 | 35 | 2 | 136 | 49 |
| Low | 0 | 23 | 31 | 0 | 21 | 32 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 3 | 1 | 0 | 6 | 0 |
| Normal | 2 | 124 | 34 | 1 | 98 | 39 |
| Low | 0 | 10 | 12 | 0 | 9 | 17 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: MONOCYTES (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 3 | 6 | 2 | 0 | 9 | 0 |
| Normal | 7 | 181 | 33 | 6 | 177 | 41 |
| Low | 0 | 21 | 21 | 1 | 27 | 19 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 4 | 3 | 1 | 1 | 6 | 0 |
| Normal | 6 | 147 | 33 | 3 | 141 | 36 |
| Low | 0 | 10 | 8 | 0 | 7 | 6 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: MONOCYTES (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 6 | 20 | 0 | 4 | 12 | 1 |
| Normal | 18 | 171 | 4 | 20 | 196 | 5 |
| Low | 0 | 2 | 2 | 0 | 5 | 3 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 4 | 3 | 0 | 2 | 5 | 0 |
| Normal | 18 | 155 | 3 | 14 | 141 | 4 |
| Low | 0 | 3 | 0 | 0 | 2 | 2 |

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Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: NEUTROPHILS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|-----------------------------------|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 143 | 16 | 0 | 140 | 26 | 0 |
| Normal | 60 | 51 | 1 | 63 | 47 | 1 |
| Low | 2 | 0 | 1 | 1 | 0 | 2 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 76 | 14 | 0 | 75 | 10 | 0 |
| Normal | 75 | 43 | 1 | 69 | 43 | 1 |
| Low | 2 | 1 | 0 | 1 | 1 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: NEUTROPHILS (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 96 | 22 | 0 | 101 | 20 | 1 |
| Normal | 48 | 55 | 0 | 62 | 55 | 3 |
| Low | 0 | 0 | 2 | 1 | 3 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 53 | 11 | 0 | 47 | 13 | 0 |
| Normal | 68 | 50 | 0 | 64 | 40 | 2 |
| Low | 2 | 1 | 1 | 1 | 3 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: NUCLEATED RED BLOOD CELLS (%) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 0 | 0 | 0 | 0 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: PROMYELOCYTE (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 25 | 0 | 0 | 31 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 0 |
| Normal | 0 | 11 | 0 | 0 | 18 | 0 |
| Low | 0 | 0 | 0 | 0 | 0 | 0 |

Clinical Review
 Alfred Sorbello, DO, MPH
 NDA 22-407/N-000
 Theravance for injection (VIBATIV™)

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: RBC (X10 ¹² /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|--|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 1 | 0 | 0 | 1 | 0 | 0 |
| Normal | 0 | 45 | 12 | 0 | 52 | 18 |
| Low | 0 | 29 | 193 | 0 | 27 | 195 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 0 | 0 | 0 | 0 | 0 | 1 |
| Normal | 1 | 43 | 32 | 1 | 37 | 31 |
| Low | 0 | 25 | 117 | 0 | 23 | 122 |

Supporting Table 191: Hematology – Shift Tables – Safety Population, Study 0019 (Cont'd)

| Lab test name: TOTAL ABS. NEUTROPHIL COUNT (X10 ⁹ /L) | Telavancin 10 mg/kg Baseline | | | Vancomycin Baseline | | |
|---|------------------------------------|------|-----|------------------------|------|-----|
| | High | Norm | Low | High | Norm | Low |
| END OF THERAPY | | | | | | |
| High | 116 | 27 | 0 | 124 | 24 | 2 |
| Normal | 58 | 59 | 1 | 66 | 57 | 1 |
| Low | 0 | 0 | 1 | 1 | 4 | 0 |
| FOLLOW-UP/TEST OF CURE | | | | | | |
| High | 60 | 12 | 0 | 57 | 14 | 0 |
| Normal | 73 | 55 | 0 | 76 | 44 | 2 |
| Low | 2 | 1 | 1 | 1 | 4 | 0 |

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------|--------------|
| NDA-22407 | GI-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |
| NDA-22407 | ORIG-1 | THERAVANCE INC | VIBATIV |

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

/s/

ALFRED F SORBELLO
09/25/2009

JANICE K POHLMAN
09/25/2009

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 22-407

Applicant: Theravance

Stamp Date: January 23, 2009

Drug Name: Telavancin

NDA/BLA Type: Standard

On initial overview of the NDA/BLA application for filing:

| | Content Parameter | Yes | No | NA | Comment |
|---------------------------------------|--|-----|----|----|---|
| FORMAT/ORGANIZATION/LEGIBILITY | | | | | |
| 1. | Identify the general format that has been used for this application, e.g. electronic CTD. | √ | | | |
| 2. | On its face, is the clinical section organized in a manner to allow substantive review to begin? | √ | | | |
| 3. | Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin? | | √ | | No Table of Contents |
| 4. | For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)? | √ | | | eCTD format allows navigation, study reports have TOC |
| 5. | Are all documents submitted in English or are English translations provided when necessary? | √ | | | |
| 6. | Is the clinical section legible so that substantive review can begin? | √ | | | |
| LABELING | | | | | |
| 7. | Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies? | √ | | | |
| SUMMARIES | | | | | |
| 8. | Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)? | √ | | | Cross reference to NDA 22-110 |
| 9. | Has the applicant submitted the integrated summary of safety (ISS)? | √ | | | |
| 10. | Has the applicant submitted the integrated summary of efficacy (ISE)? | √ | | | |
| 11. | Has the applicant submitted a benefit-risk analysis for the product? | √ | | | |
| 12. | Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug? | √ | | | 505(b)(1) |
| DOSE | | | | | |
| 13. | If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: I6424-108a Study Title: Intrapulmonary Distribution of Intravenous Telavancin (plasma, pulmonary epithelial lining fluid, and alveolar macrophages) Sample Size: 20 Arms: Location in submission: Study Report | √ | | | Cross reference to NDA 22-110, also PK/PD modeling |

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-----------------|--|-----|----|----|--|
| EFFICACY | | | | | |
| 14. | Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: 0015 Indication: HAP/VAP Pivotal Study #2: 0019 Indication: HAP/VAP | √ | | | NI margin justification is not adequate and needs further discussion |
| 15. | Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling? | √ | | | NI margin justification is not adequate and needs further discussion |
| 16. | Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints. | √ | | | Endpoints conform to those previously agreed upon. Currently use of these endpoints and NI margin are undergoing discussion, including public HAP/VAP workshop to be held 3/31, 4/1/09 |
| 17. | Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission? | | √ | | |
| SAFETY | | | | | |
| 18. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division? | √ | | | Datasets are difficult to navigate and work with |
| 19. | Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)? | √ | | | Thorough QT study performed, reported NDA 22-110 |
| 20. | Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product? | √ | | | |
| 21. | For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious? | | | √ | |
| 22. | For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division? | √ | | | |
| 23. | Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms? | √ | | | MedDRA Version 6.1 |

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|--------------------------|---|------------|-----------|-----------|--|
| 24. | Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs? | √ | | | Review Issue Missing safety labs Extent of work-up of adverse events |
| 25. | Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)? | √ | | | Narratives are not blinded to treatment assignment, narratives for deaths that occurred after TOC but before Day 28 are not included |
| OTHER STUDIES | | | | | |
| 26. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions? | √ | | | |
| 27. | For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)? | | | √ | |
| PEDIATRIC USE | | | | | |
| 28. | Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral? | √ | | | Deferral |
| ABUSE LIABILITY | | | | | |
| 29. | If relevant, has the applicant submitted information to assess the abuse liability of the product? | | | √ | |
| FOREIGN STUDIES | | | | | |
| 30. | Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population? | | √ | | |
| DATASETS | | | | | |
| 31. | Has the applicant submitted datasets in a format to allow reasonable review of the patient data? | √ | | | Not designed for ease of review, requested data definition table in .pdf to be able to print |
| 32. | Has the applicant submitted datasets in the format agreed to previously by the Division? | | | √ | Not specified |
| 33. | Are all datasets for pivotal efficacy studies available and complete for all indications requested? | √ | | | |
| 34. | Are all datasets to support the critical safety analyses available and complete? | | √ | | Missing safety labs |
| 35. | For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included? | √ | | | |
| CASE REPORT FORMS | | | | | |
| 36. | Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)? | √ | | | CRFs are not treatment-blinded |
| 37. | Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division? | √ | | | CRFs are not treatment-blinded |

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

| | Content Parameter | Yes | No | NA | Comment |
|-------------------------------|---|-----|----|----|---------|
| FINANCIAL DISCLOSURE | | | | | |
| 38. | Has the applicant submitted the required Financial Disclosure information? | √ | | | |
| GOOD CLINICAL PRACTICE | | | | | |
| 39. | Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures? | √ | | | |

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. Non-inferiority margin justification
2. Potential for presentation to the Anti-Infective Drugs Advisory Committee
3. Missing safety laboratory data
4. Treatment-blinded case report forms for deaths, serious adverse events, discontinuations due to adverse events, and random samples for studies 0015 and 0019 requested
5. Analysis of clinical cure rates in clinical subgroups, similar to that presented in Section 5.2.9.2.1 of the ISE, for Studies 0015 and 0019 separately
6. Rationale for assuming the applicability of foreign data to the U.S. population, given the difference in clinical response rates in the pooled studies between geographic groups (i.e., 10% treatment difference favoring telavancin in Group 1 versus 1% and 3% treatment difference favoring vancomycin in Groups 2 and 3, respectively) requested
7. Data definition table in .pdf format for printing in order to facilitate use of dataset variables [request previously sent]
8. Internal audit report [request previously sent]

Reviewing Medical Officer

Date

Janice Pohlman, MD MPH

March 24, 2009

Clinical Team Leader

Date

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

/s/

Janice Pohlman
3/24/2009 04:19:56 PM
MEDICAL OFFICER