CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-110

MEDICAL REVIEW(S)

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: August 31, 2009

FROM: Sumathi Nambiar M.D. M.P.H.
Deputy Director for Safety
Division of Anti-infective and Ophthalmology Products

SUBJECT: Summary Review Memo for NDA 22-110, Class II resubmission

1.0 Background

Telavancin is a lipoglycopeptide antibacterial that is active against various Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. The Applicant, Theravance had submitted the NDA on December 19, 2006 and the Agency had issued an approvable letter on October 19, 2007. A complete response was submitted by Theravance on January 21, 2008. On February 20, 2009, a complete response letter was sent to Theravance. Among the deficiencies listed in the complete response letter was the need for a Risk Evaluation and Mitigation Strategy (REMS). The need for a REMS was based on the findings of teratogenicity in animal species. The REMS was to consist of a Medication Guide, a Communication Plan, and a timetable for the submission of assessments of the REMS. Elements to assure safe use and an implementation plan were considered to be not necessary. Theravance was also informed that if the product was approved, a pregnancy registry for patients exposed to telavancin during pregnancy would be considered a post-marketing requirement. On March 13, 2009, Theravance submitted a complete response. This review summarizes the REMS, the post-marketing requirements and the post-marketing commitment associated with this NDA.

Risk Evaluation and Mitigation Strategy: Based on the findings of teratogenicity in animal species, there is a potential risk of teratogenicity in humans. To ensure that the benefits of the drug outweigh the risk of teratogenicity seen in animal studies it was determined that a REMS was necessary. The goal of the REMS is to avoid unintended exposure of pregnant women to telavancin. The specific objectives to be achieved by the REMS are:

- To educate healthcare professionals (HCP) and patients on the potential risk of fetal developmental toxicity if women are exposed to telavancin while pregnant.
- To inform HCP that a serum pregnancy test should be performed before initiating therapy with telavancin in women of childbearing potential.

- To inform HCP that women of childbearing potential, including those being treated in an outpatient setting, should be counseled about pregnancy prevention and use of effective contraception during telavancin use.
- To inform HCP and patients about the pregnancy registry for patients exposed to telavancin during pregnancy.

REMS Elements
Medication Guide: A Medication Guide will be available for distribution with each telavancin prescription in accordance with 21 CFR 208.24. Telavancin is packaged as a single unit of use and the Medication Guide is inserted inside the carton. Additional copies of the Medication Guide will also be available via sales and/or clinical representatives, and on the product website.

Communication Plan: The communication plan consists of a Dear Health Care Provider (DHCP) letter, a description of who the audience will be for the communication plan, and a schedule for when and how the DHCP letter will be distributed to HCP. The DHCP letter describes the fetal effects of telavancin seen in animals and pregnancy prevention measures and will also include information about the pregnancy registry. The communication plan will be directed to targeted healthcare providers and pharmacists. The DHCP letter will be distributed prior to commercial distribution, 6 months, 1 year, and 2 years after product approval. The DHCP letter will be distributed to the target audience either through hardcopy mailings by U.S. mail or via email. Theravance has provided detailed information on the systems they have in place to ensure that electronic dissemination of information will be adequate and their plans for hardcopy mailing if the electronic copies are not accessed in a timely fashion. The DHCP letter will also be available on the product website. The Applicant has provided a list of HCP and organizations to whom the DHCP letter will be sent.

Timing of Assessments: The Applicant will provide formal assessments of the REMS by 18 months, 3 years, and 7 years after approval. These assessments will include:

- Results of the patient and healthcare provider surveys.
- Report on the periodic assessments of the distribution and dispensing of the Medication Guide.
- Report on failures to adhere to distribution and dispensing requirements, and corrective actions taken to address noncompliance.
- Assessment and conclusion of whether each REMS is meeting its goals and whether modification to each REMS are needed.
- Summary and analysis of maternal and fetal outcomes of pregnancy exposures, a cumulative number of all fetal exposures and outcomes reported in the pregnancy registry and spontaneously.

The following sources of information will be used in conducting the assessments:

- Knowledge, Attitude, and Behavior Surveys of Healthcare Providers: Knowledge, Attitude, and Behavior (KAB) surveys in HCP will be conducted 12 months after

initial distribution of the REMS materials, and will be repeated annually for at least the first 3 years.

- Assessment of Patients: An assessment in women of child-bearing potential will be conducted to assess their understanding of the potential risk of fetal development toxicity if they are exposed to telavancin while pregnant.

- Adverse Event Monitoring, Analysis, and Reporting: Adverse events of special interest will include females who were pregnant when exposed to telavancin or pregnancies that occurred during treatment with telavancin.

- Pregnancy Registry.

- Distribution and dispensing of the Medication Guide.

Post- Marketing Requirements: The Applicant will be conducting the following studies as post-marketing requirements:

- Pregnancy Registry: The Applicant will design and maintain a pregnancy registry to track any adverse outcomes from exposure to telavancin in pregnant women. The protocol for the registry was submitted by Theravance and reviewed by the Pregnancy and Maternal Health Team (PMHT). Based on comments provided by the PMHT, the protocol has been modified by the Applicant and the changes were found to be acceptable to the PMHT and the Division.

  The pregnancy registry will be a voluntary, prospective, observational cohort study of 300 women exposed to telavancin at any time during pregnancy. The registry will be conducted in the U.S. The registry will identify and record major congenital anomalies, minor anomalies that occur in groups of three or more, spontaneous abortions, stillbirths, elective terminations, functional deficits in the child, and any serious pregnancy outcomes. For a detailed review of the protocol, please refer to the review by Chardae Araojo, Pharm.D.

- Emerging Resistance: The Applicant will conduct a prospective study over a five-year period after introduction of telavancin to the market to determine if resistance to telavancin is occurring in the target population of bacteria that are in the approved telavancin package insert.

Post-Marketing Commitment: To gain further understanding about the lower cure rates seen in telavancin-treated patients with renal impairment, the Applicant will be conducting the following trial as a post-marketing commitment:

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.

Conclusions: Appropriate provisions are in place to mitigate the potential risk of teratogenicity associated with telavancin use. The product label and REMS adequately communicate the potential risk of teratogenicity to humans based on the findings of teratogenicity in animal species. Additionally, data on adverse fetal outcomes will be collected in the pregnancy registry and reported annually. The higher incidence of renal adverse events and the finding of decreased efficacy in patients with renal impairment who were treated with telavancin are adequately described in the product label. The post-marketing commitment will further clarify the issue of decreased efficacy in patients with renal impairment.

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SUMATHI NAMBIAR
09/02/2009

CLINICAL REVIEW

Application Type	Class II Resubmission
Application Number	22-110
Submit Date	March 13, 2009
Received Date	March 16, 2009
PDUFA Goal Date	September 16, 2009
Division / Office	Division of Anti-Infective and Ophthalmology Products / Office of Antimicrobial Products
Reviewer Name	Janice Pohlman, MD, MPH
Review Completion Date	August 19, 2009
Established Name	Telavancin
Trade Name	Vibativ
Therapeutic Class	Lipoglycopeptide
Applicant	Theravance, Inc.
Formulation	Sterile Lyophilized Powder for Injection
Dosing Regimen	10 mg/kg IV q 24 hours
Indication	Complicated Skin and Skin Structure Infections
Intended Population	Adults ≥ 18 years

Introduction and Regulatory Background

Theravance, Inc. submitted this Complete Response for NDA 22-110 on March 13, 2009. This submission responds to the deficiencies outlined in the Complete Response letter issued by the Agency on February 20, 2009. The Agency requested that the Applicant:

1. Submit more comprehensive follow-up data and analyses performed on patients enrolled in the hospital acquired pneumonia trials (HAP), Studies 0015 and 0019, in whom adverse events (AE) related to renal impairment were observed.
2. Follow-up of patients enrolled in the complicated skin and skin structure infection studies (cSSSI), Studies 0017 and 0018, in whom elevation in serum creatinine (Cr) to greater than two times their baseline value was observed.
3. In accordance with provisions in the Food and Drug Administration Amendments Act of 2007, submission of a proposed Risk Evaluation and Mitigation Strategy (REMS) to ensure that the benefits of telavancin in treatment of cSSSI outweigh the risk of teratogenicity (seen only in nonclinical animal data, to date). The REMS submission was to include a Medication Guide as provided for by 21 CFR Part 208 and a communication plan for healthcare providers to provide for dissemination of information to patients in the form of a Dear Health Care Provider Letter.
4. Establish a pregnancy registry to identify any potential signal for teratogenicity in humans as a post-marketing requirement.
5. Updated draft product labeling in structured product labeling (SPL) format.

Information included in the Applicant's Complete Response included follow-up information on subjects enrolled in the cSSSI trials as described above. A summary of renal adverse events and laboratory abnormalities related to nephrotoxicity in the HAP trials, along with a cross-reference to the telavancin HAP NDA (NDA) submitted by Theravance, Inc. ( ) for was cross-referenced to provide additional data on renal impairment observed in those studies. Additionally, information required for the REMS and the protocol for a pregnancy registry were submitted. b(4)

Drug Product Overview

Telavancin is a lipoglycopeptide antibacterial agent produced through chemical modification of vancomycin. The drug product contains hydroxypropyl-β-cyclodextrin to decrease the nephrotoxicity of telavancin.

Telavancin has activity against gram positive bacteria. It acts to inhibit peptidoglycan synthesis and disrupt formation of the cell membrane. *In vitro* data show that telavancin is more active than vancomycin against *Staphylococcus aureus* (both methicillin-resistant and methicillin susceptible isolates).

The clinical development program for telavancin includes two Phase 2 studies of skin and skin structure infections (SSSI), two Phase 3 studies of cSSSI, two

Phase 3 studies of HAP, and one Phase 2 study of uncomplicated *S. aureus* bacteremia. The Applicant submitted the two Phase 3 HAP studies as the basis for NDA (C D) b(4)

The Complete Response does not contain any new chemistry, pharmacology/toxicology, microbiology, or clinical pharmacology information.

Regulatory History

For a more thorough overview, see the October 19, 2007 clinical review of NDA 22-110 and the December 22, 2008 clinical review of the Class 2 Resubmission (January 24, 2008).

NDA 22-110 was submitted on December 19, 2006. An approvable letter was issued on October 19, 2007. The deficiencies included deviations from cGMP at the Ben Venue manufacturing facility in Bedford, OH, missing financial disclosure information for three sub-investigators, and issues related to determination of the overall benefit to risk ratio for telavancin for treatment of cSSSI. The important issues in determining the benefit to risk ratio for this drug and indication included safety concerns related to nephrotoxicity, prolongation of the QTc interval, and potential teratogenicity, and decreased efficacy in patients with renal impairment.

A complete response to the approvable letter was submitted by Theravance, Inc. on January 21, 2008. A meeting of the Anti-Infective Drugs Advisory Committee (AIDAC) was scheduled for February 27, 2008, based on the Federal Food and Drug Administration Amendment Act of September 27, 2007 requirement for new molecular entities to be presented before an Advisory Committee and also due to concerns regarding benefit to risk ratio. The AIDAC meeting was cancelled shortly before the scheduled date due to the Division of Scientific Investigations (DSI) concerns related to trial conduct monitoring activities by a contract research organization (CRO) that may have impacted data integrity. An additional seven investigational sites, the Applicant, and the CRO of concern were subsequently inspected by the FDA and a comprehensive audit was performed by the Applicant. Data integrity problems were detected at three sites with possible impact on efficacy; the site identified by DSI during the first review cycle (#38091) and two sites identified by the Applicant (#37004 and #38020) during their audit were excluded from Study 0018 and pooled efficacy analyses. Additionally, two sites identified by DSI (#38016 and #38163) had significant deviation from the protocol-defined timing for ECG assessments and ECG information was excluded for these sites. Otherwise, DSI concluded that the data were considered to be reliable for review.

NDA 22-110, telavancin for the treatment of cSSSI, was presented before the AIDAC on Nov 19, 2009. The committee voted 21 to 5 that the data presented demonstrated the safety and effectiveness of telavancin for treatment of cSSSI. Committee members voted 18 to 5, with 3 abstentions, that there were clinical situations when the use of telavancin might outweigh the risks of potential

teratogenicity in pregnant women. The vote was 25 to 1 in favor of development of a risk management strategy, including pregnancy testing prior to initiation of therapy, establishment of a pregnancy registry to track outcomes in pregnant women who receive the drug, and education efforts on the potential risk of use in pregnant women.

A complete response letter was issued by the Agency on February 20, 2009. The deficiencies cited in the letter included the need for development of a Risk Evaluation and Mitigation Strategy (REMS) with requirements for a Medication Guide and a Dear Healthcare Provider Letter, additional follow-up information on patients with nephrotoxicity from the cSSSI studies and unblinded HAP studies, and a post-marketing requirement for establishment of a pregnancy registry. A revised copy of the drug product label was also required.

Clinical Review of Submission
(Based on the review of NDA 22-110 and Complete Response #1)

Efficacy Study Design Summary

The Applicant conducted two Phase 3 studies of identical design. Studies 0017 and 0018 were multicenter, randomized, double-blind, active-controlled, parallel group trials. Randomization was stratified by presence of diabetes mellitus and geographic region (three regions per study). Patients with cSSSI (primarily due to MRSA) were randomized 1:1 to receive either telavancin 10 mg/kg IV q 24 hr or vancomycin 1 gm IV q 12 hr for 7-14 days. Adjunctive aztreonam or metronidazole could be used to treat patients with infections due to suspected or culture positive gram negative and/or anaerobic organisms.

The primary objective was to compare the efficacy and safety of telavancin to vancomycin in the treatment of adults with Gram positive cSSSI with emphasis on patients with infections due to MRSA at a test-of-cure (TOC) visit 7-14 days after completion of therapy. A pre-specified secondary objective was to pool the efficacy data from each of these studies to assess the superiority of telavancin to vancomycin in patients with methicillin-resistant *S. aureus* (MRSA) infections.

Patients had baseline clinical and microbiological evaluation within 24 hours of study enrollment. After completing therapy, patients had an end-of-therapy (EOT) visit and a TOC visit 7-14 days after the EOT assessment. Efficacy assessment included clinical evaluation of the infection site and microbiological assessment only if a significant wound and/or drainage persisted at the infection site.

A Clinical Response assessment was performed by the investigator at EOT and TOC visits. The following definitions were used to assess outcome:

- **Cure**: resolution of signs and symptoms associated with the skin infection present at study admission such that no further antibiotic therapy is necessary.
- **Not Cured**: inadequate response to study therapy.
- **Indeterminate**: inability to determine outcome.
- **Missing:** no determination reported.

Microbiological responses were assessed by the Applicant based on either culture data (if available) at TOC or extrapolated from the clinical response at TOC.

In both studies, the primary efficacy analysis was to initially test the non-inferiority of telavancin relative to vancomycin using the difference in the clinical response rate at TOC in the all-treated (AT) and clinically evaluable (CE) populations, employing a non-inferiority (NI) margin of 10%. If noninferiority was established, then statistical superiority would be examined in the AT population using the

confidence interval approach to determine whether the lower bound of the 95% CI was greater than zero.

If both studies were able to demonstrate noninferiority of telavancin to vancomycin, an additional goal was to demonstrate the superiority of telavancin over vancomycin in patients infected with MRSA at baseline in the pooled AT population stratified by study.

Efficacy Results

Sites # 38091, 37004, and 38020 were excluded from all efficacy analyses and are not represented in the following efficacy tables.

Primary Endpoint

The co-primary efficacy endpoints were the clinical response rates at TOC in the AT and CE populations for Studies 0017 and 0018. Table 1 shows the results of the FDA efficacy analyses for Studies 0017 and 0018.

Table 1: Clinical Response Rates for FDA AT and CE Analysis Populations

	Telavancin Success	Vancomycin Success	Difference in Success (telavancin – vancomycin)
Population	**n/N %**	**n/N %**	**% (95% CI[1])**
All Treated			
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)
Study 0018	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)
Clinically Evaluable			
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)
Study 0018	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)

[1] 95% CI calculated using a continuity correction

In both Studies 0017 and 0018, telavancin was demonstrated to be noninferior to vancomycin for the endpoints of clinical response at TOC in both the AT and CE populations based on the treatment difference in clinical response rates using a 10% NI margin. The finding of non-inferiority was demonstrated in both FDA and Applicant analyses. Telavancin was not statistically superior to vancomycin in either of the studies.

Table 2 below shows the results of the FDA analyses of clinical response rates for patients in studies 0017 and 0018 for the AT population who had MRSA isolated from baseline microbiological cultures.

Table 2: Clinical Response Rates for the AT Population with MRSA Isolated at Baseline

	Telavancin Success	Vancomycin Success	Difference in Success (telavancin – vancomycin)
Population	**n/N %**	**n/N %**	**% (95% CI)**
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018	135/166 (81.3)	132/172 (76.7)	4.6 (-4.1, 13.2)
Pooled [1] (0017 + 0018)	227/301 (75.4)	242/323 (74.9)	0.9 (-5.8, 7.6) p-value 0.18

[1] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights.
p-value is a two-sided test based on a stratified analysis by study.

In AT patients with MRSA isolated as a pathogen at baseline, telavancin was not superior to vancomycin in clinical response at TOC.

Based on discussion at the November 18, 2008 AIDAC meeting on use of a non-inferiority trial design for the cSSSI indication, a sensitivity analysis was performed excluding patients with major abscesses. There was no consensus on an appropriate NI margin to use in antibacterial treatment trials in patients with abscesses following primary treatment with surgical drainage. Table 3 shows a sensitivity analysis for the clinical success rates in infections excluding abscesses (approximately 40% of population enrolled).

Table 3: FDA Clinical Response Rates (minus abscesses)

	FDA Analysis			FDA Analysis Excluding Patients w/Major Abscesses		
	Telavancin Success	Vancomycin Success	Difference (telavancin – vancomycin)	Telavancin Success	Vancomycin Success	Difference (telavancin – vancomycin)
Population	**n/N %**	**n/N %**	**% (95% CI[1])**	**n/N %**	**n/N %**	**% (95% CI[1])**
All Treated						
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)	176/247 (71.3)	166/236 (70.3)	0.9 (-7.6, 9.4)
Study 0018	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)	159/195 (81.5)	153/192 (79.7)	1.8 (-6.5, 10.2)
CE						
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)	196/262 (74.8)	208/277 (75.1)	-0.3 (-7.8, 7.4)
Study 0018	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)	169/205 (82.4)	188/215 (87.4)	-5.0 (-12.3, 2.3)

[1] 95% CI calculated using a continuity correction

Table 4 shows the results of the exploratory analyses in subgroups of the FDA CE analysis populations of Study 0017 and 0018 combined.

Table 4: Clinical Response Rates in Subgroups - CE Population

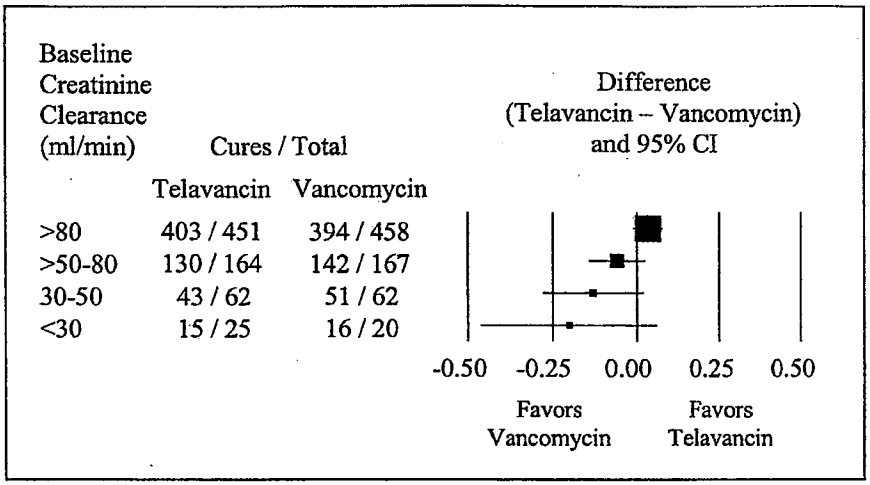
	Telavancin % (n/N)	Vancomycin % (n/N)	Difference [1] (TLV-Comparator) (95% CI)
US/Non-US			
• US	394/472 (83.5)	403/486 (82.9)	0.6 (-4.2, 5.3)
• Non-US	197/231 (85.3)	200/221 (90.5)	-5.3 (-11.2, 0.7)
History of Diabetes			
• Diabetes	128/167 (76.5)	146/183 (79.8)	-3.2 (-11.8, 5.4)
• No diabetes	462/535 (86.4)	457/524 (87.2)	-0.8 (-4.9, 3.2)
Baseline Creatinine Clearance			
• > 80 mL/min	403/451 (89.4)	394/458 (86.0)	3.3 (-1.0, 7.5)
• > 50-80 mL/min	130/164 (79.3)	142/167 (85.0)	-5.9 (-14.1, 2.4)
• 30-50 mL/min	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)
• < 30 mL/min	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.5, 5.2)
Wound type			
• Major Abscess	263/303 (86.8)	262/300 (87.3)	-0.5 (-5.9, 4.8)
• Wound Infection	87/108 (80.6)	83/96 (86.5)	-5.8 (-15.9, 4.4)
• Deep/Extensive Cellulitis	199/240 (82.9)	227/273 (83.2)	-0.2 (-6.7, 6.3)
• Infected Ulcer	30/40 (75.0)	25/31 (80.6)	-6.2 (-25.8, 13.5)
• Infected Burn	12/12 (100)	6/7 (85.7)	9.8 (-5.9, 25.6)

[1] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights

The clinical response rates were similar across geographic region (US/non-US). Response rates were lower in patients with a history of diabetes mellitus. Clinical response rates did not differ significantly across cSSSI type, although some of the groups (i.e., infected ulcer and infected burn) were small.

There was a significant difference (decrease) in clinical response rates between patients with baseline renal impairment treated with telavancin compared to those treated with vancomycin. Patients with progressive degrees of baseline renal impairment had a greater decline in clinical response rate when treated with telavancin (see Figure 1). This decline in clinical response rate seen with telavancin treatment in patients with progressive levels of baseline renal impairment is of some concern. However, conclusions regarding this finding are limited by the exploratory nature of the post hoc analyses of subgroups and small numbers. A similar pattern of decrease in clinical response rates was seen in older patients treated with telavancin while clinical response rates in patients treated with vancomycin did not decrease. The decline in response rates may be related to decreased efficacy in older patients, since aging is correlated with a decline in creatinine clearance. The decrease in apparent response rates may be related to failure to adjust (increase) the telavancin dose in response to improving renal function.

Figure 1: Clinical Response at TOC in the FDA CE Population for Studies 0017 + 0018 -- By Baseline Renal Impairment



Clinical Microbiology

Table 5 shows the clinical response rates by pathogen for the FDA Microbiologically Evaluable (ME) analysis population.

Table 5: Clinical Response at TOC in the ME Population (Study 0017 and 0018)

Pathogen	Study 0017		Study 0018	
	TLV n/N, %	VANC n/N, %	TLV n/N, %	VANC n/N, %
Staphylococcus aureus, MRSA	90/109 (82.6)	107/126 (84.9)	118/130 (90.8)	118/136 (86.8)
Staphylococcus aureus, MSSA	70/81 (86.4)	66/79 (83.5)	61/79 (77.2)	65/75 (86.7)
Enterococcus faecalis	12/12 (100)	11/14 (78.6)	10/11 (90.9)	17/21 (81.0)
Streptococcus pyogenes	9/10 (90)	9/10 (90)	7/9 (77.8)	10/11 (90.9)
Streptococcus agalactiae	8/9 (88.9)	3/3 (100)	6/10 (60)	10/12 (83.3)
Streptococcus anginosus group	7/8 (88)	5/5 (100)	6/8 (75.0)	4/4 (100)

The FDA assessment of the clinical response rate in the ME population for patients with MRSA infection in Study 0017 was 84.9% for the vancomycin treatment group compared to 82.6% for the telavancin treatment group; results for Study 0018 favored telavancin with a clinical response rate in the patients in the ME population for patients with MRSA infection to be 90.8% compared to 86.8% for vancomycin.

Response rates for MSSA appear similar and were slightly higher for telavancin compared to vancomycin in the FDA analysis of Study 0017; response rates for MSSA were higher for vancomycin compared to telavancin in the FDA analysis of Study 0018.

Efficacy Conclusions

- The results of two independent studies of identical design, Study 0017 and Study 0018, support the conclusion that telavancin demonstrates clinical noninferiority to vancomycin using a prespecified NI margin of 10% for the co-primary analysis populations. Superiority of telavancin to vancomycin in treatment of patients with cSSSI and in whom MRSA was isolated from baseline microbiological culture was not demonstrated in the prespecified pooled analysis of Study 0017 and 0018.
- The apparent decrease in clinical response rates for patients with baseline renal impairment treated with telavancin is not explained and may be of clinical concern.
- Blinding of the study may have been impacted by the observation of taste disturbance and foamy urine in recipients of telavancin.

Integrated Safety Review with Emphasis on Phase 3 cSSSI Review

For additional information see the original NDA clinical safety review which includes more complete information and narratives for patients who had an AE resulting in death, other serious adverse events (SAEs), or discontinued study medication due to an AE while participating in these studies.

The safety database at the time of the original NDA submission included healthy subjects who had received telavancin in Phase 1 studies and patients with cSSSI who were treated with telavancin in Phase 2 and Phase 3 studies. Table 6 shows the number of patients evaluated for safety in the telavancin development program.

Table 6: Number of Subjects Evaluated for Safety - All Telavancin Studies (Treatment Assignment Known)

	Number of Subjects Exposed	
Study Group	**Telavancin**	**Comparator**
Clinical Pharmacology Studies		
Single Dose Studies[1] (0.25 – 15 mg/kg)	124	47
Multiple Dose Studies (7.5 – 15 mg/kg)	144	103
Total Clinical Pharmacology Studies	**268**	**150**
Efficacy and Safety Studies in cSSSI		
Studies 0017, 0018, and 202b, 10 mg/kg telavancin dose	1029	1033
Study 202a and Studies 0017, 0018, 202b, 7.5 mg/kg telavancin	192	189
Total Efficacy and Safety Studies	**1221**	**1222**

From Summary of Clinical Safety, Table 2, pg 16.
[1] Of the telavancin-treated patients, 79 subjects received a single dose and 45 received single doses on more than one occasion separated by one week or more.

The primary safety review for NDA 22-110 was performed for patients enrolled in the Phase 3 cSSSI studies (Studies 0017 and 0018) with telavancin dose of 10

mg/kg. The 4 Month Safety Update for NDA 22-110 included unblinded safety information on 58 patients who were enrolled in Study 203a (uncomplicated *S. aureus* bacteremia study) comparing telavancin 10 mg/kg to vancomycin (or anti-staphylococcal penicillin if MSSA was isolated) for 14 days. The first Complete Response submission (January 21, 2008) contained integrated, unblinded summary safety data for HAP studies 0015 and 0019. This data included information on 751 patients treated with telavancin (10 mg/kg q 24 hr) and 752 patients treated with comparator (vancomycin). The safety data was limited to an integrated tabular listing of deaths, other SAEs, and discontinuations due to AEs, along with patient narratives. No case report forms (CRFs) or patient-level datasets were included.

Deaths

There were 18 deaths reported for the SSSI studies (0017 and 0018) for the period prior to TOC (or for 30 days after EOT in those without TOC); one death occurred in a patient treated with telavancin 7.5 mg/kg, eight deaths occurred in patients treated with telavancin 10 mg/kg, and nine deaths occurred in patients treated with the comparator. Of the nine deaths in the telavancin treatment group, the investigator assessed the AE as possibly/probably related to death in four patients with the following events noted: respiratory failure and renal insufficiency (1), renal insufficiency (1), ventricular arrhythmia (1), and cardiac arrest, unwitnessed (1).

An additional five deaths were reported in telavancin treated patients (2 in Study 0017, 3 in Study 0018 including 1 in the 7.5 mg/kg group and 2 in the 10 mg/kg group) who died outside of the study death "reporting period". One of the deaths occurred in a patient in Study 0018; this patient had a history of severe heart failure and chronic renal insufficiency and developed a progressive increase in serum creatinine from baseline of 4.1 mg/dL to 10.3 mg/dL at TOC (one week after study medication was discontinued). His death occurred 1 week after the TOC visit from acute renal failure.

For study 203a (uncomplicated *S. aureus* bacteremia study), there were five deaths in the telavancin treatment group and three in the vancomycin treatment group. The AE preferred terms with death as an outcome in telavancin-treated patients were sepsis, endocarditis bacterial, renal failure acute, dyspnea, death, renal failure chronic, pneumonia, disseminated intravascular coagulation, and empyema; none were assessed as possibly/probably related to study medication by the investigator.

As noted, mortality data from the completed Phase 3 HAP trials (0015 and 0019) was included as part of the first Complete Response (January 21, 2008). Twenty percent (149/751) of the telavancin-treated and 18% (137/752) of the vancomycin-treated patients died. This mortality rate is consistent with that of other hospital-acquired pneumonia trials (linezolid, ceftobiprole). Table 7 shows the number of patients who died by treatment group and SOC for the AEs

resulting in death. Deaths were reported through TOC or 28 days after therapy for those who did not have a TOC evaluation.

Table 7: AEs by SOC Resulting in Death (HAP Studies)

HAP Studies (0015 and 0019)		
MedDRA SOC	**TLV N=751**	**VANC N=752**
Any serious event (# patients, %)	149 (20)	137 (18)
Blood and Lymphatic System	1 (<1)	0
Cardiac Disorders	16 (2)	29 (4)
Gastrointestinal Disorders	3 (<1)	4 (<1)
General Disorders and Administration Site	24 (3)	12 (2)
Hepatobiliary Disorders	1 (<1)	1 (<1)
Infections and Infestations	48 (6)	35 (5)
Injury, Poisoning and Procedural Complications	1 (<1)	3 (<1)
Metabolism and Nutrition Disorders	2 (<1)	1 (<1)
Neoplasms benign, malignant, and unspecified	0	2 (<1)
Nervous System Disorders	11 (1)	10 (1)
Renal and Urinary Disorders	3 (<1)	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders	38 (5)	39 (5)
Vascular Disorders	5 (<1)	2 (<1)
Modified Table 3, NDA 22-110, Safety Update, January 21, 2008		

The number of patients who died in the telavancin treatment group was greater then that for the vancomycin treatment group for general and administration disorders and infections. In the General Disorders SOC the imbalance was noted primarily for multi-organ failure (22 telavancin-treated patients compared to 11 vancomycin-treated patients). In the Infections SOC, the imbalance was primarily due to sepsis and septic shock (30 patients treated with telavancin compared to 20 patients treated with vancomycin). Adverse events resulting in death that occurred with a 1% or greater difference between treatment groups where telavancin mortality was greater were multiorgan failure (3% of telavancin-treated patients compared to 1% of vancomycin-treated patients) and septic shock (3% of telavancin-treated patients compared to 2% of vancomycin-treated patients).

An imbalance in the AEs resulting in death in the Cardiac SOC was noted with a greater number of events noted in patients in the vancomycin treatment group relative to the telavancin treatment group. The majority of deaths were secondary to congestive heart failure (12 vancomycin-treated patients compared to six telavancin-treated patients) and ventricular arrhythmia (four vancomycin-treated patients compared to one telavancin-treated patient). AEs resulting in death that occurred with a 1% or greater difference between treatment groups where vancomycin mortality was greater were respiratory failure (2% of telavancin-treated patients compared to 3% of vancomycin-treated patients) and pneumonia (1% of telavancin-treated patients compared to 2% of vancomycin-treated patients).

In an exploratory analysis provided by the Applicant, an imbalance in the following baseline characteristics was noted in telavancin-treated patients who

died versus those who did not: diabetes mellitus, ventilator-associated pneumonia, acute respiratory distress syndrome at baseline, mixed gram positive and gram negative pathogens at baseline, baseline CrCL <50 mL/min, and presence of co-morbidity. An imbalance in deaths related to advanced age and baseline septic shock were seen in both treatment groups.

Serious Adverse Events (SAEs)

Table 8 shows the number (%) of patients in each of the Phase 3 cSSSI studies who had SAEs reported, along with the number (%) of patients with at least one AE within a select system organ class (SOC) based on highest frequency. There were 69/929 (7.4%) telavancin-treated patients who had 85 SAEs compared to 43/938 (4.6%) vancomycin-treated patients with 64 SAEs.

Table 8: All SAEs in cSSSI Phase 3 Studies 0017 and 0018
SAEs For Selected System Organ Class in Phase 3 cSSSI

	Study 0017		Study 0018		Study 0017 + Study 0018	
MedDRA SOC	**TLV N=426**	**VANC N=429**	**TLV N=503**	**VANC N=509**	**TLV N=929**	**VANC N=938**
Any serious event (# patients, %)	**31 (7)**	**28 (6)**	**38 (8)**	**15 (3)**	**69 (7)**	**43 (5)**
Cardiac Disorders	6 (1)	6 (1)	4 (<1)	5 (<1)	10 (1)	11 (1)
General Disorders and Administration Site	3 (<1)	2 (<1)	1	2 (<1)	4 (<1)	4 (<1)
Immune System Disorders	1 (<1)	2 (<1)	4 (<1)	1 (<1)	5 (<1)	3 (<1)
Infections and Infestations	1 (<1)	6 (1)	6 (1)	3 (<1)	7 (<1)	9 (<1)
Investigations	1 (<1)	2 (<1)	3 (<1)	1 (<1)	4 (<1)	3 (<1)
Renal and Urinary Disorders	5 (1)	1 (<1)	6 (1)	1 (<1)	11 (1)	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders	7 (2)	8 (2)	4 (<1)	1 (<1)	11 (1)	9 (<1)
Vascular Disorders	5 (1)	1 (<1)	4 (<1)	1 (<1)	9 (<1)	2 (<1)
NDA 22-110, ISS, Modified Supporting Table 64, Page 95						

Serious adverse events were most frequently reported for the cardiac and respiratory SOCs and SAEs were balanced across treatment groups.

There was an imbalance noted in the number of SAEs in the Renal and Urinary Disorder SOC; there were 11 patients in the telavancin treatment group compared to two in the vancomycin treatment group who had SAEs in this SOC. In the Phase 3 studies, four patients (0.5%) in the telavancin treatment group had acute renal failure reported compared to none in the vancomycin treatment group.

Vascular events also showed an imbalance between treatment groups with more events noted in telavancin patients, however there was no one specific observation (Medical Dictionary for Regulatory Activities (MedDRA) preferred term AE) which predominated. Reported events included both venous and arterial events, as well as blood pressure.

Summary data from the Phase 3 HAP trials showed that SAEs occurred in 31% of telavancin-treated patients compared to 26% of vancomycin-treated patients. Table 9 shows the SOCs in which SAEs occurred at a frequency of 1% or greater in a given treatment group.

Table 9: SAEs by Select SOCs in HAP

	Total HAP Studies	
MedDRA SOC	TLV N=751	VANC N=752
Any serious event (# patients, %)	232 (31)	194 (26)
Cardiac Disorders	30 (4)	38 (5)
Gastrointestinal Disorders	12 (2)	11(1)
General Disorders and Administration Site	26 (3)	15 (2)
Infections and Infestations	68 (9)	60 (8)
Nervous System Disorders	21 (3)	19 (3)
Renal and Urinary Disorders	24 (3)	16 (2)
Respiratory, Thoracic and Mediastinal Disorders	60 (8)	57 (8)
Vascular Disorders	15 (2)	9 (1)
Modified Table 6, NDA 22-110, Safety Update, January 21, 2008		

SAEs were most frequent in the Infections and Respiratory SOCs; the Infection SOC included MedDRA preferred terms of sepsis, septic shock, and pneumonia, while the Respiratory SOC included respiratory failure.

SAEs that occurred with an incidence of 1% or greater in either treatment group included: septic shock (4% for each treatment group), respiratory failure (3% for each treatment group), multi-organ failure (3% of telavancin-treated patients compared to 2% of vancomycin-treated patients), acute renal failure (2% of telavancin-treated patients compared to 1% of vancomycin-treated patients), pneumonia (1% of telavancin-treated patients compared to 2% of vancomycin-treated patients), sepsis (2% of telavancin-treated patients compared to 1% of vancomycin-treated patients), congestive cardiac failure (<1% of telavancin-treated patients compared to 1% of vancomycin-treated patients), and acute respiratory failure (<1% of telavancin-treated patients compared to 1% of vancomycin-treated patients).

Based upon review of a line listing of patients with renal SAEs, it was noted that there was an overall imbalance in the number of patients with MedDRA preferred terms indicative of renal impairment which was based on an imbalance noted in Study 0015. In Study 0015, there were 17 telavancin-treated patients compared to seven vancomycin-treated patients and in Study 0019, eight patients in each treatment group who had renal SAEs (for both studies, there were 25 telavancin-treated patients and 15 vancomycin-treated patients). Comparison of preferred terms according to treatment group showed:

- Increased serum Cr: three patients treated with telavancin compared to none treated with vancomycin

- Acute renal failure: 18 patients treated with telavancin compared to 11 patients treated with vancomycin
- Renal impairment: no patients treated with telavancin compared to one patient treated with vancomycin
- Renal insufficiency: four patients treated with telavancin compared to four patients treated with vancomycin.

Discontinuations Due to AEs in Phase 3 cSSI Studies
Treatment-emergent AEs (TEAEs) resulting in early discontinuation of study medication in cSSSI studies occurred in 72/929 (7.8%) telavancin-treated patients compared to 53/938 (5.7%) vancomycin-treated patients.

In the Phase 3 cSSSI studies there were a greater number of events in the telavancin treated patients in the following SOCs: gastrointestinal (13 and 6 AEs respectively in the telavancin and vancomycin treatment groups), infections and infestations (12 events and 5 events for telavancin and vancomycin respectively), investigations (10 and 5 events for telavancin and vancomycin respectively), and renal and urinary (8 and 0 events for telavancin and vancomycin respectively). Skin disorders were balanced between treatment groups and occurred in 18 telavancin and 20 vancomycin treated patients.

Data from the Phase 3 HAP trials showed that discontinuations due to AEs occurred in 60/751 (8%) telavancin-treated patients and 40/752 (5%) of vancomycin-treated patients. Table 10 shows those SOCs where discontinuations of study medication due to AEs were most frequent.

Table 10: Discontinuations due to AEs in HAP for Select SOCs

	Total HAP Studies	
MedDRA SOC	**TLV N=751**	**VANC N=752**
Any discontinuation event (# patients, %)	60 (8)	40 (5)
Blood and Lymphatic System	1 (<1)	4 (<1)
Cardiac Disorders	4 (<1)	2 (<1)
Gastrointestinal Disorders	2 (<1)	1 (<1)
General Disorders and Administration Site	3 (<1)	4 (<1)
Infections and Infestations	9 (1)	12 (2)
Investigations	17 (2)	3 (<1)
Nervous System Disorders	7 (<1)	1 (<1)
Renal and Urinary Disorders	11 (1)	6 (<1)
Respiratory, Thoracic and Mediastinal Disorders	6 (<1)	3 (<1)
Skin and Subcutaneous Tissue Disorders	5 (<1)	2 (<1)
Modified Table 7, NDA 22-110, Safety Update, January 21, 2008		

TEAEs that resulted in discontinuation of study medication occurring more frequently in the telavancin-treated group included acute renal failure (nine patients versus two in the vancomycin-treated group), prolonged QTc (protocol-

specified discontinuation criterion; eight versus two), and increased blood creatinine (five versus one).

TEAEs that resulted in discontinuation of study medication occurring more frequently in the vancomycin-treated group included renal impairment in two patients treated with vancomycin (no telavancin-treated patients), renal insufficiency in two patients treated with vancomycin (one treated with telavancin), and thrombocytopenia in two patients treated with vancomycin (no telavancin-treated patients).

Treatment Emergent AEs
The overall incidence of TEAEs in the Phase 3 cSSSI studies was 79.1% (735/929 patients) in the telavancin treatment group and 72.1% (676/938) in the vancomycin treatment group.

- The most commonly reported TEAE occurred in telavancin-treated patients and was dysgeusia or altered taste which was observed in 311/929 (33.5%) of telavancin-treated patients compared to 62/938 (6.7%) of vancomycin-treated patients.
- The next most commonly reported TEAEs in the telavancin-treated patients were gastrointestinal. Nausea occurred in 249/929 (26.8%) of telavancin-treated patients compared to 142/938 (15.1%) of vancomycin-treated patients. Similarly, vomiting was twice as common in telavancin-treated patients with 127/929 (13.7%) patients experiencing an episode of vomiting compared to 69/938 (7.4%) of vancomycin-treated patients.
- Also more commonly reported in telavancin-treated patients was foamy urine (coded as urine abnormality) which was observed in 122/929 (13.1%) of telavancin-treated patients compared to 27/938 (2.9%) of vancomycin-treated patients.

In the Phase 3 HAP trials, the overall incidence of TEAEs was 82% for telavancin and 81% for vancomycin. Gastrointestinal AEs were the most commonly seen and occurred in 35% of both treatment groups.

Renal Toxicity (all cSSSI studies)
Based on the number of renal SAEs and imbalance in renal AEs between the treatment groups, renal AEs were examined in greater detail.

The following preferred terms were included in the definition of renal impairment proposed by the Applicant: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, and increased blood creatinine. Renal tubular necrosis was also included in the FDA definition.

The findings included:

- Deaths: Two patients treated with telavancin had renal insufficiency listed as an SAE with death as an outcome assessed by the investigator as possibly/probably related to study medication. One patient treated with

vancomycin had acute renal failure listed as an SAE resulting in death, however the investigator assessed the event as not related to study medication. The FDA reviewer agrees with these assessments. Of patients in whom death occurred outside the study death-reporting period and were reported to the Applicant, four of five patients who received telavancin had renal insufficiency or renal failure during the course of study, with one patient reported to have ongoing renal insufficiency at the time of death.

- SAEs (including deaths): Nineteen patients had renal SAEs reported during the cSSSI studies; fifteen were in the telavancin treatment group and four in the comparator treatment group. Eleven of the fifteen SAEs in the telavancin treatment group were considered to be possibly/probably related to study medication compared to two of the four in the vancomycin treatment group. Three of the telavancin patients required hemodialysis; two (one of whom had rising creatinine prior to study) refused dialysis (and further care due to age/comorbidities) and died. Three patients treated with telavancin showed incomplete resolution of Cr with values still two times their baseline Cr.
- Discontinuation of study medication due to renal TEAEs: Fourteen patients discontinued study medication prematurely due to renal TEAEs; thirteen of the patients were treated with telavancin compared to one treated with vancomycin. Nine of the thirteen telavancin-treated patients who discontinued prematurely had renal events that were considered to be TEAEs by the investigator. There were two vancomycin-treated patients who had renal AEs assessed as possibly/probably related to study medication by investigator

Clinically significant changes in renal laboratory parameters (i.e. serum Cr and blood urea nitrogen (BUN)) were used to identify patients with potential renal impairment. These definitions were based on maximum change from baseline and included serum Cr increase to 1.25 x baseline, any post-baseline serum Cr ≥ 133 µmol/L and increase of ≥ 44 µmol/L, any post-baseline serum Cr ≥ 133 µmol/L and 50% increase from baseline, and BUN post-baseline > 11 mmol/L. Two to three times as many patients treated with telavancin in Studies 0017 and 0018 combined developed clinically significant elevations in serum Cr and BUN compared to patients treated with vancomycin, regardless of which particular functional definition of renal impairment was used.

Cardiac Toxicity

A "thorough QT Study" (designed with guidelines as defined in the 2002 FDA – Health Canada Concept paper[1]) demonstrated that telavancin prolonged the QTc interval > 10 msec, the threshold for regulatory concern. Based on a step-wise linear mixed-effects model describing the relationship between telavancin concentrations and ΔΔQTcF interval, the expected ΔΔQTcF of telavancin (10 mg/kg) was estimated to be 12-15 msec. The mean ΔΔQTcF for the control

[1] FDA-Health Canada Concept paper: The Clinical Evaluation Of QT/QTc Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs Preliminary Concept Paper. November 15, 2002.

(moxifloxacin) was 24 msec which is longer than reported for moxifloxacin, however moxifloxacin was administered IV and for three days, as opposed to a single oral dose.

Phase 2/3 SSSI ECG Monitoring

Patients in the Phase 2 and Phase 3 studies had ECGs obtained at baseline, at 3-5 days of treatment and EOT. The on-drug average and on-drug maximum change in QTcF interval compared to baseline were analyzed for both groups of study patients.

The results showed that both mean and median post-drug average change and maximum change from baseline in QTcF were greater for the telavancin treatment groups at both the 7.5 and 10 mg/kg dose than those for the vancomycin treatment groups. The average and maximum change appear to be higher where telavancin was administered at a dose of 7.5 mg/kg indicating that the higher, proposed therapeutic dose did not have any greater effect than the lower dose (i.e., threshold effect reached). However the higher values noted may be influenced by the more frequent ECG testing in the Phase 2 202a and 202b studies than in the Phase 3 studies, with greater opportunity for measurement of outlier values.

The Integrated Summary of Safety (ISS) dataset of AEs was searched for AEs (both investigator reported and MedDRA preferred terms) that might be indicative of a clinically significant event due to QT prolongation and/or ventricular arrhythmia such as Torsades de pointes. The following terms were searched: bradycardia, arrhythmia, palpitations, ventricular arrhythmias, ventricular tachycardia, ventricular extrasystoles, ventricular bigeminy, cardio-respiratory arrest, cardiac arrest, sudden death, fall, syncope, and light headedness. There were no patients treated with telavancin who had AEs that were preceded by CRF evidence of ventricular arrhythmia due to Torsades de pointes.

Cardiac Adverse Event Summary

- Deaths: Four patients treated with telavancin had cardiac events resulting in death, with two of the patient's events assessed as possibly or probably related to study medication by the investigator; both of these events were unwitnessed. Six patients treated with vancomycin had cardiac events resulting in death, with none of the cardiac events assessed as related to study medication by the investigator.
- Other SAEs: Twenty-six patients experienced at least one SAE in the Cardiac Disorders System SOC; thirteen patients were in the telavancin treatment groups (11 treated with 10 mg/kg and 2 with 7.5 mg/kg) and thirteen in the comparator treatment group.
- Discontinuations of study medication due to cardiac TEAEs were also balanced across treatment groups, with four events in the telavancin treatment group and three in the vancomycin group.

Hepatic Adverse Event Summary
Preclinical studies of 6-13 week duration were associated with elevated transaminase levels (AST, ALT) in rats and dogs.

In the ISS database, there were three patients with hepatobiliary-related SAEs; two patients received telavancin and one patient comparator. These events included one telavancin-treated patient who had worsening of hepatic cirrhosis following treatment with telavancin and chemoembolization of hepatic carcinoma and the second telavancin-treated patient had a history of cholelithiasis and developed acute cholecystitis requiring cholecystectomy at the end of telavancin treatment. The vancomycin-treated patient had elevated transaminases (ALT, AST) that were attributed to chronic alcohol use.

Low level (≥ 3 x ULN) elevation in transaminases were more common in patients treated with vancomycin and seen in approximately 2% of patients. Elevation in total bilirubin and alkaline phosphatase were slightly more common in patients treated with telavancin, but were seen in approximately 1% of patients. No patients treated with telavancin or vancomycin met Hy's Rule criteria for drug-induced liver injury.

Hematologic Laboratory Adverse Events
There were four patients treated with telavancin who had a potentially clinically significant decrease in platelet count to $\leq 75 \times 10^9$/L AND $\geq 50 \times 10^9$/L below baseline. Two patients were treated in Study 0017; one patient received 5 minutes of a telavancin infusion and had a nadir platelet count of 55,000 six days after discontinuation, most likely due to a concomitant medication and the second patient had a nadir platelet count of 38,000 on Day 8 of treatment and rebounded while on therapy to 202,000 at EOT (Day 14). Two patients in a Phase 2 study had similar decreases noted in platelet counts; one patient had necrotizing fasciitis and was noted to have a platelet count of 59,000 at the time study medication was infusing and the second patient likely had a false decrease related to clumping of platelets.

Teratogenicity
Based on the results of the Segment 2 (embryo-fetal development) teratology studies in rats, rabbits, and minipigs, the Pharmacology/Toxicology reviewer, along with the Reproductive and Developmental Toxicity PTCC Subcommittee, and Maternal Health Team concluded that the limb defects observed were drug-related and that telavancin had demonstrated multi-species teratogenicity related to the skeletal system. A consensus on whether the product should be labeled Pregnancy Category C or X was not reached. The following factors were recommended for consideration in assigning a pregnancy category to this drug:

- Seriousness of the indication and potential for serious complications in pregnancy associated with the indication
- Availability of alternative treatments
- Teratogenic effect occurring at or near the proposed human dose

• "Potential benefit" of the treatment should exceed the risk

The clinical review team acknowledges the results of the animal findings, but has concerns regarding the interpretation of findings in the minipig study given confounding issues including: the small number of fetuses available for examination, skeletal abnormality observed in a fetus in the placebo group, no skeletal defects observed in the high dose group, and use of multiple other antibiotic agents for unspecified reasons.

The concern regarding potential teratogenicity, need for telavancin for treatment of cSSSI in females of childbearing potential, and risk management strategies to ensure safe use of telavancin if approved were discussed at the AIDAC meeting on November, 19, 2008. At that meeting, members of the AIDAC voted 18 to 5, with 3 abstentions, that there were clinical situations in the treatment of cSSSI when the use of telavancin might outweigh the risks of potential teratogenicity in pregnant women. The vote was 25 to 1 in favor of development of a risk management strategy which would include obtaining a pregnancy test prior to initiation of therapy, a pregnancy registry to track outcomes in pregnant women who receive the drug, and education efforts associated with the risk of telavancin use during pregnancy.

Safety Conclusions

- In two independent, adequate and well-controlled Phase 3 cSSSI studies telavancin demonstrated nephrotoxicity which appeared to be consistently greater compared to vancomycin when considered in a variety of ways:
  - Renal SAEs and discontinuations from study medication due to renal AEs were more frequent in the telavancin treatment arm than in the vancomycin treatment arm.
  - Potentially clinically significant elevations in serum creatinine occurred more frequently in the telavancin treatment groups than in vancomycin treatment groups.
  - There were five patients treated with telavancin who had relatively normal serum Cr at baseline and reported SAEs or discontinuation of medication due to renal events who had incomplete resolution of elevation in serum creatinine at the final study laboratory assessment. This makes conclusions regarding reversibility of renal effects difficult.
  - Factors that may influence or exacerbate the degree of renal insufficiency, such as hydration status and time from development of increase in serum Cr to telavancin dose adjustment, have not been thoroughly examined.
- Evidence of teratogenicity was demonstrated in multiple animal species, with limb abnormalities noted in rat, rabbit, and minipig fetuses. These effects were seen at doses with exposures approximately 1-2X the human exposure at the proposed therapeutic dose. However, these effects were noted in a limited number of animals compared to the number exposed (but higher than historical rates) and findings in the minipig study were

compromised by the small number of fetuses available for examination and positive findings in a control animal. It is unclear to the FDA clinical reviewer whether the limb abnormalities are the same in all species (i.e., whether they are all skeletal and/or related to soft tissue differentiation). If approved, the FDA clinical reviewer would support Category C pregnancy labeling, but recommend not using this drug in females of childbearing potential unless the benefits of use clearly outweigh the potential risk to the fetus.

- Although a "thorough QT study" demonstrated that televancin has an effect (i.e., prolongs) the QTcF interval, the effect appears to be less than that seen with moxifloxacin based on the FDA clinical reviewer's assessment.

Complete Response #2 (March, 13, 2009)

Deficiency 1: Additional information relating to renal function and potential for nephrotoxicity from the HAP studies (0015 and 0019) is required. Information should include case report forms (CRFs) for patients with renal adverse events, analyses pertaining to renal laboratory parameters, and any exploratory analyses performed to assess factors associated with nephrotoxicity.

Applicant Response: The Applicant cross-referenced NDA( ) submitted ( ) for telavancin for the indication of HAP. An abstracted version of the evaluation of renal safety from the HAP ISS was included with the CR. The Phase 3 studies for HAP were randomized, double-blind, active-controlled trials comparing telavancin 10 mg/kg q 24 hr to vancomycin 1 g IV q 12 hr in the treatment of patients with HAP caused by gram positive pathogens, primarily MRSA. Adjunctive aztreonam for gram negative bacterial coverage was recommended, but piperacillin-tazobactam was allowed if aztreonam was not appropriate. Treatment duration was generally 7-14 days in duration, although extension to 21 days was permitted. There were 751 patients treated with telavancin and 732 patients treated with vancomycin (an additional 20 patients received an antistaphylococcal penicillin instead of vancomycin). b(4)

The review of NDA ( ) by the Agency is ongoing. A synopsis of AEs leading to death, other SAEs, and discontinuations due to AEs was previously reviewed with the first Complete Response (January 21, 2008) and discussed above. b(4)

Similar to the cSSSI Phase 3 trials, there was no protocol-specified definition for renal impairment; investigators determined whether a specified renal AE had occurred. There were protocol-defined changes in serum creatinine that were designated as "potentially clinically significant" to objectively capture changes in renal function for all patients.

The following MedDRA preferred terms were used by the Applicant to define renal impairment: blood creatinine increased, renal failure acute, renal failure chronic, renal impairment, and renal insufficiency. The TEAEs associated with renal impairment for Study 0015 and 0019 are shown in Table 11 below.

Table 11: Treatment Emergent AEs (Renal Impairment)

	0015		0019		0015 + 0019	
MedDRA System Organ Class Preferred Term	**TLV N=372 n/N (%)**	**VAN[1] N=374 n/N (%)**	**TLV N=379 n/N (%)**	**VANC[2] N=378 n/N (%)**	**TLV N=751 n/N (%)**	**VANC[3] N=752 n/N (%)**
Any Event	37 (10)	28 (7)	37 (10)	29 (8)	74 (10)	57 (8)
Investigations						
Any Event	11 (3)	6 (2)	7 (2)	6 (2)	18 (2)	12 (2)
Blood Creatinine Increased	11 (3)	6 (2)	7 (2)	6 (2)	18 (2)	12 (2)
Renal and Urinary Disorders						
Any Event	27 (7)	22 (6)	30 (8)	24 (6)	57 (8)	46 (6)
Renal Failure Acute	18 (5)	10 (3)	16 (4)	18 (5)	34 (5)	28 (4)
Renal Failure Chronic	2 (<1)	1 (<1)	2 (<1)	0	4 (<1)	1 (<1)
Renal Impairment	2 (<1)	3 (<1)	6 (2)	4 (1)	8 (1)	7 (1)
Renal Insufficiency	5 (1)	8 (2)	7 (2)	3 (<1)	12 (2)	11 (1)

[1] 9 patients received antistaphylococcal penicillin instead of vancomycin
[2] 11 patients received antistaphylococcal penicillin instead of vancomycin
[3] 20 patients received antistaphylococcal penicillin instead of vancomycin
From NDA 22-110, Response to CR Letter, 13 MAR 2009, Table 1

Elevated creatinine and acute renal failure were more common in the telavancin treatment group in Study 0015. The renal adverse events of interest were more evenly distributed between treatment groups in Study 0019, although renal impairment and renal insufficiency were more common in the telavancin treatment group. The overall imbalance in occurrence of renal adverse events is driven by the results from Study 0015.

The reversibility or continuation of the renal impairment AEs for the pooled study data appears to be consistent across treatment groups. However, while the number (%) of renal AEs indicative of renal impairment remained consistent in the telavancin treatment group across studies, there was a notable difference (in opposite directions) for the number of events in the vancomycin treatment group that remained unchanged. This is shown in Table 12 below.

Table 12: Renal TEAE by Outcome

	0015		0019		0015 + 0019	
	TLV n/N (%)	**VAN n/N (%)**	**TLV n/N (%)**	**VAN n/N (%)**	**TLV n/N (%)**	**VANC n/N (%)**
Any Renal Event of Interest	**37**	**28**	**37**	**29**	**74**	**57**
Outcome						
Patient Died	1 (3)	1 (4)	2 (5)	1 (3)	3 (4)	2 (4)
Completely Recovered	17 (45)	13 (46)	13 (35)	10 (34)	30 (41)	23 (40)
Recovered with Sequelae	2 (5)	1 (4)	2 (5)	1 (3)	4 (5)	2 (4)
Condition Still Present and Unchanged	16 (43)	9 (32)	15 (41)	15 (52)	31 (42)	24 (42)
Condition Improving	1 (3)	4 (14)	5 (14)	2 (7)	6 (8)	6 (11)

Adapted from NDA 22-110, Response to CR Letter, 13 MAR 2009, Supporting Table 4

For patients with baseline moderate or severe renal impairment (creatinine clearance 30-50 mL/min and <30 mL/min, respectively), patients treated with telavancin were more likely to have an adverse outcome (i.e., death, recovery

with sequelae, or condition unchanged) than were those treated with vancomycin.

The Applicant reports that four patients treated with telavancin died secondary to a renal AE (three within the "death reporting" window and one after the window); three had moderate renal impairment and one severe renal impairment at baseline. Four vancomycin-treated patients died secondary to renal AE (two patients within the reported window and two after); one had mild, one had moderate, and two had severe renal impairment at baseline.

Twenty six telavancin-treated patients and 16 vancomycin-treated patients experienced SAEs indicative of renal impairment as shown in Table 13 below.

Table 13: Renal Impairment SAEs (HAP Trials)

	0015		0019		0015 + 0019	
MedDRA System Organ Class Preferred Term	**TLV N=372 n/N (%)**	**VAN[1] N=374 n/N (%)**	**TLV N=379 n/N (%)**	**VANC[2] N=378 n/N (%)**	**TLV N=751 n/N (%)**	**VANC[3] N=752 n/N (%)**
Any Event	17 (5)	7 (2)	9 (2)	9 (2)	26 (3)	16 (2)
Investigations Any Event	3 (<1)	0	0	0	3 (<1)	0
Blood Creatinine Increased	3 (<1)	0	0	0	3 (<1)	0
Renal and Urinary Disorders Any Event	14 (4)	7 (2)	9 (2)	9 (2)	23 (3)	16 (2)
Renal Failure Acute	11 (3)	3 (<1)	7 (2)	8 (2)	18 (2)	11 (1)
Renal Failure Chronic	0	0	1 (<1)	0	1 (<1)	0
Renal Impairment	0	0	0	1 (<1)	0	1 (<1)
Renal Insufficiency	3 (<1)	4 (1)	1 (<1)	0	4 (<1)	4 (<1)

[1] 9 patients received antistaphylococcal penicillin instead of vancomycin
[2] 11 patients received antistaphylococcal penicillin instead of vancomycin
[3] 20 patients received antistaphylococcal penicillin instead of vancomycin
From NDA 22-110, Response to CR Letter, 13 MAR 2009, Table 3

Renal AEs indicative of renal impairment resulted in discontinuation of study medication in 14 telavancin-treated patients and 7 vancomycin-treated patients. The renal AEs of interest leading to discontinuation of study medication are listed in Table 14 below.

Table 14: Renal Impairment AEs leading to Discontinuation of Study Medication

	0015		0019		0015 + 0019	
MedDRA System Organ Class Preferred Term	**TLV N=372 n/N (%)**	**VAN[1] N=374 n/N (%)**	**TLV N=379 n/N (%)**	**VANC[2] N=378 n/N (%)**	**TLV N=751 n/N (%)**	**VANC[3] N=752 n/N (%)**
Any Event	10 (3)	3 (<1)	4 (1)	4 (1)	14 (2)	7 (<1)
Investigations Any Event	4 (1)	0	1 (<1)	1 (<1)	5 (<1)	1 (<1)
Blood Creatinine Increased	4 (1)	0	1 (<1)	1 (<1)	5 (<1)	1 (<1)
Renal and Urinary Disorders Any Event	7 (2)	3 (<1)	3 (<1)	3 (<1)	10 (1)	6 (<1)
Renal Failure Acute	6 (2)	0	3 (<1)	2 (<1)	9 (1)	2 (<1)
Renal Impairment	0	1 (<1)	0	1 (<1)	0	2 (<1)
Renal Insufficiency	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)

[1] 9 patients received antistaphylococcal penicillin instead of vancomycin
[2] 11 patients received antistaphylococcal penicillin instead of vancomycin
[3] 20 patients received antistaphylococcal penicillin instead of vancomycin
From NDA 22-110, Response to CR Letter, 13 MAR 2009, Table 7

Renal AEs leading to discontinuation of study medication were considered to be possibly/probably related to study medication by the investigator in 12/14 telavancin-treated patients and 6/7 vancomycin-treated patients. Eight of the fourteen telavancin-treated patients and one of the seven vancomycin-treated patients were considered to have completely recovered from the AE.

As noted previously, the Applicant had pre-defined criteria for potentially clinically significant laboratory values to objectively monitor patients for evidence of renal impairment during the clinical trial. The definitions used in the HAP trials included a maximum change from baseline serum creatinine of at least 1.25 x baseline or any post-baseline creatinine ≥133 umol/L and 50% greater than baseline. They also included a decline in baseline creatinine clearance to ≤50% of baseline. Patients with normal baseline serum creatinine were presented separately from those with abnormal baseline serum creatinine and are shown in Table 15 and 16 below for normal baseline creatiinine and abnormal baseline creatinine, respectively.

Table 15: Potentially Clinically Significant Changes in Renal Function - Normal Baseline (BL) – HAP studies

Parameter and PCS Criteria	0015						0019						0015+0019					
	TLV			VANC[1]			TLV			VANC[2]			TLV			VANC[3]		
	#	Abnormal		#	Abnormal		#	Abnormal		#	Abnormal		#	Abnormal		#	Abnormal	
		N	%		N	%		N	%		N	%		N	%		N	%
Serum Creatinine Maximum Change from BL																		
Any post-BL Cr ≥133 umol/L and at least 50% > BL	281	45	(16)	296	26	(9)	318	39	(12)	308	29	(9)	599	84	(14)	604	55	(9)
Highest post-BL result																		
133 umol/L - < 177 umol/L and at least 50% > BL	281	12	(4)	296	16	(5)	318	16	(5)	308	12	(4)	599	28	(5)	604	28	(5)
177 umol/L - < 265 umol/L and at least 50% > BL	281	15	(5)	296	7	(2)	318	14	(4)	308	7	(2)	599	29	(5)	604	14	(2)
265 umol/L - < 442 umol/L and at least 50% > BL	281	14	(5)	296	2	(<1)	318	8	(3)	308	4	(1)	599	22	(4)	604	6	(<1)
442 umol/L and at least 50% > BL	281	4	(1)	296	1	(<1)	318	1	(<1)	308	6	(2)	599	5	(<1)	604	7	(1)
Creatinine Clearance Lowest post-BL result																		
≤ 50% of BL	137	19	(14)	145	26	(18)	175	28	(16)	173	24	(14)	312	47	(15)	318	50	(16)

The total number of patients for each parameter should represent the number of patients for the treatment group who (1) had that parameter assessed at baseline and at least one follow-uptime and (2) for whom the baseline value was not elevated.
1 Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin
2 Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin
3 Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin
4 Creatinine Clearance estimated by Cockcroft-Gault Equation
Source: NDA22-110, Response to CR letter 13 MAR 2009, Table 10

In evaluation of potentially clinically significant changes in serum creatinine in the cSSSI trials, the maximum change from baseline of at least 1.25 x the baseline serum creatinine was too sensitive a measure to use. It is anticipated it would similarly be too sensitive a measure in this critically ill population. Therefore, the focus in this review is on the measurement of any serum creatinine of ≥133 umol/L and at least 50% greater than baseline and the 50% reduction in baseline creatinine clearance.

As shown in Table 15 above, in both studies telavancin-treated patients were more likely to have an on-study serum creatinine of at least 133 umol/L and > 50% of baseline than were vancomycin-treated patients. This finding was more notable in Study 0015 patients. For the pooled studies, 84/599 (14%) of telavancin treated patients compared to 55/604 (9%) of vancomycin-treated patients had such a change. The increase in serum creatinine for two-thirds of the telavancin-treated patients was ≥177 umol/L compared to only about one-half of the vancomycin treated patients.

The Applicant states in their submission that creatinine clearance is a better measure of change in renal function, however in ICU patients who tend to have fluctuations in fluid status, an estimation of the creatinine clearance may not be the best measure, since it was the patient's enrollment weight being used to calculate clearance. In looking at this parameter, telavancin and vancomycin appear to have the similar effects on creatinine clearance with approximately 50% of each treatment group experiencing such a change.

The following table, Table 16, shows the results for patients with abnormal baseline serum creatinine.

Table 16: Potentially Clinically Significant Changes in Renal Function - Abnormal Baseline (BL) – HAP studies

Parameter and PCS Criteria	0015						0019						0015+0019					
	TLV			VANC[1]			TLV			VANC[2]			TLV			VANC[3]		
	#	Abnormal		#	Abnormal		#	Abnormal		#	Abnormal		#	Abnormal		#	Abnormal	
		N	%		N	%		N	%		N	%		N	%		N	%
Serum Creatinine Maximum Change from BL																		
Any post-BL Cr ≥133 umol/L and at least 50% > BL	73	18	(25)	66	10	(15)	44	9	(20)	53	4	(8)	117	27	(23)	119	14	(12)
Highest post-BL result																		
133 umol/L - < 177 umol/L and at least 50% > BL	73	0		66	0		44	0		53	0		117	0		119	0	
177 umol/L - < 265 umol/L and at least 50% > BL	73	3	(4)	66	4	(6)	44	4	(9)	53	1	(2)	117	7	(6)	119	5	(4)
265 umol/L - < 442 umol/L and at least 50% > BL	73	9	(12)	66	3	(5)	44	5	(11)	53	1	(2)	117	14	(12)	119	4	(3)
442 umol/L and at least 50% > BL	73	6	(8)	66	3	(5)	44	0		53	2	(4)	117	6	(5)	119	5	(4)
Creatinine Clearance Lowest post-BL result																		
≤ 50% of BL	207	36	(17)	206	17	(8)	179	21	(12)	182	15	(8)	386	57	(15)	388	32	(8)

The total number of patients for each parameter should represent the number of patients for the treatment group who (1) had that parameter assessed at baseline and at least one follow-uptime and (2) for whom the baseline value was abnormal (high).
1 Includes 9 patients who received an antistaphylococcal penicillin instead of vancomycin
2 Includes 11 patients who received an antistaphylococcal penicillin instead of vancomycin
3 Includes 20 patients who received an antistaphylococcal penicillin instead of vancomycin
4 Creatinine Clearance estimated by Cockcroft-Gault Equation
Source: NDA22-110, Response to CR letter 13 MAR 2009, Table 11

Based on Table 16 above, the telavancin-treated patients with abnormal serum creatinine at baseline appear to have more patients meeting the criteria of on-study serum creatinine of ≥133 umol/L and > 50% of baseline than do vancomycin treated patients; 27/117 or 23% of telavancin-treated patients compared to 14/119 or 12% of vancomycin-treated patients reach this threshold. This finding is also noted in the percentage of patients having a decline in creatinine clearance of ≤ 50% of baseline.

Deficiency 2: Patients participating in the cSSSI trials (0017 and 0018) in whom test-of-cure or follow-up laboratory data indicated a serum creatinine level of greater than two times the baseline value should be identified and follow-up information for such subjects, including creatinine levels and renal related adverse events (e.g., need for dialysis or death) should be obtained and submitted.

To address the Applicant's conclusion that the nephrotoxicity was reversible, the Agency requested that the Applicant obtain follow-up information on patients whose safety laboratory data indicated a serum creatinine level of greater than two times their baseline level.

Applicant Response: The Applicant identified 28 patients in their cSSSI safety database who had a serum creatinine > 2X baseline at the TOC/FU visit; 19/929 patients treated with telavancin 10 mg/kg, 2/93 patients treated with telavancin 7.5 mg/kg, and 7/1027 patients treated with vancomycin.

Of the 19 patients treated with telavancin, only 6 had been identified during the study as having an AE indicative of renal impairment. Only 7 of the 19 patients had follow-up beyond the TOC/FU visit, despite a serum Cr of > 2 x baseline. Two of the 7 had demonstrated resolution of the increase in serum creatinine over time:

- Patient 0017-38111-0380 with baseline Cr of 133 umol/L, received furosemide, lisinopril, and gentamicin concomitantly, and was noted to have elevation of creatinine to 283 umol/L on Study Day #25. On Study Day 123, the patient's creatinine had returned to baseline of 133 umol/L.
- Patient 0018-20006-2337 with baseline Cr of 78 umol/L, received teicoplanin at some point during the study, and had elevation of serum Cr to 173 umol/L on Study Day 22. On Study Day 39, the patient's Cr had decreased to 97 umol/L (considered to be resolved by FDA reviewer).

Five patients did not show resolution of increase in serum Cr despite longer F/U of variable duration:

- Patient 0017-09004-0498: baseline Cr of 75 umol/L, concomitant diclofenac, furosemide, vancomycin, amikacin, Study Day 9 Cr of 261 umol/L with follow-up Study Day 35 Cr of 393 umol/L

- Patient 0017-38271-0827: baseline Cr 62 umol/L, concomitant captopril and furosemide, on Study Day 18 Cr of 256 umol/L with F/U Study Day 109 Cr of 159 umol/L
- Patient 0018-38148-2498: baseline Cr 61.88, concomitant indomethacin and furosemide, Study Day 11 Cr of 133 umol/L with F/U on Study Day 20 with Cr of 106.06 ("AE outcome stated as completely recovered")
- Patient 0018-38160-2232: baseline Cr 62, concomitant furosemide, Study Day 25 Cr of 133 umol/L with F/U Study Day 63 Cr of 106 umol/L
- Patient 0018-38260-2099: baseline Cr 80 umol/L, no concomitant meds, Study Day 13 Cr of 248 umol/L with F/U Study Day 26 Cr of 133 umol/L

Three of the seven vancomycin-treated patients with TOC/FU serum Cr > 2 times baseline had a F/U Cr which had normalized (one at Day 29, one at Day 30, and one at Day 203).

Deficiency 3: Proposed Risk Evaluation and Mitigation Strategy (REMS). The proposed REMS was to include: a Medication Guide, a communication plan targeted to healthcare providers likely to prescribe telavancin to include a Dear Healthcare Provider Letter, and a timetable for submission of assessments.

Based on the teratogenic effects noted in animals, there is a potential risk for teratogencity in humans. Therefore, it was determined that a REMS was necessary 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 is to prevent unnecessary 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. For further details see the memo by Sumathi Nambiar, MD, MPH, Deputy Director of Safety, Division of Anti-Infective and Ophthalmology Products.

Deficiency 4: Revised draft labeling including the following

- Boxed warning containing information regarding teratogenicity
- Warning containing information regarding potential for nephrotoxicity and recommended monitoring of serum creatinine
- Currently the data regarding the efficacy and safety in patients with moderate and severe renal impairment is currently insufficient to recommend treatment with Vibativ. Language should be included in the Warning and Precautions section of the label to advise clinicians of the risk.
- A statement in Warnings and Precautions regarding the incidence, nature and reversibility of the nephrotoxicity, population at increased risk, and recommended avoidance of other concomitant nephrotoxic drugs should be included.
- A bold statement to the carton and container labeling to indicate that "each patient is required to receive a Medication Guide."

- Updated draft labeling should be submitted in structures product labeling (SPL) format.

Draft labeling was provided by the Applicant. Following discussions between all review disciplines and the Applicant, agreement on the majority of the product label was reached at the time this review was completed. The remaining discussion involves clarifying information about the decrease in efficacy observed in patients with renal impairment and the correct information (number of patients) who were assessed and found to have reversibility of their AE associated with renal impairment.

Deficiency 5: A post-marketing requirement for development and maintenance of a pregnancy registry to assess the signal for teratogenicity, with a protocol submitted with your CR and plans to implement the registry shortly thereafter.

The Pregnancy Registry Protocol was reviewed by Richardee Araojo, Pharm.D. The registry is a voluntary, prospective, observational cohort study of 300 women exposed to telavancin at any time during their pregnancy. Recommended changes to the protocol were accepted by the Applicant a revised Pregnancy Exposure Registry Protocol was submitted to the Agency and approved by the Maternal Health Team.

The proposed product labeling was also reviewed and agreed upon by MHT and Applicant.

Recommendations on Regulatory Action

Based upon review of the Complete Response submission (March 13, 2009) and discussion and recommendations from the November 19, 2009 Anti-Infective Drugs Advisory Committee meeting, I recommend approval for this application once agreement is reached between the Agency and the Applicant on the final product label.

My reservation in regard to approval of this drug and my previous recommendations for nonapproval (October 18, 2007 and July 24, 2008) were based upon concerns about the overall benefit to risk ratio of telavancin for treatment of complicated skin and skin structure infections. The potential for nephrotoxicity, particularly in patients with pre-existing renal impairment, incomplete knowledge about reversibility based on the extent and duration of follow-up in patients who had developed renal impairment (elevated serum Cr), and the apparent decrease in efficacy in patients with moderate and severe renal impairment were factors considered in determining this ratio. Although the decrease in efficacy noted in patients with pre-existing moderate or severe impairment was based on a post hoc subgroup analysis, it was not observed with the comparator, vancomycin.

The Applicant has responded to Agency requests to obtain additional follow-up information for patients who had AEs indicative of renal impairment or had developed elevation in serum Cr to ≥ 2 x their baseline Cr, but follow-up was not complete for all patients.

The Anti-Infective Drugs Advisory Committee voted 21 to 5 that the data from the telavancin cSSSI trials had demonstrated the safety and effectiveness of telavancin for this indication and that there was a public health need for additional drugs to treat infections caused by MRSA.

The Applicant has provided significant revisions in the label addressing the potential for nephrotoxicity including monitoring of renal function (serum Cr), addressed the Agency's requests for institution of safety measures to prevent nonessential or unintended use of telavancin in pregnant women, and has provided information about QTc prolongation in the product label.

For these reasons, I am recommending approval at this time.

Recommendations for Additional Post-Marketing Studies

1. A surveillance study to evaluate the reversibility of increases in serum Cr to ≥ 1.5 times baseline in patients treated with telavancin for cSSSI. The study should include patients with normal renal function as well as those with renal impairment.

2. Compare the chemically based assay for determining telavancin plasma concentrations with a bioassay method for patients with normal renal function and those with severe renal insufficiency.
3. Conduct a prospective surveillance study over a five year period after introduction of telavancin to the market to determine if resistance to telavancin is occurring in the target population.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22110	ORIG 1	THERAVANCE INC	TELAVANCIN
NDA 22110	ORIG 1	THERAVANCE INC	TELAVANCIN

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/s/

JANICE K POHLMAN
08/20/2009

CLINICAL REVIEW

Application Type	NDA 22-110 Class II Resubmission
Letter Date	1/24/08
Stamp Date	1/24/08
PDUFA Goal Date	7/24/08
Reviewer Name	Janice K. Pohlman, MD MPH
Review Completion Date	12/22/08
Established Name	Telavancin hydrochloride
Trade Name	(Vibativ)
Therapeutic Class	Glycopeptide Antibacterial
Applicant	Theravance, Inc.
Formulation	Powder for Reconstitution and IV Administration
Dosing Regimen	10 mg/kg
Indication	cSSSI
Intended Population	Adults

Executive Summary

Recommendation on Regulatory Action

The initial clinical review recommendation for NDA 22-110 was a Not Approvable action based on an unfavorable risk to benefit assessment for the complicated skin and skin structure infection (cSSSI) indication.

- Patients treated with telavancin had a higher number of renal serious adverse events (SAEs) and discontinuations from therapy associated with renal adverse events (AEs), along with a greater number of patients with potentially clinically significant (PCS) laboratory evidence of renal impairment by a variety of prespecified measurements than did patients treated with vancomycin. Three patients treated with telavancin required hemodialysis (one of whom had rising serum creatinine documented prior to study participation); two of these patients refused dialysis based on comorbid conditions and died. There were a few patients identified who were noted to have improving renal function at test of cure (TOC) or last study laboratory who had serum creatinine values that were still two times the baseline value.
- There are concerns about teratogenicity based on findings in embryo-fetal development studies in rats, rabbits, and minipigs. Limb abnormalities were noted in all species, although it is not clear whether they were the same in all species and related to appendicular skeletal abnormalities and/or related to soft tissue differentiation. Interpretation of the minipig study was compromised by the small number of fetuses available for examination, as well as limb findings in one control group fetus.
- Telavancin has demonstrated an effect on the QT interval, although based on the FDA clinical reviewer interpretation of the data, the effect appears to be less than that seen for moxifloxacin, an antibacterial agent which has an oral formulation and is administered to outpatients.
- There was no clinical evidence provided that telavancin provides an additional treatment benefit over vancomycin in patients with cSSSI, including infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and causes more renal toxicity than vancomycin.

Telavancin did demonstrate non-inferiority to vancomycin in two independent Phase 3 studies in the treatment of patients with cSSSI thought to be caused by gram positive bacteria. Both Phase 3 studies demonstrated non-inferiority (NI) based upon a prespecified margin of 10%. Telavancin did not demonstrate superiority relative to vancomycin in the treatment of patients who had MRSA identified from baseline microbiology cultures.

Clinical review of the Applicant's January 21, 2007 complete response to the approvable action taken on October 19, 2007, did not change the previously identified safety concerns. Telavancin did demonstrate non-inferiority to vancomycin in the treatment of cSSSI caused by gram positive pathogens using a NI margin of 10% (acceptable to the FDA and Anti-Infective Drugs Advisory Committee (AIDAC), November 18, 2008 meeting). This finding was robust enough to meet this margin (10%) in all clinical efficacy analyses except in the CE population of Study 18 when patients with abscess were excluded. However, the benefit to risk ratio is not favorable for use in treatment of cSSSI for reasons previously stated with the original NDA review.

The current recommendation for issuing a complete response letter, rather than approval, is based on the ongoing concern about nephrotoxicity and potential for decreased benefit in patients

with moderate to severe renal impairment. Additional safety concerns relate to the potential teratogenicity of the drug and use in females of child-bearing potential when alternative drugs may be available and adequate to treat the infection. Telavancin has also demonstrated the potential to prolong the QT interval, although this effect has not precipitated recognized adverse events such as Torsades de pointes in clinical studies to date.

Deficiencies to be addressed in this complete response include:

- In order to further evaluate the potential for nephrotoxicity, all safety data and analyses performed which pertain to renal function for the Phase 3 HAP studies should be submitted.
- Patients participating in the cSSSI studies (0017 and 0018) in whom test-of-cure or follow-up laboratory data indicated a serum creatinine of greater than two times the baseline value should be identified, and follow-up information submitted for all patients.
- A pregnancy registry will be necessary to evaluate the safety of this product in pregnant women/offspring. You will be required to evaluate the safety of telavancin use during pregnancy by developing and maintaining a prospective, observational pregnancy exposure registry study conducted in the United States. The study should compare pregnancy and fetal/infant outcomes of women exposed to telavancin during pregnancy to an unexposed control population. The registry should identify and record major congenital anomalies, minor anomalies that occur in groups of three or more, spontaneous abortions, stillbirths, elective terminations, functional deficits in the child, and any serious pregnancy outcomes. Infants should be assessed through at least the first year of life.
- Draft labeling should be revised as follows:
  - A boxed warning containing information regarding the potential for teratogenicity based on findings in animal studies should be included. Although telavancin should be classified as pregnancy category C, the boxed warning should include a statement that females of childbearing potential should have a negative pregnancy test prior to administration.
  - The boxed warning should also contain information regarding potential for nephrotoxicity. A baseline serum creatinine assessment, along with on-therapy (day 3) and end-of-therapy serum creatinine assessments should be performed.
  - A statement recommending avoidance of other concomitant nephrotoxic drugs (such as non-steroidal anti-inflammatory drugs) where other alternative therapies are available should be included.
  - The data regarding efficacy and safety in treatment of patients with moderate and severe renal impairment (CrCL < 30 mL/min) is insufficient to determine a positive benefit to risk ratio for treatment of cSSSI with telavancin. Therefore, a statement should be included in the precautions section of the label indicating that telavancin is not recommended for use in patients with severe renal impairment.
  - The data regarding full reversibility of renal impairment in patients with normal or mild renal impairment is limited due to short duration of follow-up in the Phase 3 clinical studies.
- Submission of a proposed Risk Evaluation and Mitigation Strategy (REMS) and a REMS Supporting Document. Your proposed REMS must include the following:
  - **Medication Guide**: FDA has determined that telavancin is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use telavancin.

- **Communication Plan**: A communication plan to healthcare providers likely to prescribe, dispense, and administer your drug, such as pharmacists, infectious disease specialists, internists, general practitioners, surgeons, critical care specialists, emergency room providers, and obstetrician/gynecologists will support implementation of the elements of your REMS. The communication plan must include the dissemination of information about the elements of the REMS, including the Medication Guide to encourage implementations by healthcare providers of relevant portions of the REMS.
- **Timetable for Assessments**: Your REMS must include a timetable for assessments that shall be no less frequent than 18 months, 3 years, and 7 years after the REMS is approved.

Background
Telavancin is a lipoglycopeptide antibacterial agent produced through chemical modification of vancomycin. It contains hydroxypropyl-β-cyclodextrin as a solubilizing agent.

Telavancin has activity against gram positive bacteria. It acts to inhibit peptidoglycan synthesis and disrupt the cell membrane. *In vitro* data show that telavancin is more active than vancomycin against *S. aureus* (MRSA and MSSA) and has activity against vancomycin-resistant *Enterococcus faecalis*, but not vancomycin-resistant *Enterococcus faecium*.

The clinical development program for telavancin to date includes two Phase 2 studies of SSSI, two Phase 3 studies of cSSSI, two Phase 3 studies of hospital-acquired pneumonia (HAP), and one Phase 2 study of uncomplicated *S. aureus* bacteremia. To date, the study reports for the HAP and uncomplicated *S. aureus* bacteremia studies have not been submitted to the FDA for review.

Regulatory History
The Investigational New Drug (IND) submission for telavancin hydrochloride (IND 60,237) was submitted to the Food and Drug Administration (FDA) on May 25, 2002. The Applicant had previously conducted a Phase 1 single and multiple ascending dose study in the United Kingdom (UK). The IND contained the protocol for a Phase 2 Skin and Skin Structure Infection (SSSI) study. The FDA requested that the Applicant perform a study in humans to evaluate potential effects of telavancin on the QT interval prior to initiating the SSSI study.

An End-of-Phase 2 meeting was held after completion of the Phase 2 SSSI study on July 12, 2004. The Applicant proposed performing two independent studies of identical design for two indications, complicated skin and skin structure infections (cSSSI) and hospital-acquired pneumonia (HAP). The Applicant proposed pooling efficacy results from the two studies within a given indication to test for the superiority of telavancin versus comparator in patients with infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). The Applicant proposed that the safety database for the NDA would include approximately 1,375 telavancin-treated patients (625 in the 10 mg/kg dose HAP studies and 750 in the 7.5 mg/kg dose cSSSI studies). The FDA stated that the safety database should contain adequate information to support the to-be-marketed dose and that absent a safety signal the proposed safety database would be sufficient.

A pre-NDA meeting was held between the FDA and Applicant on December 15, 2005. The FDA confirmed that the clinical program in cSSSI (Studies 0017 and 0018) might be adequate to support the use of the proposed 10 mg/kg dose of telavancin if efficacy was demonstrated and there was no safety signal. The Agency was asked by the Applicant whether it was acceptable to seek approval for the cSSSI indication in an initial NDA and HAP in a supplemental NDA. The FDA indicated that given demonstration of apparent toxicity in the preclinical program, the NDA would be strengthened by the demonstration of efficacy in cSSSI and an additional indication, such as HAP. The FDA indicated that the proposed safety database of 750 to 800 patients dosed at the 10 mg/kg dose of telavancin was sufficient to demonstrate adverse events (AEs) occurring in at least 1% of patients. Absent a safety signal, this would be sufficient to support use of 10 mg/kg dose for 7-14 days for this indication. However, the Applicant was reminded that the FDA had not yet received a study report on safety of the 10 mg/kg dose with particular concern noted about nephrotoxicity.

The New Drug Application (NDA) was submitted to the FDA on December 6, 2006, although the official receipt date was recorded on December 19, 2006, due to the Applicant's request for a waiver of the application fee. The review was a standard 10 month review, with a goal date of October 19, 2007.

On October 19, 2007, the FDA issued an approvable letter for the application citing the following three deficiencies:

Deficiency 1: FDA inspection of the Ben Venue facility in Bedford, Ohio revealed significant deviations from the Current Good Manufacturing Practice Regulations.

Deficiency 2: Financial disclosure information for three sub-investigators was not included in the application.

Deficiency 3: The benefit to risk ratio of the drug product is in question because of the following:

- Decreased efficacy of telavancin in patients as baseline creatinine clearance decreased and age increased, relative to vancomycin
- Relative to vancomycin, an imbalance in the reported rates of serious renal disorders and vascular disorders was noted
- The thorough QT/QTc study demonstrated that telavancin prolonged the QTc interval
- The drug product appeared to be teratogenic in at least one and possibly up to three species
- Insufficient information was provided to recommend a dosing regimen for patients with creatinine clearance of less than 10 mL/min including patients on hemodialysis.

The Applicant was requested to submit either through additional clinical data or re-analyses of previously conducted trials, a justification of why the risks associated with the issues identified above do not outweigh the potential benefit observed as a result of the treatment of cSSSI with telavancin. Alternatively, the Applicant was requested to submit revised labeling with the goal of minimizing the risk associated with use of the drug.

The NDA action date occurred after implementation of Food and Drug Administration Amendments Act (FDAAA), September 27, 2007. Therefore, the Applicant was advised that upon resubmission of a complete response and FDA review of that response, the information would need to be presented before a meeting of the AIDAC because the drug was a new molecular entity (NME) and also because of the benefit to risk concerns. This meeting was scheduled for February 27, 2008.

Just prior to the February AIDAC meeting, the FDA Division of Scientific Investigation (DSI) inspection findings from one of the Applicant's contract research organization (CRO) inspection were communicated to the Division of Anti-Infective and Ophthalmology Products (DAIOP), raising questions about reliability of some of the data contained in the application. The CRO inspection had been initiated due to the nature of inspectional findings at one investigator site. The concerns regarding data integrity necessitated the meeting's cancellation. A summary of these inspectional issues are described in further detail below.

Six inspections were conducted for the first review cycle between March and December of 2007: 4 clinical sites, Applicant, and CRO. The inspectional findings at two of these inspections raised serious concerns about data integrity:

- Clinical Investigator (Site 38091): This clinical site enrolled 51 subjects and was the second highest enrolling site in Study 0018 and the fourth largest overall for the two pivotal studies. FDA's inspection of this clinical site revealed major deficiencies in good clinical practice (GCP) which included retrospective alteration of efficacy data and losing or discarding critical source documents. Further, the inspectional observations suggested inadequate study monitoring, which resulted in an inspection of the CRO responsible for study monitoring.
- Contract Research Organization: One CRO that served as the monitor for most of the clinical investigators in Studies 0017 and 0018 was inspected. FDA's inspection of the CRO's monitoring targeted the four clinical sites inspected by the FDA, including Site 38091. The inspection showed that the CRO had identified all major GCP violations that the FDA identified at this site, but study monitoring was inadequate in that the CRO failed to implement appropriate corrective actions as stipulated in the contractual agreement with the Applicant. The CRO's monitoring of the remaining three clinical sites was adequate.

An additional seven sites were inspected during the second cycle of inspections. The additional clinical sites were selected based on: (1) large enrollment size, (2) efficacy data favoring the telavancin over the active control (vancomycin), and (3) study monitoring by the CRO noted above. The sites were selected to include at least one foreign clinical site.

At all 7 sites, the observed level of GCP compliance supported the integrity of the data reported from these sites. Major violations with the potential to affect data integrity consisted of electrocardiographic safety data from two sites, which were not obtained according to the time-frame specified in the study protocols. Study monitoring by the CRO routinely included the effective implementation of corrective actions when necessary. The results of FDA's inspections were also consistent with the results of the Applicant's own audit, as further described below.

The FDA requested that the Applicant conduct an internal audit of the two pivotal studies. In the Targeted Audit (4/21/08 - 6/12/08), the Applicant inspected 31 sites (24% of all sites) and

audited the records for 683 subjects (36% of all subjects). The audited sites, selected by the Applicant using prior monitoring reports to identify those suggestive of significant GCP violations, included 5 of the 11 clinical sites inspected by the FDA; Site 38091 was not included in this audit. The Applicant concluded that there was no systematic pattern or incidence of GCP violations that could affect interpretation of the reported safety and efficacy data. The audit, however, identified two clinical sites (Sites 37004, 38020) at which study monitoring was not adequate for 22 subjects.

Data that FDA considers unreliable in support of the NDA consists of efficacy data from one DSI inspectional site (Site 38091), two sites where the Applicant's audit identified issues with monitoring (Sites 37004, 38020), and electrocardiographic (ECG) safety data from two sites identified by DSI (Sites 38016 and 38163). Patient efficacy data from Sites 38091, 37004, and 38020 has been excluded from the efficacy analyses and the revised analyses below replace those included in the initial clinical review of NDA 22-110.

The European Medicines Agency (EMEA) announced that Astellas Pharma Europe B.V. withdrew the application for marketing authorization for telavancin for treatment of complicated skin and skin structure infections on October 24, 2008.

A meeting of the AIDAC was held on November 19, 2008, seeking expert advice on the risk to benefit ratio of telavancin for treatment of cSSSI, including infections in pregnant women. Advice regarding labeling or risk management programs required to insure safe use of telavancin for cSSSI was also sought. The AIDAC voted 20 to 5 that telavancin demonstrated a favorable benefit to risk profile for treatment of cSSSI, including infections caused by MRSA. Committee members felt that renal toxicity, QTc prolongation, and teratogenic effects could be addressed in product labeling. Post-marketing studies evaluating alterations of dosing regimen or discontinuation of therapy in the setting of rising serum creatinine levels and evaluating circumstances in which treatment with telavancin was involved a prolonged or repeated courses would also be important. The vote was 18 to 5, with 3 abstentions, for supporting use of telavancin in defined, life-threatening circumstances or where antimicrobial resistance precluded use of alternatives in pregnant women. The AC agreed (with vote of 25:1) that risk management strategies would be necessary to prevent unnecessary use in women of child-bearing potential. Requiring pregnancy tests prior to initiation of therapy, prospectively collecting data when telavancin therapy in pregnancy was required, use of pregnancy registries to track outcome of use in pregnant women, and educating women of child-bearing potential on risks associated with use of the drug during pregnancy were strategies that were discussed.

Overview: Phase 3 cSSSI Efficacy Review
(Revised Efficacy Analyses excluding sites 38091, 37004, and 38020)

The Applicant conducted two independent Phase 3 studies evaluating the safety and efficacy of telavancin compared to vancomycin in the treatment of adults (≥ 18 yrs of age) with cSSSI suspected to be caused by gram positive bacteria, including MRSA. The two studies (0017 and 0018) were of the same design and were multi-center, randomized, double-blind, active-controlled studies comparing telavancin 10 mg/kg IV q 24 hrs to vancomycin 1 gram IV q12 hrs. Telavancin dosage adjustments were to be made based on renal function, with adjustment of vancomycin per institution practice. The primary objective was to demonstrate non-inferiority of telavancin compared to vancomycin for the efficacy endpoint of clinical response at test-of-cure (TOC) using a non-inferiority margin of 10%.

Treatment duration was 7 to 14 days. Aztreonam and/or metronidazole could be used as adjunctive therapy for gram negative and/or anaerobic bacteria, respectively, but were not required. An appropriate baseline specimen was to be obtained for gram stain and microbiological culture at the local laboratory, with any pathogens isolated sent to a central microbiology laboratory for confirmation of identification and antimicrobial susceptibility. The primary efficacy outcome was assessed by the investigator and was based on the clinical response at the TOC visit 7-14 days after the end of therapy.

The co-primary efficacy endpoints were the clinical response at the TOC visit in the All-Treated (AT) and Clinically Evaluable (CE) populations. Secondary efficacy endpoints included clinical response in the Microbiological All-Treated (MAT) and Microbiological Evaluable (ME) population, as well as by-pathogen and by-patient response in the microbiological analysis populations.

The FDA analysis populations in the original clinical review differed from those reported in the Applicant's study reports for Study 0017 and 0018 in the following ways:

- Patients enrolled in Study 0018 at site #38091were excluded from the efficacy analyses based on FDA DSI inspectional findings. This site, along with sites 37004 and 38020 (based on Theravance internal audit) were subsequently excluded from the FDA and Applicant analyses.
- Patients who received a potentially effective non-study antibacterial(s) for the cSSSI from the time of initiation of study therapy to TOC were assessed as clinically evaluable failures if they had received at least 72 hours of prior study therapy.
- Patients who required surgical/wound-related procedures with impact on outcome after 96 hours of study treatment were assessed as clinically evaluable failures.
- Patients with only gram negative bacteria isolated from the baseline microbiology culture from the cSSSI site were excluded from the MAT and ME analysis populations.
- FDA recommended the following changes to the Applicant's final statistical analysis plan:
  - Test-of-Cure (TOC) window of 7-21 days after End-of-Therapy (EOT) which was more consistent with the protocol definition
  - At least 5 days (or 10 doses) of study medication for 80% compliance

- Coagulase-negative staphylococci accepted as pathogens if the gram stain was consistent with infection for cultures of wounds
- Baseline pathogen window of Day -1 to Day 1
- Only pathogens identified at the central microbiology laboratory were included in microbiological analysis.

The primary statistical analysis was to determine the non-inferiority of telavancin compared to vancomycin in adult patients with cSSSI caused by suspected gram positive bacteria, using a pre-specified non-inferiority margin for the difference in success (telavancin – vancomycin) of -10%. Since studies 0017 and 0018 were of identical design but conducted independently, the Applicant proposed pooling the results of the two studies in order to assess superiority of telavancin compared to vancomycin in the treatment of patients with MRSA isolated from baseline cultures. The FDA agreed to allow this analysis if both studies 0017 and 0018 demonstrated the non-inferiority of telavancin and if that telavancin benefit in MRSA patients did not compromise the benefit in non-MRSA patients.

For a detailed discussion of FDA's justification for use of a 10% NI margin in the cSSSI indication, see the Statistical Review completed by Scott Komo, Dr.P.H.

Baseline Characteristics
Table 1 shows the baseline demographic information for patients randomized and treated in Study 0017 and Study 0018.

Table 1: Demographics of Study Population – All Treated Population

	Study 0017[1]		Study 0018	
	Telavancin N=426	**Vancomycin N=429**	**Telavancin N=458**	**Vancomycin N=481**
Age (years)				
• Mean (range)	48.9 (18-96)	47.7 (17-90)	49.2 (18-95)	49.9 (18-91)
Age Distribution				
• <65 years	337 (79%)	357 (83%)	377 (82%)	379 (79%)
• ≥65 years	89 (21%)	72 (17%)	81 (18%)	102 (21%)
Sex				
• Male	230 (54%)	248 (58%)	258 (56%)	294 (61%)
• Female	196 (46%)	181 (42%)	200 (44%)	187 (39%)
Race				
• Black, of African heritage	59 (14%)	52 (12%)	69 (15%)	74 (15%)
• White	349 (82%)	353 (82%)	336 (73%)	343 (71%)
• Other	18 (4%)	24(6%)	53 (12%)	64 (13%)
US vs. International				
• US	306 (72%)	316 (74%)	287 (63%)	310 (64%)
• Non-US	120 (28%)	113 (26%)	171 (37%)	171 (36%)

[1]From CSR 0017, Table 8-3, pgs 108-109.

The study populations had a slight male predominance, with approximately 20% of the population > 65 years of age. Study 0017 enrolled more patients from the United States than did Study 0018.

Table 2 shows the baseline characteristics related to the cSSSI infection studied and the distribution of baseline renal function (based on estimated creatinine clearance) for each study population.

Table 2: Baseline Characteristics of the All Treated Study Population

	Study 0017		Study 0018	
Baseline Characteristics	**Telavancin N=426**	**Vancomycin N=429**	**Telavancin N=458**	**Vancomycin N=481**
Medical/Surgical Conditions Directly Associated with cSSSI				
• Recent trauma	115 (27%)	125 (29%)	59 (13%)	65 (14%)
• Diabetes mellitus	109 (26%)	109 (25%)	113 (25%)	118 (25%)
• Bite	33 (8%)	50 (12%)	34 (7%)	34 (7%)
• Recent surgical procedure	37 (9%)	42 (10%)	58 (13%)	48 (10%)
• Peripheral vascular disease	42 (10%)	28 (7%)	33 (7%)	49 (10%)
• Chronic skin disease	34 (8%)	25 (6%)	25 (5%)	44 (9%)
• Chronic edema	21 (5%)	20 (5%	21 (5%)	32 (7%)
• Other	74 (17%)	66 (15%)	61(13%)	73 (15%)
Description of cSSSI				
• Major Abscess	179 (42%)	193 (45%)	196 (43%)	204 (42%)
• Deep/Extensive Cellulitis	156 (37%)	161 (38%)	153 (33%)	176 (37%)
• Wound Infection	72 (17%)	60 (14%)	67 (15%)	61 (13%)
• Infected Ulcer	16 (4%)	12 (3%)	29 (6%)	36 (7%)
• Infected Burn	3 (<1%)	3 (<1%)	13(3%)	6 (1%)
Baseline Creatinine Clearance (ml/min)				
• >80	274 (64%)	291 (68%)	279 (61%)	286 (60%)
• >50-80	85 (20%)	85 (20%)	112 (24%)	118 (25%)
• 30-50	41 (10%)	35 (8%)	32 (7%)	45 (9%)
• <30	21 (5%)	12 (3%)	17 (4%)	16 (3%)
• Missing	5 (1%)	6 (1%)	18 (4%)	16 (3%)

Counts (and percentages) represent the number (percentage) of patients with each medical condition.
Source: CSR, Tables 8-3, 8-4, 8-5, 8-7, and 8-8 excluding Sites 38091, 37004, and 38020 from Study 0018

Approximately 25% of each study population had diabetes mellitus (stratification factor). The majority of patients had major abscesses (42-45%), with cellulitis being the next most common infection type (33-38%). Patients with wound infections accounted for 13-17% of the population. Eighty percent of the patients from Study 0017 and 60% of the patients in Study 0018 were hospitalized for the initial portion of their study therapy (based on inpatient status on Day 2 of the study).

Table 3 shows the results of the co-primary efficacy analyses for study 0017 and 0018.

Table 3: Clinical Response Rates
FDA-AT and FDA-CE, Studies 0017 and 0018

	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
FDA Population	n/N %	n/N %	% (95% CI)
AT			
Study 0017	309/426 (72.5)	307/429 (71.6)	0.9 (-6.4, 8.3)
Study 0018	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)
CE			
Study 0017	289/343 (84.3)	288/348 (82.8)	1.6 (-5, 8.3)
Study 0018	302/360 (83.9)	315/359 (87.7)	-3.8(-9.2, 1.5)

Study 0018 population excludes patients from sites 38091, 37004, 38020

The results of Study 0017 and Study 0018 demonstrate the non-inferiority of telavancin to vancomycin in the treatment of patients with cSSSI caused by suspected gram positive bacteria, including MRSA. Although the point estimate for the difference in success rates for the CE population favors telavancin in Study 0017 and vancomcyin in Study 0018, the lower bound of the 95% confidence interval is greater than -10%, the pre-specified non-inferiority margin.

Table 4 shows the Study 0017 and Study 0018 pooled clinical response rates in patients in the FDA-AT analysis population with MRSA isolated from baseline microbiological culture. The AT population was used to test for superiority of telavancin compared to vancomycin.

Table 4: Clinical Response Rates for the FDA-AT Population
MRSA Isolated at Baseline

	Telavancin Success	Vancomycin Success	Difference in Success Percents (telavancin – vancomycin)
Population	**n/N %**	**n/N %**	**% (95% CI)**
Study 0017	92/135 (68.1)	110/151 (72.8)	-4.7 (-15.3, 5.9)
Study 0018	135/166 (81.3)	132/172 (76.7)	4.6 (-4.1, 13.2)
Pooled (0017 + 0018)	227/301 (75.4)	242/323 (74.9)	0.9 (-5.8, 7.6)[1] p-value 0.18

[1] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights.
p-value is a two-sided test based on a stratified analysis by study.
Study 0018 population excludes patients from sites 38091, 37004, 38020

Telavancin failed to demonstrate superiority compared to vancomycin in the treatment of patients with cSSSI caused by MRSA.

Based on discussion at the AIDAC, a sensitivity analysis was performed excluding patients with major abscesses. Based on the discussion by the AIDAC on November 18, 2008, it was felt that the NI margin for abscesses was probably lower than that for other types of infection, reflecting the importance of primary surgical drainage. There was no consensus on what a good estimate of

the NI margin would be for abscesses. Table 5 shows a sensitivity analysis for the clinical success rates in infection types excluding abscesses (approximately 40% of population enrolled).

Table 5: FDA Clinical Response Rates (minus abscesses)

	FDA Analysis			FDA Analysis Excluding Patients w/Major Abscesses		
	Telavancin Success	**Vancomycin Success**	**Difference (telavancin – vancomycin)**	**Telavancin Success**	**Vancomycin Success**	**Difference (telavancin – vancomycin)**
Population	**n/N %**	**n/N %**	**% (95% CI[1])**	**n/N %**	**n/N %**	**% (95% CI[1])**
All Treated						
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.3, 7.2)	176/247 (71.3)	166/236 (70.3)	0.9 (-7.6, 9.4)
Study 0018	342/458 (74.7)	356/481 (74.0)	0.7 (-5.1, 6.5)	159/195 (81.5)	153/192 (79.7)	1.8 (-6.5, 10.2)
CE						
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.3, 7.3)	196/262 (74.8)	208/277 (75.1)	-0.3 (-7.8, 7.4)
Study 0018	302/360 (83.9)	315/359 (87.7)	-3.8 (-9.2, 1.5)	169/205 (82.4)	188/215 (87.4)	-5.0 (-12.3, 2.3)

[1] 95% CI calculated using a continuity correction

In the AT populations of both studies, telavancin performed slightly better than vancomycin (based on point estimate of success). In the CE population for both studies, vancomycin performed slightly better than telavancin. However, based on the lower bound of the 95% confidence interval (CI) >-10% in all populations except Study 0018 CE, telavancin was shown to be non-inferior to vancomycin (CIs have widened due to smaller population size).

Additional subgroup analyses of clinical response rates were performed based on demographic and baseline characteristics of the study populations.

Table 6 shows the pooled FDA-CE clinical response rates for each type of cSSSI studied.

Table 6: Clinical Response Rates in Subgroups – FDA CE Population

	Telavancin % (n/N)	Vancomycin % (n/N)	Difference [1] (TLV-Comparator) (95% CI)
US/Non-US			
• US	394/472 (83.5)	403/486 (82.9)	0.6 (-4.2, 5.3)
• Non-US	197/231 (85.3)	200/221 (90.5)	-5.3 (-11.2, 0.7)
Age			
• <65 years	503/581 (86.6)	492/570 (86.3)	0.2 (-3.8, 4.1)
• ≥65 years	88/122 (72.1)	111/137 (81.0)	-8.6 (-19.1, 1.8)
History of Diabetes			
• Diabetes	128/167 (76.5)	146/183 (79.8)	-3.2 (-11.8, 5.4)
• No diabetes	462/535 (86.4)	457/524 (87.2)	-0.8 (-4.9, 3.2)
Baseline Creatinine Clearance			
• > 80 mL/min	403/451 (89.4)	394/458 (86.0)	3.3 (-1.0, 7.5)
• > 50-80 mL/min	130/164 (79.3)	142/167 (85.0)	-5.9 (-14.1, 2.4)
• 30-50 mL/min	43/62 (69.4)	51/62 (82.3)	-12.6 (-27.7, 2.5)
• < 30 mL/min	15/25 (60.0)	16/20 (80.0)	-21.1 (-47.5, 5.2)
Wound type			
• Major Abscess	263/303 (86.8)	262/300 (87.3)	-0.5 (-5.9, 4.8)
• Wound Infection	87/108 (80.6)	83/96 (86.5)	-5.8 (-15.9, 4.4)
• Deep/Extensive Cellulitis	199/240 (82.9)	227/273 (83.2)	-0.2 (-6.7, 6.3)
• Infected Ulcer	30/40 (75.0)	25/31 (80.6)	-6.2 (-25.8, 13.5)
• Infected Burn	12/12 (100)	6/7 (85.7)	9.8 (-5.9, 25.6)

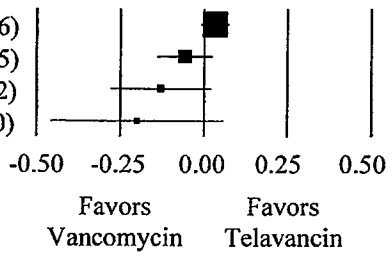
[1] Difference and 95% CI are computed using a stratified analysis by study with Mantel-Haenszel weights

The clinical response rates were similar for telavancin and vancomycin based on type of cSSSI studied. Clinical response rates decreased for telavancin relative to vancomycin as the age of the population increased. There was a similar clinical response rate in patients with diabetes mellitus treated with either drug.

Figure 1 shows the greater decline in clinical response rates with progressive degrees of baseline renal impairment in patients treated with telavancin.

Figure 1: Clinical Response at TOC in the FDA CE Population Studies 0017 and 0018 - By Baseline Renal Impairment

Baseline Creatinine Clearance (ml/min)	Cures / Total (%)	
	Telavancin	Vancomycin
>80	403/451 (89)	394/458 (86)
>50-80	130/164 (79)	142/167 (85)
30-50	43/62 (69)	51/62 (82)
<30	15/25 (60)	16/20 (80)



Excluded patients from Sites 38091, 37004, and 38020 in Study 0018

There was a significant difference (decline) in clinical response rates between patients with increasing baseline renal impairment treated with telavancin compared to those treated with vancomycin. This decline in clinical response rate seen with telavancin treatment is of some clinical concern. However, conclusions regarding this finding are limited by the exploratory nature of the post hoc analyses of subgroups and small numbers. A similar pattern of decrease in clinical response rates was seen in older patients treated with telavancin while clinical response rates in patients treated with vancomycin did not decrease to the same degree. The decline in response rates may be related to decreased efficacy in older patients, since aging is correlated with a decline in creatinine clearance. The decrease in apparent response rates may also be related to failure to adjust (increase) the telavancin dose in response to improving renal function.

The next two tables show the clinical response rates by baseline pathogen in the FDA-MITT (AT patients with baseline microbiology culture for gram positive pathogen) and ME populations (CE patients with central laboratory confirmation of identification and antimicrobial susceptibility of baseline pathogens). Table 7 shows the results for the MITT and 8 results for the ME population.

Table 7: Clinical response at TOC
FDA Microbiological All-treated Population by Baseline Pathogen

Pathogen	Study 0017		Study 0018		Pooled	
	TLV	VANC	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	92/135 (68.2)	110/151 (72.8)	134/166 (80.7)	132/172 (76.7)	226/301 (75.1)	242/323 (74.9)
Staphylococcus aureus, MSSA	77/96 (80.2)	67/89 (75.3)	66/89 (74.2)	76/111 (68.5)	143/185 (77.3)	143/200 (71.5)
Enterococcus faecalis	14/15 (93.3)	12/17 (70.6)	11/14 (78.6)	18/25 (72.0)	25/29 (86.2)	30/42 (71.4)
Streptococcus pyogenes	9/10 (90.0)	9/11 (81.8)	7/11 (63.6)	12/17 (70.6)	16/21 (76.2)	21/28 (75.0)
Streptococcus agalactiae	8/10 (80.0)	4/6 (66.7)	7/11 (63.6)	12/14 (85.7)	15/21 (71.4)	16/20 (80.0)
Streptococcus anginosus group	8/10 (80.0)	5/6 (83.3)	6/10 (60.0)	7/9 (77.8)	14/20 (70.0)	12/15 (80.0)

Table 8: Clinical response at TOC
FDA Microbiological Evaluable Population by Baseline Pathogen

Pathogen	Study 0017		Study 0018		Pooled	
	TLV	VANC	TLV	VANC	TLV	VANC
Staphylococcus aureus, MRSA	90/109 (82.6)	107/126 (84.9)	118/130 (90.8)	118/136 (86.8)	208/239 (87.0)	225/262 (85.9)
Staphylococcus aureus, MSSA	71/82 (86.6)	66/79 (83.5)	61/79 (77.2)	65/75 (86.7)	132/161 (82.0)	131/154 (85.1)
Enterococcus faecalis	12/12 (100)	11/14 (78.6)	10/11 (90.9)	17/21 (81.0)	22/23 (95.6)	28/35 (80.0)
Streptococcus pyogenes	9/10 (90)	9/10 (90)	7/9 (77.8)	10/11 (90.9)	16/19 (84.2)	19/21 (90.5)
Streptococcus agalactiae	8/9 (88.9)	3/3 (100.0)	6/10 (60.0)	10/12 (83.3)	14/19 (73.7)	13/15 (86.7)
Streptococcus anginosus group	7/8 (87.5)	5/5 (100.0)	6/9 (66.7)	4/4 (100.0)	13/17 (76.5)	9/9 (100.0)

The clinical response rates for *S. aureus* (MRSA and MSSA) are relatively similar for both treatment groups, although response rates tend to favor vancomycin against MRSA in Study 0017 and telavancin in Study 0018, while the reverse is seen for MSSA.

Telavancin has demonstrated *in vitro* activity against vancomycin-intermediate (VISA), heterogeneous vancomycin-intermediate (hVISA), and vancomycin-resistant (VRSA) *S. aureus*. However, *S. aureus* isolates from the telavancin SSSI studies had a telavancin MIC range of 0.03-1 mcg/mL and MIC_{90} of 0.5 mcg/mL and vancomycin MIC range of 0.25-2 mcg/mL and MIC_{90} of 1. MRSA isolates had a telavancin MIC range of 0.06-1 mcg/mL and MIC_{90} of 1and vancomycin MIC range of 0.25-2 mcg/mL and MIC_{90} of 1.

NDA Efficacy Conclusions

- The results of two independent studies of identical design, Study 0017 and Study 0018, support the conclusion that telavancin demonstrates clinical non-inferiority to vancomycin using a prespecified non-inferiority margin of 10% for the co-primary analysis populations for efficacy. Superiority of telavancin to vancomycin in treatment of patients with cSSSI and

in whom MRSA was isolated from baseline microbiological culture was not demonstrated in the prespecified pooled analysis of Study 0017 and 0018.

- Investigator assessment of clinical outcome in patients who prematurely discontinued study medication and were subsequently treated with non-study antibiotics may have been inconsistent based on strict application of outcome definitions and assessment as "Not cured" or looser interpretation and assessment as "Indeterminate". These assessments impacted whether a patient was a CE failure or "not" CE but cured (i.e. cure in the AT population). Investigator assessment may have been "Not Cured" if the definition was strictly interpreted and the patient would have been assessed as a clinically evaluable failure (if otherwise not excluded from the CE population).
- The FDA and Applicant differed in the adjudication of pathogen status for microbiological isolates and outcome assessment for patients undergoing significant wound care procedures after a minimum duration (96 hours) of study therapy.
- The apparent decrease in clinical response rates for patients with renal impairment treated with telavancin is not explained and may be of clinical concern.
- Blinding of the study may have been impacted by the observation of taste disturbance and foamy urine in recipients of telavancin.

Integrated Safety Review with Emphasis on Phase 3 cSSSI Review

(For additional information see the original NDA clinical safety review which includes more complete information and narratives for patients who had an AE resulting in death, other SAEs, or discontinued study medication due to an AE while participating in these studies.)

The safety database at the time of the original NDA submission included healthy subjects who had received telavancin in Phase 1 studies and patients with cSSSI who were treated with telavancin in Phase 2 and Phase 3 studies. Table 9 shows the number of patients evaluated for safety in the telavancin development program.

Table 9: Number of Subjects Evaluated for Safety - All Telavancin Studies (Treatment Assignment Known)

	Number of Subjects Exposed	
Study Group	**Telavancin**	**Comparator**
Clinical Pharmacology Studies		
Single Dose Studies[1] (0.25 – 15 mg/kg)	124	47
Multiple Dose Studies (7.5 – 15 mg/kg)	144	103
Total Clinical Pharmacology Studies	**268**	**150**
Efficacy and Safety Studies in cSSSI		
Studies 0017, 0018, and 202b, 10 mg/kg telavancin dose	1029	1033
Study 202a and Studies 0017, 0018, 202b, 7.5 mg/kg telavancin	192	189
Total Efficacy and Safety Studies	**1221**	**1222**

From Summary of Clinical Safety, Table 2, pg 16.
[1] Of the telavancin-treated patients, 79 subjects received a single dose and 45 received single doses on more than one occasion separated by one week or more.

The primary safety review was performed for patients enrolled in the Phase 3 cSSSI studies (Studies 0017 and 0018) with a telavancin dose of 10 mg/kg. Safety information was also examined for the entire SSSI study population (Phase 2 and Phase 3 studies) allowing for a limited examination of possible dose-response relationship for AEs for patients enrolled in the 7.5 mg/kg and 10 mg/kg studies. Conclusions on dose response were limited by the small sample size of patients enrolled in the 7.5 mg/kg telavancin studies relative to patients treated in the 10 mg/kg studies.

Deaths

There were 18 deaths reported for the SSSI studies for the period prior to TOC (or for 30 days after EOT in those without TOC); one death occurred in a patient treated with telavancin 7.5 mg/kg, eight deaths occurred in patients treated with telavancin 10 mg/kg, and nine deaths occurred in patients treated with the comparator. Of the nine deaths in the telavancin treatment group, the investigator assessed the AE as possibly/probably related to death in four patients with the following events noted: respiratory failure and renal insufficiency (1), renal insufficiency (1), ventricular arrhythmia (1), and cardiac arrest, unwitnessed (1).

An additional five deaths in telavancin treated patients (2 in Study 0017, 3 in Study 0018 including 1 in the 7.5 mg/kg group and 2 in the 10 mg/kg group) who died outside of the study death "reporting period". One of the deaths occurred in a patient in Study 0018; this patient had a history of severe heart failure and chronic renal insufficiency and developed a progressive increase in serum creatinine from baseline of 4.1 mg/dL to 10.3 mg/dL at TOC (one week after study medication was discontinued). His death occurred 1 week after the TOC visit from acute renal failure.

The 4 Month Safety Update (4MSU) included unblinded safety information on 58 patients who were enrolled in Study 203a (uncomplicated *S. aureus* bacteremia study) comparing telavancin 10 mg/kg to vancomycin (or anti-staphylococcal penicillin if MSSA was isolated) for 14 days. Five deaths occurred in the telavancin treatment group and three in the vancomycin treatment group. The AE preferred terms with death as an outcome in telavancin-treated patients were sepsis, endocarditis bacterial, renal failure acute, dyspnea, death, renal failure chronic, pneumonia, disseminated intravascular coagulation, and empyema; none were assessed as possibly/probably related to study medication by the investigator.

Serious Adverse Events (SAEs)

Table 10 shows the number (%) of patients in each of the Phase 3 cSSSI studies who had SAEs reported, along with the number (%) of patients with at least one AE within a select system organ class (SOC) based on highest frequency. There were 69/929 (7.4%) telavancin-treated patients who had 85 SAEs compared to 43/938 (4.6%) vancomycin-treated patients with 64 SAEs.

Table 10: All SAEs in cSSSI Phase 3 Studies 0017 and 0018
SAEs For Selected System Organ Class in Phase 3 cSSSI

	Study 0017		Study 0018		Study 0017 + Study 0018	
MedDRA SOC	**TLV N=426**	**VANC N=429**	**TLV N=503**	**VANC N=509**	**TLV N=929**	**VANC N=938**
Any serious event (# patients, %)	31 (7)	28 (6)	38 (8)	15 (3)	69 (7)	43 (5)
Cardiac Disorders	6 (1)	6 (1)	4 (<1)	5 (<1)	10 (1)	11 (1)
General Disorders and Administration Site	3 (<1)	2 (<1)	1	2 (<1)	4 (<1)	4 (<1)
Immune System Disorders	1 (<1)	2 (<1)	4 (<1)	1 (<1)	5 (<1)	3 (<1)
Infections and Infestations	1 (<1)	6 (1)	6 (1)	3 (<1)	7 (<1)	9 (<1)
Investigations	1 (<1)	2 (<1)	3 (<1)	1 (<1)	4 (<1)	3 (<1)
Renal and Urinary Disorders	5 (1)	1 (<1)	6 (1)	1 (<1)	11 (1)	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders	7 (2)	8 (2)	4 (<1)	1 (<1)	11 (1)	9 (<1)
Vascular Disorders	5 (1)	1 (<1)	4 (<1)	1 (<1)	9 (<1)	2 (<1)
NDA 22-110, ISS, Modified Supporting Table 64, Page 95						

Serious adverse events were most frequently reported for the cardiac and respiratory SOCs and SAEs were balanced across treatment groups.

There was an imbalance noted in the number of SAEs in the Renal and Urinary Disorder SOC; there were 11 patients in the telavancin treatment group compared to two vancomycin treatment group patients who had SAEs in this SOC. In the Phase 3 studies, four patients (0.5%) in the telavancin treatment group had acute renal failure reported compared to none in the vancomycin treatment group.

Vascular events also showed an imbalance between treatment groups with more events noted in telavancin patients, however there was no one specific observation (Medical Dictionary for Regulatory Activities (MedDRA) preferred term AE) which predominated. Reported events included both venous and arterial events, as well as blood pressure.

Discontinuations Due to AEs in Phase 3 cSSI Studies
Treatment-emergent AEs (TEAEs) resulting in early discontinuation of study medication in cSSSI studies occurred in 72/929 (7.8%) telavancin-treated patients compared to 53/938 (5.7%) vancomycin-treated patients.

In the Phase 3 cSSSI studies there were a greater number of events in the telavancin treated patients in the following SOCs: gastrointestinal (13 and 6 AEs respectively in the telavancin and vancomycin treatment groups), infections and infestations (12 events and 5 events for telavancin and vancomycin respectively), investigations (10 and 5 events for telavancin and vancomycin respectively), and renal and urinary (8 and 0 events for telavancin and vancomycin respectively). Skin disorders were balanced between treatment groups and occurred in 18 telavancin and 20 vancomycin treated patients.

Treatment Emergent AEs
The overall incidence of TEAEs in the Phase 3 cSSSI studies was 79.1% (735/929 patients) in the telavancin treatment group and 72.1% (676/938) in the vancomycin treatment group.

- The most commonly reported TEAE occurred in telavancin-treated patients and was dysgeusia or altered taste which was observed in 311/929 (33.5%) of telavancin-treated patients compared to 62/938 (6.7%) of vancomycin-treated patients.
- The next most commonly reported TEAEs in the telavancin-treated patients were gastrointestinal. Nausea occurred in 249/929 (26.8%) of telavancin-treated patients compared to 142/938 (15.1%) of vancomycin-treated patients. Similarly, vomiting was twice as common in telavancin-treated patients with 127/929 (13.7%) patients experiencing an episode of vomiting compared to 69/938 (7.4%) of vancomycin-treated patients.
- Also more commonly reported in telavancin-treated patients was foamy urine (coded as urine abnormality) which was observed in 122/929 (13.1%) of telavancin-treated patients compared to 27/938 (2.9%) of vancomycin-treated patients.

Renal Toxicity (all cSSSI studies)
Based on the number of renal SAEs and imbalance in renal AEs between treatment groups, renal AEs were examined in greater detail.

The following preferred terms were included in the definition of renal impairment proposed by the Applicant: renal failure acute, renal failure chronic, renal insufficiency, renal impairment, and increased blood creatinine. Renal tubular necrosis was also included in the FDA definition.

The findings included:

- Deaths: Two patients treated with telavancin had renal insufficiency listed as an SAE with death as an outcome assessed by the investigator as possibly/probably related to study medication. One patient treated with vancomycin had acute renal failure listed as an SAE resulting in death, however the investigator assessed the event as not related to study medication. The FDA reviewer agrees with these assessments. Of patients in whom death occurred outside the study death-reporting period and were reported to the Applicant, four of five patients who received telavancin had renal insufficiency or renal failure during the course of study, with one patient reported to have ongoing renal insufficiency at the time of death.
- SAEs (including deaths): Nineteen patients had renal SAEs reported during the cSSSI studies; fifteen were in the telavancin treatment group and four in the comparator treatment group. Eleven of the fifteen SAEs in the telavancin treatment group were considered to be possibly/probably related to study medication compared to two of the four in the vancomycin treatment group. Three of the telavancin patients required hemodialysis; two (one of whom had rising creatinine prior to study), refused dialysis (and further care due to age/comorbidities), and died. Three patients treated with telavancin showed incomplete resolution of Cr with values still two times their baseline Cr.
- Discontinuation of study medication due to renal TEAEs: Fourteen patients discontinued study medication prematurely due to renal TEAEs; thirteen of the patients were treated with telavancin compared to one treated with vancomycin. Nine of the thirteen telavancin-treated patients who discontinued prematurely had renal events that were considered to be TEAEs by

the investigator. There were two vancomycin-treated patients who had renal AEs assessed as possibly/probably related to study medication by investigator

Clinically significant changes in renal laboratory parameters (i.e. serum Cr and blood urea nitrogen (BUN)) were used to identify patients with potential renal impairment. These definitions were based on maximum change from baseline and included serum Cr increase to 1.25 x baseline, any post-baseline serum Cr ≥ 133 µmol/L and increase of ≥.44 µmol/L, any post-baseline serum Cr ≥ 133 µmol/L and 50% increase from baseline, and BUN post-baseline > 11 mmol/L. Two to three times as many patients treated with telavancin in Studies 0017 and 0018 combined developed clinically significant elevations in serum Cr and BUN compared to patients treated with vancomycin, regardless of which particular functional definition of renal impairment was used.

Cardiac Toxicity
A "thorough QT Study" (designed with guidelines as defined in the 2002 FDA – Health Canada Concept paper[13]) demonstrated that telavancin prolonged the QTc interval > 10 msec, the threshold for regulatory concern. Based on a step-wise linear mixed-effects model describing the relationship between telavancin concentrations and ΔΔQTcF interval, the expected ΔΔQTcF of telavancin (10 mg/kg) was estimated to be 12-15 msec. The mean ΔΔQTcF for the control (moxifloxacin) was 24 msec which is longer than reported for moxifloxacin, however moxifloxacin was administered IV and for three days, as opposed to a single oral dose.

Phase 2/3 SSSI ECG Monitoring
Patients in the Phase 2 and Phase 3 studies had ECGs obtained at baseline, at 3-5 days of treatment and EOT. The on-drug average and on-drug maximum change in QTcF interval compared to baseline were analyzed for both groups of study patients.

The results showed that both mean and median post-drug average change and maximum change from baseline in QTcF were greater for the telavancin treatment groups at both the 7.5 and 10 mg/kg dose than those for the vancomycin treatment groups. The average and maximum change appear to be higher where telavancin was administered at a dose of 7.5 mg/kg indicating that the higher, proposed therapeutic dose did not have any greater effect than the lower dose (i.e., threshold effect reached). However the higher values noted may also be influenced by the more frequent ECG testing in the Phase 2 202a and 202b studies than in the Phase 3 studies with greater opportunity for measurement of outlier values.

The Integrated Summary of Safety (ISS) dataset of AEs was searched for AEs (both investigator reported and MedDRA preferred terms) that might be indicative of a clinically significant event due to QT prolongation and/or ventricular arrhythmia such as Torsades de pointes. The following terms were searched: bradycardia, arrhythmia, palpitations, ventricular arrhythmias, ventricular tachycardia, ventricular extrasystoles, ventricular bigeminy, cardio-respiratory arrest, cardiac arrest, sudden death, fall, syncope, and light headedness. There were no patients treated with telavancin who had AEs that were preceded by case report form (CRF) evidence of ventricular arrhythmia due to Torsades de pointes.

Cardiac Adverse Event Summary

- Deaths: Four patients treated with telavancin had cardiac events resulting in death, with two of the patient's events assessed as possibly or probably related to study medication by the investigator; both of these events were unwitnessed. Six patients treated with vancomycin had cardiac events resulting in death, with none of the cardiac events assessed as related to study medication by the investigator.
- Other SAEs: Twenty-six patients experienced at least one SAE in the Cardiac Disorders System SOC; thirteen patients were in the telavancin treatment groups (11 treated with 10 mg/kg and 2 with 7.5 mg/kg) and thirteen in the comparator treatment group.
- Discontinuations of study medication due to cardiac TEAEs were also balanced across treatment groups, with four events in the telavancin treatment group and three in the vancomycin group.

Hepatic Adverse Event Summary

Preclinical studies of 6-13 week duration were associated with elevated transaminase levels (AST, ALT) in rats and dogs.

In the ISS database, there were three patients with hepatobiliary-related SAEs; two patients received telavancin and one patient comparator. These events included one telavancin-treated patient who had worsening of hepatic cirrhosis following treatment with telavancin and chemoembolization of hepatic carcinoma and the second telavancin-treated patient had a history of cholelithiasis and developed acute cholecystitis requiring cholecystectomy at the end of telavancin treatment. The vancomycin-treated patient had elevated transaminases (ALT, AST) that were attributed to chronic alcohol use.

Low level (≥ 3 x ULN) elevation in transaminases were more common in patients treated with vancomycin and seen in approximately 2% of patients. Elevation in total bilirubin and alkaline phosphatase were slightly more common in patients treated with telavancin, but were seen in approximately 1% of patients. No patients treated with telavancin or vancomycin met Hy's Rule criteria for drug-induced liver injury.

Hematologic Laboratory Adverse Events

There were four patients treated with telavancin who had a potentially clinically significant decrease in platelet count to $\leq 75 \times 10^9$/L AND $\geq 50 \times 10^9$/L below baseline. Two patients were treated in Study 0017; one patient received 5 minutes of a telavancin infusion and had a nadir platelet count of 55,000 six days after discontinuation, most likely due to a concomitant medication and the second patient had a nadir platelet count of 38,000 on Day 8 of treatment and rebounded while on therapy to 202,000 at EOT (Day 14). Two patients in a Phase 2 study had similar decreases noted in platelet counts; one patient had necrotizing fasciitis and was noted to have a platelet count of 59,000 at the time study medication was infusing and the second patient likely had a false decrease related to clumping of platelets.

A safety update was provided with the resubmission of NDA 22-110 on January 21, 2008. This safety data will be discussed in the review of the Applicant's complete response submission following the original NDA safety conclusions.

Teratogenicity
Based on the results of the Segment 2 (embryo-fetal development) teratology studies in rats, rabbits, and minipigs, the Pharmacology/Toxicology reviewer, along with the Reproductive and Developmental Toxicity PTCC Subcommittee, and Maternal Health Team agreed concluded that the limb defects observed are drug-related and that telavancin has demonstrated multi-species teratogenicity related to the skeletal system. A consensus on whether the product should be labeled Pregnancy Category C or X was not reached. The following factors were recommended for consideration in assigning a pregnancy category to this drug:

- Seriousness of the indication and potential for serious complications in pregnancy associated with the indication
- Availability of alternative treatments
- Teratogenic effect occurring at or near the proposed human dose
- "Potential benefit" of the treatment should exceed the risk

The clinical review team acknowledges the results of the animal findings, but has concerns regarding the strength of findings in the minipig study given the confounding issues including: the small number of fetuses available for examination, skeletal abnormality observed in a fetus in the placebo group, no skeletal defects observed in the high dose group, and use of multiple other antibiotic agents for unspecified reasons.

The concern regarding potential teratogenicity, need for telavancin for treatment of cSSSI in females of childbearing potential, and risk management strategies to ensure safe use of telavancin if approved were discussed at the AIDAC meeting on November, 19, 2008 and will be discussed later in this document.

<u>NDA Safety Conclusions</u>

- In two independent, adequate and well-controlled Phase 3 cSSSI studies telavancin demonstrated nephrotoxicity which appeared to be consistently greater compared to vancomycin when considered in a variety of ways:
  - Renal SAEs and discontinuations from study medication due to renal AEs were more frequent in the telavancin treatment arm than in the vancomycin treatment arm.
  - Potentially clinically significant elevations in serum creatinine occurred more frequently in the telavancin treatment groups than in vancomycin treatment groups.
  - There were five patients treated with telavancin who had relatively normal serum Cr at baseline and reported SAEs or discontinuation of medication due to renal events who had incomplete resolution of elevation in serum creatinine at the final laboratory assessment. This makes conclusions regarding reversibility of renal effects difficult.
  - Factors that may influence or exacerbate the degree of renal insufficiency, such as hydration status and time from development of increase in serum Cr to telavancin dose adjustment, have not been thoroughly examined.
- Evidence of teratogenicity was demonstrated in multiple animal species, with limb abnormalities noted in rat, rabbit, and minipig fetuses. These effects were seen at doses with exposures approximately 1-2X the human exposure at the proposed therapeutic dose. However, these effects were noted in a limited number of animals compared to the number exposed (but higher than historical rates) and findings in the minipig study were compromised by the small number of fetuses available for examination and positive

findings in a control animal. It is unclear to the FDA clinical reviewer whether the limb abnormalities are the same in all species (i.e., whether they are all skeletal and/or related to soft tissue differentiation). If approved, the FDA clinical reviewer would support Category C pregnancy labeling, but recommend not using this drug in females of childbearing potential unless the benefits of use clearly outweigh the potential risk to the fetus.

- Although a "thorough QT study" demonstrated that televancin has an effect (i.e., prolongs) the QTcF interval, the effect appears to be less than that seen with moxifloxacin based on the FDA clinical reviewer's assessment.

Review of Theravance's Complete Response Submission (January 21, 2008)

Deficiency 1: As noted in the September 5, 2008 Chemistry and Manufacturing Review of Balajee Shanmugam, Ph.D., the cGMP non-compliance deficiency at the Ben Venue facility manufacturing the drug product have been resolved. The Office of Compliance issued a recommendation of Acceptable for the facility on June 4, 2008, indicating that the facility was now in conformance with cGMP operations.

Deficiency 2: The outstanding financial disclosure data for three investigators not contained in the original NDA is provided in this complete response submission. This deficiency has been resolved.

Deficiency 3: The Applicant was asked to provide additional information or reanalyses to address both efficacy and safety issues including:

- Lower efficacy in those with decreased renal function and increased age (correlated)
- Imbalance in SAEs related to renal and vascular disorders
- QT/QTc study demonstrated that the QTcF interval was lengthened greater than 10 msec
- The drug product appears to be a teratogen in at least one and possibly three species
- Insufficient information is available to suggest a dose for patients with creatinine clearance less than 10 mL/min including patients on hemodialysis.

Lower efficacy in those with decreased renal function and increased age
Subgroup analysis showed a progressive decline in efficacy in the telavancin-treated patients as baseline renal function decreased; this decline was not seen in the vancomcyin-treated population. An interaction between age and decline in efficacy rates was also noted.

In their response, the Applicant cited all the inherent difficulties in interpreting subgroup analyses performed to assess consistency of treatment effect across subgroups. Factors for incorrect conclusions were cited. The Applicant also noted that each individual cSSSI study identified different treatment-by-subgroup interactions raising questions regarding the validity of interpretations in the pooled subgroup analysis.

- Study 0017: only sex met the threshold for further investigation of treatment by subgroup interaction although renal status was close to that threshold value.
- Study 0018: age, MRSA at baseline, sex, US/non-US, and bacteremia met the threshold for further investigation of treatment by subgroup interaction, although renal status was marginal with respect to treatment interaction.

Patients with severe renal impairment (CrCL < 30 mL/min) made up 3% (47/1489) of the CE population with unequal distribution between telavancin and vancomycin (27 and 20 patients, respectively). Patients with moderate renal impairment (CrCL from 30 to 50 mL/min)made up 9% (132/1489) of the CE population.

The difference in outcome between treatment groups based on CrCL ≤ 50 mL/min at EOT was 78% (71/91) for telavancin compared to 85% (75/88) for vancomcyin. This difference was driven primarily by patients discontinuing therapy early due to AE; 7 telavancin-treated patients discontinued compared to two vancomycin-treated patients. Only three of the telavancin patients

AEs, two of which were renal adverse events, were thought to be possibly/probably related to study medication.

Patients with moderate to severe renal impairment had low cure rates with other associated factors predictive of poor outcome: age, diabetes, peripheral vascular disease, and lower extremity infections. Older patients treated with telavancin had worse responses to treatment along with poorer renal function were more likely to have cellulitis or ulcers, diabetes mellitus, and peripheral vascular disease.

Renal Toxicity in cSSSI Studies

The Applicant states that renal impairment was highly associated with baseline comorbidities which increase risk for development of renal impairment such as heart failure, blood pressure abnormalities, and diabetes mellitus. In the NDA ISS, other contributing factors noted were concomitant medications such as diuretics, ACE inhibitors, or non-steroidal anti-inflammatory medications.

The presence of any baseline comorbidity was associated with a renal AE in 32/510 (6%) telavancin-treated patients and 9/501 (2%) vancomycin-treated patients. In patients without baseline comorbidities, three patients in each treatment group had renal AEs. Comorbidities included: atheroembolic disease, hypertension, peripheral vascular disease, cutaneous and systemic lupus erythematosus, diabetes mellitus, heart failure, HIV infection, liver disease, prostate disease, kidney disease, and sepsis.

The presence of any baseline comorbidity was associated with a serious renal AE (renal SAE) in 10/510 (2%) telavancin-treated patients and 3/501 (<1%) vancomycin-treated patients. In patients without baseline comorbidities, two patients treated with telavancin and one patient treated with vancomycin experienced renal SAEs.

The Applicant provided an assessment of the outcome of renal AEs in patients who prematurely discontinued study medication for any AE (renal and non-renal) and in those who completed the course of study medication for the cSSSI studies in support of the general reversibility of the nephrotoxicity. In patients discontinued for any AE (renal and non-renal):

- 16/1029 telavancin-treated patients with renal AEs who discontinued study medication due to any AE, outcomes were as follows: 1 patient died, 1 was improving, 1 recovered with sequelae, and 13 were completely recovered
- 19/1029 telavancin-treated patients with renal AEs who were not discontinued from study medication due to any AE: no patient died, 7 patients still had the renal AE present and unchanged, 5 patients were improving, and 7 patients had recovered (compared to 9/1033 vancomycin-treated patients who had renal AEs and were not discontinued; 4 patients had the renal AE present and unchanged, 1 patient was improving, and 4 patients had recovered.

For patients with normal or mild impairment of renal function, the incidence of renal AEs was low for both treatment groups (<1%), majority were resolved or improving at final assessment.

Vascular Adverse Events in cSSSI Studies
There was no specific vascular AE identified. Vascular AEs included arterial and venous events, along with abnormalities in blood pressure.

Thorough QT/QTc Study
The Applicant provided revised labeling to more accurately describe the design and results of the QT/QTc study, including the electrophysiologic effects of telavancin on the OT interval in relation to effects on a concurrently studies positive control. The proposal also included cautionary statements adequate and appropriate to manage the risk of QT prolongation with telavancin.

An analysis of changes from baseline in QTcF interval for the HAP studies (Studies 0015 and 0019) and cSSSI studies using telavancin at a 10 mg/kg dose (Studied 202b, 0017, and 0018) was provided. The post-medication average QTcF change for HAP studies was 6.1 msec and 2.1 msec and post-medication maximium change of 19.3 msec and 15.1 msec, for telavancin and vancomycin respectively. In the HAP studies, 12 patients (2%) in each treatment group had a maximum post-drug QTcF of >500 msec and maximum post-drug change in QTcF >60 msec in 48/751 (8%) and 44/752 (7%) of patients treated with telavancin and vancomycin, respectively. There were no reported SAEs or deaths associated with Torsades de pointes.

Teratogenicity
The Applicant's response cited the previously submitted analysis completed by Dr. Anthony Scialli who concluded that the primary evidence of developmental toxicity in the rat was manifested as reduction in litter weight. He also indicated that there was no embryologically coherent mechanism to postulate that the limb defects could be caused by telavancin.

Dose Regimen in Patients with Creatinine Clearance < 10 mL/min, Including Patients on Hemodialysis
The Applicant acknowledged that there was insufficient data in the NDA to determine an appropriate dose regimen in this subgroup of patients.

Safety Update
An additional 751 patients were treated with telavancin and 752 with comparator (vancomycin) in 2 HAP studies. The safety data was presented for the rate of adverse events by total population (Studies 0015 and 0019) and was not presented separately for each study. Only summary safety data (i.e. tabular listing of events, line-listing of patients) along with the narratives from patients who had SAEs (including those resulting in death) and discontinuations due to AEs were provided. Approximately 50% of the enrolled population received 8-14 days of therapy.

Deaths
Table 11 shows the number of patients who died by treatment group and SOC for the AEs resulting in death. Deaths were reported through TOC or 28 days after therapy for those who did not have a TOC evaluation. The mortality rate for the telavancin treatment group was 20% compared to 18% for vancomycin. This mortality rate is consistent with that of other hospital-acquired pneumonia trials (linezolid, ceftobiprole).

Table 11: AEs by SOC Resulting in Death (HAP Studies)

HAP Studies (0015 and 0019)		
MedDRA SOC	**TLV N=751**	**VANC N=752**
Any serious event (# patients, %)	149 (20)	137 (18)
Blood and Lymphatic System	1 (<1)	0
Cardiac Disorders	16 (2)	29 (4)
Gastrointestinal Disorders	3 (<1)	4 (<1)
General Disorders and Administration Site	24 (3)	12 (2)
Hepatobiliary Disorders	1 (<1)	1 (<1)
Infections and Infestations	48 (6)	35 (5)
Injury, Poisoning and Procedural Complications	1 (<1)	3 (<1)
Metabolism and Nutrition Disorders	2 (<1)	1 (<1)
Neoplasms benign, malignant, and unspecified	0	2 (<1)
Nervous System Disorders	11 (1)	10 (1)
Renal and Urinary Disorders	3 (<1)	2 (<1)
Respiratory, Thoracic and Mediastinal Disorders	38 (5)	39 (5)
Vascular Disorders	5 (<1)	2 (<1)
Modified Table 3, NDA 22-110, Safety Update, January 21, 2008		

The number of patients who died in the telavancin treatment group was greater then that for the vancomycin treatment group for general and administration disorders and infections. In the General Disorders SOC the imbalance was noted primarily for multi-organ failure (22 telavancin-treated patients compared to 11 vancomycin-treated patients. In the Infections SOC, the imbalance was primarily due to sepsis and septic shock (30 patients treated with telavancin compared to 20 patients treated with vancomycin). AEs resulting in death that occurred with a 1% or greater difference between treatment groups where telavancin mortality was greater were multiorgan failure (3% of telavancin-treated patients compared to 1% of vancomycin-treated patients) and septic shock (3% of telavancin-treated patients compared to 2% of vancomycin-treated patients).

An imbalance in the AEs resulting in death in the Cardiac SOC was noted with a greater number of events noted in patients in the vancomycin treatment group relative to the telavancin treatment group. The majority of deaths were secondary to congestive heart failure (12 vancomycin-treated patients compared to six telavancin-treated patients) and ventricular arrhythmia (four vancomycin-treated patients compared to one telavancin-treated patient). AEs resulting in death that occurred with a 1% or greater difference between treatment groups where vancomycin mortality was greater were respiratory failure (2% of telavancin-treated patients compared to 3% of vancomycin-treated patients) and pneumonia (1% of telavancin-treated patients compared to 2% of vancomycin-treated patients).

An imbalance in the following baseline characteristics was noted in telavancin treatment group patients who died versus those who did not for diabetes mellitus, ventilator-associated pneumonia, acute respiratory distress syndrome at baseline, mixed gram positive and gram negative pathogens at baseline, baseline CrCL <50 mL/min, and presence of co-morbidity. An imbalance in deaths related to advanced age and baseline septic shock were seen in both treatment groups.

Serious Adverse Events
Serious AEs occurred in 31% of telavancin-treated patients compared to 26% of vancomycin-treated patients. Table 12 shows the SOCs in which SAEs occurred at a frequency of 1% or greater in a given treatment group.

Table 12: SAEs by Select SOCs in HAP

	Total HAP Studies	
MedDRA SOC	TLV N=751	VANC N=752
Any serious event (# patients, %)	232 (31)	194 (26)
Cardiac Disorders	30 (4)	38 (5)
Gastrointestinal Disorders	12 (2)	11(1)
General Disorders and Administration Site	26 (3)	15 (2)
Infections and Infestations	68 (9)	60 (8)
Nervous System Disorders	21 (3)	19 (3)
Renal and Urinary Disorders	24 (3)	16 (2)
Respiratory, Thoracic and Mediastinal Disorders	60 (8)	57 (8)
Vascular Disorders	15 (2)	9 (1)
Modified Table 6, NDA 22-110, Safety Update, January 21, 2008		

SAEs were most frequent in the Infections and Respiratory SOCs; the Infection SOC included MedDRA preferred terms of sepsis, septic shock, and pneumonia, while the Respiratory SOC included respiratory failure.

SAEs that occurred with an incidence of 1% or greater in either treatment group included: septic shock (4% for each treatment group), respiratory failure (3% for each treatment group), multi-organ failure (3% of telavancin-treated patients compared to 2% of vancomycin-treated patients), acute renal failure (2% of telavancin-treated patients compared to 1% of vancomycin-treated patients), pneumonia (1% of telavancin-treated patients compared to 2% of vancomycin-treated patients), sepsis (2% of telavancin-treated patients compared to 1% of vancomycin-treated patients), congestive cardiac failure (<1% of telavancin-treated patients compared to 1% of vancomycin-treated patients), and acute respiratory failure (<1% of telavancin-treated patients compared to 1% of vancomycin-treated patients).

There was an imbalance in the number of patients with MedDRA preferred terms indicative of renal impairment with a greater number observed in the telavancin treatment group. In Study 0015, there were 17 telavancin-treated patients compared to seven vancomycin-treated patients and in Study 0019, eight patients in each treatment group who had renal SAEs (for both studies, there were 25 telavancin-treated patients and 15 vancomycin-treated patients). Comparison of preferred terms according to treatment group showed:

- Increase serum Cr: three patients treated with telavancin compared to none treated with vancomycin
- Acute renal failure: 18 patients treated with telavancin compared to 11 patients treated with vancomycin
- Renal impairment: no patients treated with telavancin compared to one patient treated with vancomycin
- Renal insufficiency: four patients treated with telavancin compared to four patients treated with vancomycin.

Treatment-Emergent AEs Resulting in Premature Discontinuation of Study Medication
Discontinuations due to TEAEs occurred in 60/751 (8%) telavancin-treated patients and 40/752 (5%) of vancomycin-treated patients. Table 13 shows those SOCs where discontinuations of study medication due to AEs were most frequent.

Table 13: Discontinuations due to AEs in HAP for Select SOCs

	Total HAP Studies	
MedDRA SOC	**TLV N=751**	**VANC N=752**
Any discontinuation event (# patients, %)	60 (8)	40 (5)
Blood and Lymphatic System	1 (<1)	4 (<1)
Cardiac Disorders	4 (<1)	2 (<1)
Gastrointestinal Disorders	2 (<1)	1 (<1)
General Disorders and Administration Site	3 (<1)	4 (<1)
Infections and Infestations	9 (1)	12 (2)
Investigations	17 (2)	3 (<1)
Nervous System Disorders	7 (<1)	1 (<1)
Renal and Urinary Disorders	11 (1)	6 (<1)
Respiratory, Thoracic and Mediastinal Disorders	6 (<1)	3 (<1)
Skin and Subcutaneous Tissue Disorders	5 (<1)	2 (<1)
Modified Table 7, NDA 22-110, Safety Update, January 21, 2008		

TEAEs that resulted in discontinuation of study medication occurring more frequently in the telavancin-treated group included acute renal failure (nine patients versus two), prolonged QTc (protocol-specified discontinuation criterion; eight versus two), and increased blood creatinine (five versus one).

TEAEs that resulted in discontinuation of study medication occurring more frequently in the vancomycin-treated group included renal impairment in two patients treated with vancomycin (no telavancin-treated patients), renal insufficiency in two patients treated with vancomycin (one treated with telavancin), and thrombocytopenia in two patients treated with vancomycin (no telavancin-treated patients).

The overall incidence of TEAEs was 82% for telavancin and 81% for vancomycin. Gastrointestinal AEs were the most commonly seen and occurred in 35% of both treatment groups. Adverse events in the metabolism and nutrition SOC and the infection and infestations SOC occurred in approximately 25% of each treatment group.

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/s/

Janice Pohlman
12/22/2008 01:05:53 PM
MEDICAL OFFICER
Medical Officer

Office Director Memorandum

Date	October 19, 2007
From	Edward Cox, MD MPH
Subject	Office Director Memorandum
NDA/BLA # Supp #	22-110
Proposed Proprietary / Established (USAN) Names	Vibativ / (telavancin)
Dosage Forms / Strength	powder for injection/intravenous infusion, 250mg and 750 mg
Proposed Indication(s)	1. treatment of complicated skin and skin structure infections
Action:	Approvable

Please see the Approvable Letter for the list of deficiencies.

1. Introduction to Review

Theravance has submitted NDA 22-110 for telavancin for injection for the indication of complicated skin and skin structure infections. Telavancin is a lipoglycopeptide antibacterial agent that is derived from vancomycin. The clinical data from phase 3 studies in support of safety and efficacy are derived from two active controlled studies designed to show non-inferiority of telavancin to vancomycin. From the developmental and reproductive toxicology animal studies, telavancin was found to be teratogenic in animals. Telavancin also has an effect on the QT estimated from the thorough QT study to be in the range of 12-15 msec at a dose of 10 mg/kg. Based on in vitro studies, telavancin does not appear to be a CYP450 inhibitor or substrate. Renal adverse events, including some serious renal adverse reactions, appear to occur at a greater frequency in telavancin-treated patients than in comparator-treated patients.

The review team has reviewed the issues in detail in their respective disciplines with regards to the safety and efficacy of telavancin for treatment of complicated skin and skin structure infections. For a detailed discussion of NDA 22-110, the reader is referred to the individual discipline specific reviews. In addition Dr.Nambiar's Team Leader's Memo and Dr. Chambers' Division Director's Memo summarize key issues in the NDA submission. This memorandum will focus on selected issue from the application.

2. Background/Regulatory History/Previous Actions/Foreign Regulatory Actions/Status

This is the initial submission of NDA 22-110 telavancin for treatment of complicated skin and skin structure infections. Telavancin has not been approved for marketing outside of the United States.

3. CMC/Microbiology/Device

The review of the chemistry, manufacturing and controls for telavancin finds that the applicant has provided adequate information describing the CMC for Vibativ (telavancin HCl) for injection. However, FDA inspection of the Ben Venue facility in Bedford, Ohio 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 product quality microbiology review found the manufacturing issues related to the sterility of the drug product to be adequate. Of note is that Vibativ includes among its excipients the solubilizing agent hydroxypropylbetadex which is further discussed in the section of this memorandum addressing pharmacology and toxicology.

4. Nonclinical Pharmacology/Toxicology

Dr. Chen reviewed the pharm tox studies and provided labeling recommendations in a subsequent review. His labeling recommendations include a Warning statement regarding teratogenicity and he recommends pregnancy Category C in his review of October 10, 2007.

The major organs of toxicity in animal studies were the liver and kidneys. Renal toxicity was observed in both rats and dogs and was generally reversible after 4-weeks, but only partially reversible in the 13 and 26-week studies. Hepatic toxicity was noted in rats and dogs and manifestations included elevations in alkaline phosphatase, ALT, AST, hepatocellular degeneration and macrophage accumulation. In the pharm tox studies hydroxypropylbetadex was utilized in order to assess its impact upon observed findings.

The results of the reproductive and developmental toxicology studies were discussed extensively. The findings from the rat and rabbit studies included skeletal abnormalities in the mid and high dose groups in rats and in the high dose group in rabbits. A study in mini-pigs was also conducted and findings of increased pre-implanation loss in all dose groups, increase in late resorptions in the high dose group, external malformations in the low and mid-dose groups were noted. Of note, in the minipig study, many animals required treatment with other antimicrobials.

The findings were reviewed by the pharmacology toxicology reviewers and the Reproductive and Developmental Toxicity PTCC Subcommittee who found that telavancin was a multi-species teratogen. The recommendation from the Maternal Health Team recommended classification of the drug as Pregnancy Category X based upon the absence of a demonstrated benefit over existing therapeutic options. They recommended a boxed warning, indicate the drug only in men and women not of childbearing potential, and restricted distribution at the pharmacy level requiring documentation of the age and gender of the patient.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology of telavancin is discussed in Dr. Tworzyanski's Clinical Pharmacology Review. In vitro CYP P450 isoform assays did not find metabolism by the multiple isoforms tested nor was telavancin an inhibitor. Telavancin is predominantly eliminated by the kidney. Dosage adjustment is recommended for patients with renal impairment. No dosage adjustment is recommended based upon age, gender, or hepatic impairment. Telavancin penetrates into skin blister fluid and achieves an AUC approximately 40% of the AUC in serum. Also of note is that telavancin interferes with some tests used to assess coagulation parameters. Telavancin does not alter coagulation, but it does interfere with some types of testing.

In a thorough QT study, the QTcF interval was prolonged greater than 10 msec. At doses of 7.5 mg/kg and 15 mg/kg the mean ΔΔQTcFs after three days of dosing were 14 and 18 msec, respectively, while the ΔΔQTcF for moxifloxacin 400 mg the positive control was 24 msec. Using a step-wise linear mixed-effects model the expected mean ΔΔQTcF is 12 to 15 msec for telavancin at a dose of 10 mg/kg. The proposed labeling from the IRT consult includes a description of the thorough QT study and identification of groups of patients that may be at increased risk for prolongation of the QT interval and associated adverse events.

6. Clinical Microbiology

Telavancin is a lipoglycopeptide antibiotic that is active against gram-positive organisms generally associated with complicated skin and skin structure infections. Telavancin inhibits glycopeptide synthesis and also there is some information on a second mechanism of action involving disruption of the cell membrane of gram-positive bacteria. In vitro studies have shown a low potential for the development of resistance to telavancin in selected species of gram-positive organisms and in clinical trials emergence of resistance was not noted in the available clinical data. From the data from the clinical studies, telavancin is active against methicillin resistant *Staph. aureus*. From the standpoint of the clinical microbiology reviewer the application may be approved with their proposed revision to the microbiological information included in the product labeling.

7. Clinical/Statistical

The results of the clinical review are discussed in detail in Dr. Pohlman's Medical Officer Review and Dr. Komo's Statistical Review. Dr. Pohlman recommends an action of not approvable and notes the renal adverse events with telavancin, teratogenicity in animals, and effect on QT. Dr. Nambiar's Team Leader review recommends an action of approvable and cites renal adverse reactions, deviations from cGMP, and the need to convey the risk of the drug appropriately. Dr. Komo's statistical review notes that non-inferiority has been demonstrated for telavancin compared to vancomycin; the Medical Officer and Medical Team

Leader reviews agree with this assessment. Please see these reviews for a detailed analysis of the findings. A brief summary of findings is described below.

Efficacy

The applicant has submitted results from two phase 2 studies and two phase 3 studies in complicated skin infections. The dose of 10 mg/kg IV q24 hours was selected based upon higher microbiologic eradication rates in study 202b than was observed with 7.5 mg/kg. The data from the two phase 3 studies 0017 and 0018 includes analyses of data after the dose had been changed to 10 mg/kg IV q 24 hours. Studies 0017 and 0018 were randomized, double-blind, multi-center, active controlled trials comparing telavancin 10 mg/kg q24 hours to vancomycin 1 gram IV q12 hours for 7-14 days. Investigators could also add aztreonam and/or metronidazole to treat gram negative or anaerobic infections. The results from the FDA analysis of the trials are provided in Table 1. Telavancin was found to be non-inferior to vancomycin in the as treated and clinically evaluable populations in studies 0017 and 0018. Dr. Komo notes in his review that based upon data submitted by the sponsor and the Agency's review of the literature and other supportive evidence, the applicant's 10% non-inferiority margin is acceptable for the treatment of cSSSI using vancomycin as the comparator.

Table 1. FDA Analysis of Clinical Cure Rate at Test of Cure

	Telavancin n/N (%)	Vancomycin n/N (%)	Treatment Difference % (95% CI)
As Treated Population			
Study 0017	309/426 (72.5)	307/429 (71.6)	1.0 (-5.0, 7.0)
Study 0018	348/472 (72.5)	360/489 (73.6)	0.1 (-5.5, 5.7)
Clinically Evaluable Population			
Study 0017	289/343 (84.3)	288/348 (82.8)	1.5 (-4.0, 7.0)
Study 0018	306/365 (83.8)	318/363 (87.6)	-3.8 (-8.8, 1.3)

Evaluation of response rates by age and by creatinine clearance found a differential effect across treatment arms with a greater loss of efficacy in the telavancin arm compared to the vancomycin arm in patients with renal impairment and in patients older than 65 years of age. (Please see Figure 2 and Figure 3. in Dr. Komo's review.) For the per pathogen microbiological cure rates, the reader is referred to the Medical Officer and Medical Team Leader reviews.

Safety

The total safety database for telavancin was comprised of 1697 subjects who received telavancin in the clinical development program. Over 1000 patients received telavancin at the dose of 10 mg/kg in Studies 0017, 0018, and 202b. The most common adverse events included dyguesia which was reported in 33% of telavancin-treated patients and 7% of vancomcyin-treated patients; nausea 27% of telavancin-treated patients and 15% of vancomycin-treated patients; foamy urine 13% of telavancin-treated patients and 3% of

vancomycin-treated patients. The adverse event of infusion-related reactions was reported in 20% of vancomycin-treated patients and 11% of telavancin-treated patients.

Renal adverse events were reported in 2.3% of telavancin-treated patients compared to 0.5% of comparator-treated patients. From table 41 from Dr. Pohlman's review, there were 11 telavancin-treated patients with serious adverse events in the renal and urinary disorders category compared to 2 for vancomycin-treated patients in studies 0017 and 0018. Four of the SAEs in the telavancin arm were "renal failure acute" and there were no adverse events of renal failure acute in the comparator arm. There were 2 "renal impairment" SAEs in the telavancin arm and none in the comparator. There were 3 "renal insufficiency" SAEs in the telavancin arm and none in the vancomycin arm. Additional information on renal adverse reactions is discussed in the Medical Officer and Medical Team Leader Reviews. From the data, renal adverse reactions are reported at a higher frequency in patients receiving telavancin compared to comparator patients.

The results for the thorough QT study are described in the section on clinical pharmacology. ECGs were also performed periodically in the phase 3 trials. These studies excluded patients with congenital long QT syndrome, baseline QTc>500 msec, severe left ventricular hypertrophy, and uncompensated heart failure. The studies did enroll patients with other risk factors for QT prolongation; approximately 35% of patients had other risk factors for QT prolongation (e.g., hypokalemia, taking medications that prolong the QT interval). In the phase 3 studies, 1% of telavancin-treated patients and 0.5% of vancomycin-treated patients had QT interval prolongation >60 msec. There were 4 telavancin-treated patients with cardiac adverse events resulting in death; two of these events were assessed as possibly or probably related. There were 6 vancomycin-treated patients with cardiac adverse events resulting in death, none were assessed as possibly or probably related to the drug by the investigator and one of these events was assessed as related to the drug by the Medical Officer. It will be important to evaluate any additional cardiac events that may occur in ongoing clinical studies and address the effect on QT appropriately.

Review of liver related laboratory analytes and adverse events by treatment arm did not reveal hepatic findings of concern.

8. Advisory Committee Meeting

During this review cycle, NDA 22-110 was not presented to an FDA Advisory Committee. During the course of the review cycle the issues related to teratogenicity in animals, the impact upon the risk / benefit profile, and how this risk would be managed was the topic of considerable discussion. Given the findings here of teratogenicity in animals, renal adverse reactions, effect on QT, and the overall risk benefit profile, this application should be presented to an FDA advisory committee.

9. Other Regulatory Issues

As noted previously there are outstanding issues related to the CMC of the product. These will need to be resolved prior to approval.

10. Financial Disclosure

Information on financial disclosure is still outstanding for three subinvestigators in the clinical trials. The applicant was notified of the lack of information on these three individuals on October 9th, 2007.

11. Labeling

Only preliminary discussions were held regarding some sections of the product label. Given the deficiencies that need to be addressed prior to an approval action and the plan to take this application to an advisory committee during a subsequent cycle, labeling discussions will take place after consideration of this additional information.

12. DSI Audits

DSI inspections were performed at four sites; two sites each in study 17 and 18. The DSI Clinical Inspection Summary notes that data from three of these four sites inspected appear to be acceptable. DSI noted that data from the fourth site is questionable and certain data from the site should not be used in support of the NDA. An additional inspection is pending at this time.

13. Conclusions and Recommendations

I concur with the assessments of the review team and the Medical Officer, Team Leader and Division Director's recommendations that there are outstanding deficiencies that need to be addressed. The Team Leader and Division Director have recommended an approvable action and the Medical Officer has recommended a not approvable action. The information needed and areas of concern are similar across the reviews. I concur with the recommendation from the Team Leader and Division Director for an action of approvable.

FDA inspection of the Ben Venue facility in Bedford, Ohio revealed significant deviations from the Current Good Manufacturing Practice regulations. This deficiency related to cGMP will need to be adequately addressed.

Studies 0017 and 0018 demonstrate non-inferiority of telavancin to vancomycin in complicated skin and skin structure infections. Additional analyses of the efficacy data find a decrement in the cure rate compared to comparator for elderly patients and patients with reduced creatinine clearance. Renal adverse events, including serious adverse events, were reported more frequently in patients receiving telavancin than with comparator. Based upon

results from a thorough QT study, the estimated effect of telavancin on the QT interval is 12-15 msec at the 10mg/kg dose. Telavancin does not appear to be a substrate or inhibitor of CYP450 isoforms, based upon in vitro data. Evaluation of the animal developmental and reproductive toxicology studies has shown findings of teratogenicity. Given these issues, there are remaining questions on the benefit risk ratio for telavancin that need to be addressed and how these risk will be managed needs to be further addressed. Given these issues, it is also expected that this application will be presented to an FDA Advisory Committee during a subsequent review cycle.

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/s/

Edward Cox
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MEDICAL OFFICER